

PRODUCT MONOGRAPH

CIPRO[®] XL[™]

Ciprofloxacin Hydrochloride and Ciprofloxacin Extended Release Tablets

Ciprofloxacin 500 mg, 1000 mg

Antibacterial Agent

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PRODUCT MONOGRAPHCIPRO[®] XL[™]

Ciprofloxacin Hydrochloride and Ciprofloxacin Extended Release Tablets

Ciprofloxacin 500 mg, 1000 mg

THERAPEUTIC CLASSIFICATION

Antibacterial Agent

ACTION AND CLINICAL PHARMACOLOGY**ACTION**

CIPRO[®] XL[™] (ciprofloxacin) extended release tablets contain ciprofloxacin, a synthetic broad-spectrum antimicrobial agent for oral administration. CIPRO[®] XL[™] tablets are coated, bi-layer tablets consisting of an immediate release layer and an erosion-matrix type controlled-release layer. The tablets contain a combination of two types of ciprofloxacin drug substance, ciprofloxacin hydrochloride and ciprofloxacin (base).

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

Clinical pharmacology studies have compared the pharmacokinetics of CIPRO[®] XL[™] to CIPRO[®] (ciprofloxacin) (immediate release formulation) (CIPRO[®] XL[™] 500 mg vs CIPRO[®] 250 mg bid and CIPRO[®] XL[™] 1000 mg vs CIPRO[®] 500 mg bid, respectively), examined the effects of various meals on the pharmacokinetics of CIPRO[®] XL[™], and investigated possible drug interactions.

Since the mean peak plasma concentration (C_{max}) of CIPRO[®] XL[™] 500 mg tablets (1.59 mg/L) does not exceed that of CIPRO[®] 500 mg tablets (2.36 mg/L), the effect of CIPRO[®] XL[™] 500 mg with respect to special populations (elderly, renal impairment, hepatic impairment) (see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations**) and drug-drug interactions is expected to be similar to that of CIPRO[®] 500 mg tablets, which has been extensively studied.

Since the CIPRO[®] XL[™] formulation entails only a slight modification of drug release, the overall performance of the CIPRO[®] XL[™] 1000 mg formulation with respect to special populations and drug-drug and drug-disease interactions is expected to be similar to that of CIPRO[®], which has been extensively studied.

Absorption

CIPRO[®] XL[™] tablets are formulated to release drug at a slower rate compared to CIPRO[®] tablets, which are immediate release. Approximately 35% of the ciprofloxacin dose in the CIPRO[®] XL[™] tablet is contained within an immediate release component, while the remaining 65% is contained in a slow-release matrix.

CIPRO[®] XL[™] 500 mg

The C_{\max} of once daily treatment with 500 mg CIPRO[®] XL[™] is 1.59 mg/L, which is 40% higher than the C_{\max} of CIPRO[®] (ciprofloxacin) 250 mg tablets (immediate release formulation) (1.14 mg/L). The mean area under the plasma-concentration time curve (AUC) over 24 hours at steady state following CIPRO[®] XL[™] 500 mg once daily is 7.97 mg*h/L, which is equivalent to the AUC of CIPRO[®] 250 mg tablets bid (8.25 mg*h/L). Maximum plasma concentrations are attained between 1 and 2.5 hours after dosing of CIPRO[®] XL[™] 500 mg (median t_{\max} = 1.5 h).

The following table (**Table 1**) compares the pharmacokinetic parameters obtained at steady state for CIPRO[®] XL[™] 500 mg tablets and CIPRO[®] 250 mg tablets bid.

Table 1: Ciprofloxacin Pharmacokinetics (Mean ± SD) Following CIPRO[®] (Ciprofloxacin) 250 mg Tablets (Immediate Release Formulation) BID and CIPRO[®] XL[™] (Ciprofloxacin) Extended Release 500 mg Tablets Administration

	C_{\max} (mg/L)	AUC _{0-24h} (mg* h/L)	$t_{1/2}$ (h)	t_{\max} (h) ^a
CIPRO [®] XL [™] (ciprofloxacin) extended release 500 mg tablets	1.59 ± 0.43	7.97 ± 1.87	6.6 ± 1.4	1.5 (1.0-2.5)
CIPRO [®] (ciprofloxacin) 250 mg tablets (immediate release formulation) bid	1.14 ± 0.23	8.25 ± 2.15	4.8 ± 0.6	1.0 (0.5-2.5)

a Median (range)

CIPRO[®] XL[™] 1000 mg

The C_{\max} of once daily treatment with 1000 mg CIPRO[®] XL[™] is 3.11 mg/L, which is 51% higher than the C_{\max} of CIPRO[®] (ciprofloxacin) 500 mg tablets (immediate release formulation) (2.06 ± 0.41 mg/L). The mean area under the plasma-concentration time curve (AUC) over 24 hours at steady state following CIPRO[®] XL[™] 1000 mg once daily is 16.83 mg*h/L, which is equivalent to the AUC of CIPRO[®] 500 mg tablets bid (17.04 mg* h/L). Maximum plasma concentrations are attained between 1 and 4 hours after dosing (median t_{\max} = 2.0 h).

The following table (**Table 2**) compares the pharmacokinetic parameters obtained at steady state for CIPRO[®] XL[™] 1000 mg and CIPRO[®] 500 mg bid.

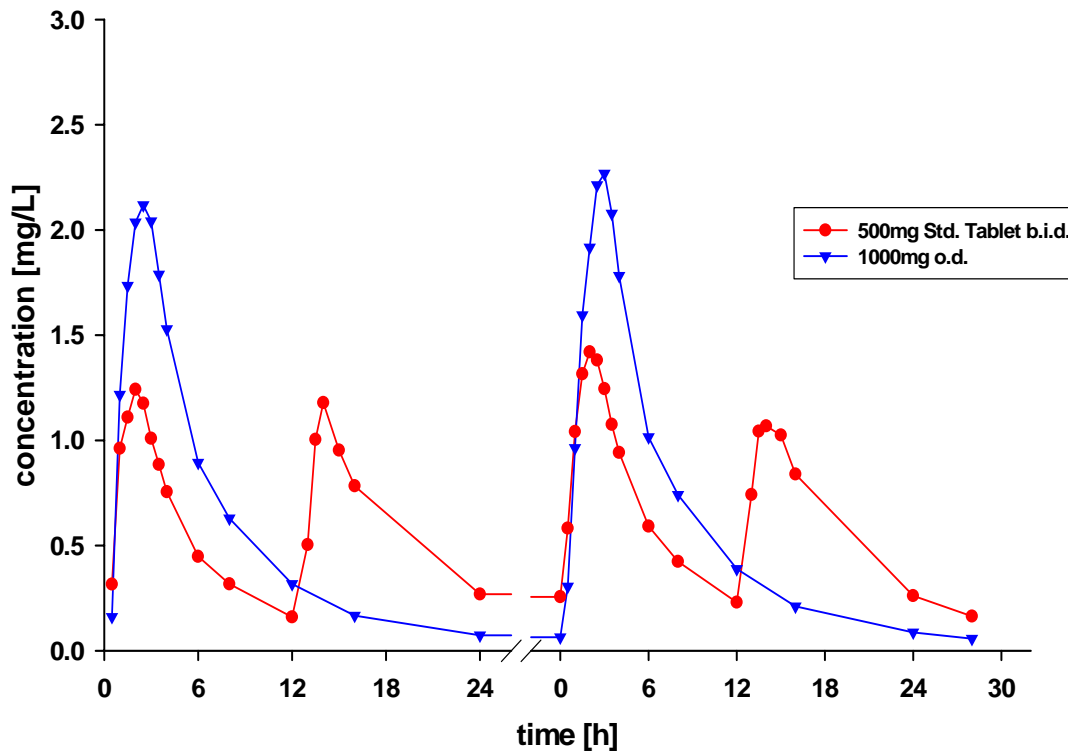
Table 2: Ciprofloxacin Pharmacokinetics (Mean \pm SD) Following CIPRO[®] (Ciprofloxacin) 500 mg Tablets (Immediate Release Formulation) BID and CIPRO[®] XL[™] (Ciprofloxacin) Extended Release 1000 mg Tablets Administration

	C_{max} (mg/L)	AUC_{0-24h} (mg* h/L)	$t_{1/2}$ (h)	t_{max} (h) ^a
CIPRO [®] XL [™] (ciprofloxacin) extended release 1000 mg tablets	3.11 \pm 1.08	16.83 \pm 5.65	6.31 \pm 0.72	2.0 (1 - 4)
CIPRO [®] (ciprofloxacin) 500 mg (immediate release formulation) bid	2.06 \pm 0.41	17.04 \pm 4.79	5.66 \pm 0.89	2.0 (0.5 - 3.5)

a Median (range)

The relative bioavailability of CIPRO[®] XL[™] 1000 mg compared to CIPRO[®] 500 mg tablet bid was examined in a crossover study of 20 healthy male volunteers under fasted conditions. Mean concentrations for Day 1 are shown in **Figure 1**.

Figure 1: Relative Bioavailability of CIPRO[®] XL[™] 1000 mg Versus CIPRO[®] 500 mg BID



The pharmacokinetics of CIPRO[®] XL[™] are not altered by coadministration with food. AUC values were comparable following administration of CIPRO[®] XL[™] with a high-fat meal, a low-fat meal, or under fasted conditions (see [HUMAN PHARMACOLOGY](#)) (see [Table 3](#)).

Table 3: Pharmacokinetics of CIPRO[®] XL[™] (Ciprofloxacin) Extended Release 500 mg Tablets Under Fed and Fasted Conditions

Parameter	Fed	Fasted	Ratio (Fed/Fasted)	90% CI
AUC (mg*h/L) ^a	7.12 (21%)	7.05 (36%)	1.01	0.89 - 1.15
C _{max} (mg/L) ^a	1.30 (26%)	1.34 (42%)	0.97	0.79 - 1.18
t _{max} (h) ^b	3.5 (1.5 - 4.0)	1.5 (0.5 - 3.5)	Not evaluated	

a Geometric mean (% CV)

b Median (range)

Distribution

In one study, the apparent volume of distribution (V_{darea}) of CIPRO[®] was estimated from kinetic data recorded after oral doses and found to be approximately 3.5 L/kg. Studies with the oral and intravenous forms of ciprofloxacin have demonstrated penetration of ciprofloxacin into a variety of tissues. A single dose study in healthy subjects has demonstrated penetration of ciprofloxacin into prostate tissue following administration of CIPRO[®] XL[™] 1000 mg. One and three hours after dosing, mean ciprofloxacin concentrations were greater than 4 µg/g. The binding of ciprofloxacin to serum proteins is 20% to 40%, which is not likely to be high enough to cause significant protein binding interactions with other drugs. Following administration of a single dose of CIPRO[®] XL[™] (500 mg or 1000 mg), ciprofloxacin concentrations in urine, collected up to 4 hours after dosing, averaged over 300 mg/L and over 500 mg/L, respectively; in urine excreted from 12 to 24 hours after dosing, ciprofloxacin concentration averaged 27 mg/L for CIPRO[®] XL[™] 500 mg and 58 mg/L for CIPRO[®] XL[™] 1000 mg (see [HUMAN PHARMACOLOGY](#)).

Metabolism

Four metabolites of ciprofloxacin were identified in human urine. The primary metabolites are oxociprofloxacin (M3) and sulfociprofloxacin (M2), each accounting for roughly 3% to 8% of the total dose. Other minor metabolites are desethylene ciprofloxacin (M1) and formylciprofloxacin (M4). The relative proportion of drug and metabolite in serum corresponds

to the composition found in urine. Excretion of these metabolites was essentially complete by 24 hours after dosing (see [HUMAN PHARMACOLOGY](#)).

Elimination

The elimination kinetics of ciprofloxacin are similar for CIPRO[®] XL[™] and CIPRO[®] (immediate release formulation). The mean serum elimination half-life ($t_{1/2}$) of CIPRO[®] XL[™] (ciprofloxacin) extended release is 6.6 (\pm 1.4) hours and 6.3 (\pm 0.7) hours, for the 500 mg and 1000 mg tablets, respectively (see [HUMAN PHARMACOLOGY](#)). The major route of elimination of ciprofloxacin in humans is as unchanged drug in urine.

Special Populations

Renal Impairment

In patients with reduced renal function, the half-life of ciprofloxacin is slightly prolonged. Since the total drug exposure attained with CIPRO[®] XL[™] 500 mg does not exceed that achieved with CIPRO[®] 500 mg tablets (immediate release formulation), which is approved as a total daily dose for use in renally impaired patients, no dosage adjustment for renal disease is required with CIPRO[®] XL[™] 500 mg.

For complicated urinary tract infections or acute uncomplicated pyelonephritis, where 1000 mg is the appropriate dose, the dosage of CIPRO[®] XL[™] should be reduced to 500 mg CIPRO[®] XL[™] once daily in patients with creatinine clearance below 30 mL/min (see [DOSAGE AND ADMINISTRATION, Impaired Renal Function](#)).

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 elucidated (see [HUMAN PHARMACOLOGY](#)).

In a study of 7 cirrhotic patients and healthy volunteers given CIPRO[®] 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[®]

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.

Elderly

No dosage adjustment based on age alone is necessary for elderly patients. Pharmacokinetic studies of the immediate-release oral tablet (single dose) and intravenous (single and multiple dose) forms of ciprofloxacin indicate that plasma concentrations of ciprofloxacin are higher in elderly subjects (>65 years) as compared to young adults. C_{max} is increased 16% to 40%, and mean AUC is increased approximately 30%, which can be at least partially attributed to decreased renal clearance in the elderly. Elimination half-life is only slightly (~20%) prolonged in the elderly (see **HUMAN PHARMACOLOGY**).

Since ciprofloxacin is substantially excreted by the kidney, the risk of adverse reactions may be greater in patients with impaired renal function. No significant accumulation of ciprofloxacin is anticipated in elderly subjects with renal impairment who take CIPRO[®] XL[™] 500 mg, therefore, no reductions in dosage are required.

However, in patients with renal impairment where CIPRO[®] XL[™] 1000 mg once daily is the appropriate dose, dosage may need to be reduced to CIPRO[®] XL[™] 500 mg once daily (see **DOSAGE AND ADMINISTRATION, Impaired Renal Function**).

INDICATIONS AND CLINICAL USES

CIPRO[®] XL[™] (ciprofloxacin) extended release is indicated solely for the treatment of urinary tract infections, caused by susceptible strains of the designated microorganisms as listed below. CIPRO[®] XL[™] AND CIPRO[®] (CIPROFLOXACIN) TABLETS (IMMEDIATE RELEASE FORMULATION) ARE NOT INTERCHANGEABLE (see **DOSAGE AND ADMINISTRATION** for specific recommendations).

Uncomplicated Urinary Tract Infections (Acute Cystitis) in Females caused by:*Escherichia coli**Enterococcus faecalis**Proteus mirabilis**Staphylococcus saprophyticus***Complicated Urinary Tract Infections caused by:***Escherichia coli**Klebsiella pneumoniae**Enterococcus faecalis**Proteus mirabilis**Pseudomonas aeruginosa***Acute Uncomplicated Pyelonephritis caused by:***Escherichia coli*

THE SAFETY AND EFFICACY OF CIPRO[®] XL[™] IN TREATING INFECTIONS OTHER THAN URINARY TRACT INFECTIONS HAS NOT BEEN DEMONSTRATED.

Appropriate culture and susceptibility tests should be performed before treatment in order to isolate and identify organisms causing infection and to determine their susceptibility to ciprofloxacin. Therapy with CIPRO[®] XL[™] may be initiated before results of these tests are known; once results become available, appropriate therapy should be continued.

CONTRAINDICATIONS

CIPRO[®] XL[™] (ciprofloxacin) extended release tablets are contraindicated in persons with a history of hypersensitivity to ciprofloxacin, or any member of the quinolone class of 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

Cardiac Disorders

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

Children

The safety of CIPRO[®] XL[™] (ciprofloxacin) extended release tablets in pediatric patients and adolescents (under the age of 18 years), pregnant women and nursing women has not yet been established (see **PRECAUTIONS: Pediatric Use, Pregnancy, 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) events including tremors, restlessness, lightheadedness, confusion and hallucinations, depression, nervousness, agitation, insomnia, anxiety, paranoia, nightmares and,

rarely, suicidal thoughts or acts. In rare cases, depression or psychosis can progress to self-endangering behaviour. These reactions may occur following the first dose. If these reactions occur in patients receiving ciprofloxacin, the drug should be discontinued and appropriate measures instituted. As with all quinolones, ciprofloxacin should be used with caution in patients with known or suspected CNS disorders, such as severe cerebral arteriosclerosis, epilepsy, and other factors that predispose to seizures or lower the seizure threshold (see [ADVERSE REACTIONS](#)).

Cytochrome P450

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

Gastrointestinal

Clostridium Difficile-Associated Disease

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

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

If the diagnosis of CDAD is suspected or confirmed, appropriate therapeutic measures should be initiated. Mild cases of CDAD usually respond to discontinuation of antibacterial agents not directed against *Clostridium difficile*. In moderate to severe cases, consideration should be given

to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial agent clinically effective against *Clostridium difficile*. Drugs that inhibit peristalsis may delay clearance of *Clostridium difficile* and its toxins, and therefore should not be used in the treatment of CDAD. Surgical evaluation should be instituted as clinically indicated since surgical intervention may be required in certain severe cases. (See **ADVERSE REACTIONS**.)

Hypersensitivity

Serious hypersensitivity and/or anaphylactic reactions have been reported in patients receiving quinolone therapy, including ciprofloxacin. These reactions may occur following the first dose. Some reactions have been accompanied by cardiovascular collapse, hypotension/shock, seizure, loss of consciousness, tingling, angioedema (including tongue, laryngeal, throat or facial edema/swelling), airway obstruction (including bronchospasm, shortness of breath and acute respiratory distress), dyspnea, urticaria, itching, and other serious skin reactions.

Ciprofloxacin should be discontinued at the first appearance of a skin rash or any other sign of hypersensitivity. Serious acute hypersensitivity reactions may require treatment with epinephrine and other resuscitative measures, including oxygen, intravenous fluids, antihistamines, corticosteroids, pressor amines, and airway management, as clinically indicated.

Serious and sometimes fatal events, some due to hypersensitivity and some due to uncertain etiology, have been reported in patients receiving therapy with all antibiotics. These events may be severe and generally occur following the administration of multiple doses. Clinical manifestations may include one or more of the following: fever, rash or severe dermatologic reactions (eg, toxic epidermal necrolysis, Stevens-Johnson Syndrome), vasculitis, arthralgia, myalgia, serum sickness, allergic pneumonitis, interstitial nephritis, acute renal insufficiency or failure, hepatitis, jaundice, acute hepatic necrosis or failure, hepatic necrosis with fatal outcome, anemia including hemolytic and aplastic, thrombocytopenia including thrombotic thrombocytopenic purpura, leukopenia, agranulocytosis, pancytopenia, and/or other hematologic abnormalities (see **CONTRAINDICATIONS** and **PRECAUTIONS, Drug Interactions**).

Interaction With Tests

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

Musculoskeletal

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

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

PRECAUTIONS

SERIOUS AND FATAL REACTIONS HAVE BEEN REPORTED IN PATIENTS RECEIVING CONCURRENT ADMINISTRATION OF CIPROFLOXACIN AND THEOPHYLLINE. These reactions have included cardiac arrest, seizure, status epilepticus, and respiratory failure. Although similar serious adverse effects have been reported in patients receiving theophylline alone, the possibility that these reactions may be potentiated by ciprofloxacin cannot be eliminated. If concomitant use cannot be avoided, serum levels of theophylline should be monitored and dosage adjustments made as appropriate.

Crystalluria related to ciprofloxacin has been reported only rarely in man because human urine is usually acidic. Crystals have been observed in the urine of laboratory animals, usually from alkaline urine. Patients receiving ciprofloxacin should be well hydrated and alkalinity of the urine should be avoided. The recommended daily dose should not be exceeded.

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

Prolonged use of ciprofloxacin may result in the overgrowth of nonsusceptible organisms. Careful observation of the patient is therefore essential, and if superinfection should occur during therapy, appropriate measures should be taken.

Pregnancy

Adequate and well-controlled studies have not been performed in pregnant women. Ciprofloxacin should not be used in pregnant women unless the potential benefits outweigh the potential risk to the fetus (see **WARNINGS**).

Nursing Women

Ciprofloxacin is excreted in human milk. Because of the potential for serious adverse reactions in infants nursing from mothers taking ciprofloxacin, a decision should be made whether to discontinue the drug, taking into account the importance of the drug to the mother and 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**).

Renal Impairment

In patients with reduced renal function, the half-life of ciprofloxacin is slightly prolonged. Since the total drug exposure attained with CIPRO[®] XL[™] (ciprofloxacin) extended release 500 mg tablets does not exceed that achieved with CIPRO[®] (ciprofloxacin) 500 mg tablets (immediate release formulation), which is approved as a total daily dose for use in renally impaired patients, no dosage adjustment for renal disease is required with CIPRO[®] XL[™] 500 mg (see **HUMAN PHARMACOLOGY**).

For complicated urinary tract infections or acute uncomplicated pyelonephritis, where 1000 mg is the appropriate dose, the dosage of CIPRO[®] XL[™] should be reduced to 500 mg CIPRO[®] XL[™] once daily in patients with creatinine clearance below 30 mL/min (see **DOSAGE AND ADMINISTRATION**).

Hepatic Impairment

In preliminary studies in patients with stable chronic liver cirrhosis (with mild to moderate hepatic impairment), no significant changes in CIPRO[®] 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 elucidated. An increased incidence of nausea, vomiting, headache and diarrhea were observed with the use of CIPRO[®] in this patient population. No dosage adjustment is required with CIPRO[®] XL[™] in patients with stable chronic cirrhosis (with mild to moderate hepatic impairment) (see **HUMAN PHARMACOLOGY**).

Ability to Drive and Operate Machinery

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

Elderly

No dosage adjustment based on age alone is necessary for elderly patients. Since ciprofloxacin is substantially excreted by the kidney, the risk of adverse reactions may be greater in patients with impaired renal function. No significant accumulation of ciprofloxacin is anticipated in elderly subjects with renal impairment who take CIPRO[®] XL[™] 500 mg, therefore, no reductions in dosage are required.

However, in patients with renal impairment, where CIPRO[®] XL[™] 1000 mg once daily is the appropriate dose, dosage may need to be reduced to CIPRO[®] XL[™] 500 mg once daily (see **DOSAGE AND ADMINISTRATION, Impaired Renal Function**).

Drug Interactions

Caffeine and Other Xanthine Derivatives

Ciprofloxacin has also been shown to interfere with the metabolism of caffeine. This may lead to reduced clearance of caffeine and a prolongation of its serum half-life.

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

Class IA or III Antiarrhythmics

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

Clozapine

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

Cyclosporine

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

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 CIPRO[®] XL[™] 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 CIPRO[®] XL[™] be administered at least 2 hours before or 2 hours after substantial calcium intake (>800 mg) (see **DOSAGE AND ADMINISTRATION**).

Glyburide

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

Histamine H₂-receptor Antagonists

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

Lidocaine

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

Methotrexate

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

Metoclopramide

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

Multivalent Cations

Concurrent administration of a quinolone, including ciprofloxacin, with multivalent cation-containing products such as magnesium/aluminum antacids, polymeric phosphate binders such as sevelamer, lanthanum carbonate, sucralfate, Videx[®] (didanosine) chewable/buffered tablets or pediatric powder, mineral supplements or products containing calcium, iron, or zinc may substantially interfere with the absorption of the quinolone, resulting in serum and urine levels considerably lower than desired. CIPRO[®] XL[™] should be administered at least 2 hours before or 6 hours after these preparations. When CIPRO[®] XL[™], given as a single 1000 mg dose, was administered 2 hours before or 4 hours after a magnesium/aluminum-containing antacid (900 mg aluminum hydroxide and 600 mg magnesium hydroxide as a single oral dose) to 18 healthy volunteers, there was a 4% and 19% reduction, respectively, in the mean C_{max} of ciprofloxacin. The reduction in the mean AUC was 24% and 26%, respectively (see **DOSAGE AND ADMINISTRATION**).

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.

Omeprazole

Absorption of the CIPRO[®] XL[™] tablet was slightly diminished (20%) when given concomitantly with omeprazole.

Probenecid

Probenecid interferes with renal tubular secretion of ciprofloxacin and produces an increase in the level of ciprofloxacin in the serum. This should be considered if patients are receiving both drugs concomitantly.

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.

Sildenafil

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

Theophylline

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

Tizanidine

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

Vitamin K Antagonists

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

ADVERSE REACTIONS

CIPRO[®] XL[™] 500 mg

In a phase III clinical trial involving 444 patients, the incidence of adverse drug reactions in patients treated with CIPRO[®] XL[™] (ciprofloxacin) extended release 500 mg tablets was 10%. Most adverse events reported in the trial were described as mild to moderate in severity and required no treatment. CIPRO[®] XL[™] 500 mg was discontinued due to adverse reactions thought to be drug-related in 0.2% of patients.

Adverse reactions, judged by investigators to be at least possibly drug-related, occurring in greater than or equal to 1% of CIPRO[®] XL[™] 500 mg treated patients were nausea (3%) and headache (2%).

Additional uncommon adverse reactions, judged by investigators to be at least possibly drug-related, that occurred in less than 1% of CIPRO[®] XL[™] 500 mg treated patients were:

Body as a Whole: abdominal pain, photosensitivity reaction

Cardiovascular: migraine

Digestive: anorexia, constipation, diarrhea, dyspepsia, flatulence, thirst, vomiting

Skin/Appendages: maculopapular rash, pruritus, rash, skin disorder, vesiculobullous rash

Special Senses: taste perversion

Urogenital: dysmenorrhea, vaginal candidiasis, vaginitis

CIPRO[®] XL[™] 1000 mg

In a phase III clinical trial involving 517 patients, the incidence of adverse drug reactions in patients treated with CIPRO[®] XL[™] (ciprofloxacin) extended release 1000 mg tablets was 13.2%. Most adverse events reported in the trial were described as mild to moderate in severity and required no treatment. CIPRO[®] XL[™] 1000 mg was discontinued due to adverse reactions thought to be drug-related in 3.1% of patients.

Adverse reactions, judged by investigators to be at least possibly drug-related, occurring in greater than or equal to 1% of CIPRO[®] XL[™] 1000 mg treated patients, were nausea (3%), diarrhea (2%), headache (1%), dizziness (1%), dyspepsia (1%), and vaginal moniliasis (1%).

Additional uncommon adverse reactions, judged by investigators to be at least possibly drug-related, that occurred in less than 1% of CIPRO[®] XL[™] 1000 mg treated patients were:

Body as a Whole: abdominal pain, asthenia, malaise, moniliasis, photosensitivity reaction

Cardiovascular: bradycardia, migraine, syncope

Digestive: anorexia, constipation, dry mouth, flatulence, liver function tests abnormal, thirst, vomiting

Hemic/Lymphatic: prothrombin/INR decreased

Nervous: abnormal dreams, depersonalization, depression, hypertonia, incoordination, insomnia, somnolence, tremor, vertigo

Metabolic: hyperglycemia

Skin/Appendages: dry skin, maculopapular rash, pruritus, rash, skin disorder, urticaria, vesiculobullous rash

Special Senses: diplopia, taste perversion

Urogenital: dysmenorrhea, hematuria, kidney function abnormal, vaginitis

Ciprofloxacin - Other Formulations

The following adverse drug reactions have been reported during clinical trials and subsequent postmarketing surveillance with other formulations of ciprofloxacin.

In patients treated orally with CIPRO[®] (tablet and suspension), the most frequently reported events, possibly, probably drug-related were: nausea (1.3%), and diarrhea (1.0%).

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

Events possibly or probably drug-related occurring at a frequency of less than 1% with CIPRO[®] (ciprofloxacin) tablets (immediate release formulation) oral and CIPRO[®] I.V. treatment during clinical trials and subsequent postmarketing surveillance are as follows:

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

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

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 (> 0.01% - < 0.1%): moniliasis (oral), cholestatic jaundice, 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, leukopenia (granulocytopenia), leukocytopenia, leukocytosis, pancytopenia. The following have been reported very rarely: altered prothrombin levels/INR, hemolytic anaemia, marrow depression (life threatening), pancytopenia (life threatening), thrombocytemia (thrombocytosis).

Hypersensitivity: rash. The following have been reported rarely: allergic reaction, anaphylactic/anaphylactoid reactions including facial, vascular and laryngeal edema, drug fever, vasculitis (petechia, haemorrhagic bullae, papules, crust formation), hepatitis, interstitial nephritis, petechia (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 failure), epidermal necrolysis (Lyell Syndrome, potentially life-threatening).

IV Infusion Site: thrombophlebitis, injection site reaction. The following have been reported very rarely: burning, erythema, pain, paresthesia, and swelling.

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

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

Nervous: agitation, confusion, convulsion, dizziness, hallucinations, headache, hypesthesia, increased sweating, insomnia, somnolence, tremor (trembling). The following have been reported rarely: paresthesia (peripheral paralgesia).

The following have been reported very rarely: abnormal dreams (nightmares), anxiety, apathy, ataxia, depersonalization, depression, diplopia, hemiplegia, hyperesthesia, hypertonia, increase of intracranial pressure, meningism, migraine, nervousness, neuritis, polyneuritis, sleep disorder, twitching, grand mal convulsion, abnormal (unsteady) gait, psychosis, intracranial hypertension. In some instances, these reactions occurred after the first administration of ciprofloxacin. In these instances, ciprofloxacin is 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: dyspnea. The following have been reported very rarely: hiccup, hyperventilation, increased cough, larynx edema, lung edema, lung hemorrhage, pharyngitis, stridor, voice alteration.

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

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

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

The following additional adverse events, in alphabetical order, regardless of incidence or relationship to drug, have been reported during clinical trials and from worldwide postmarketing experience in patients given ciprofloxacin (includes all formulations, all dosages, all drug-therapy durations, and in all indications): arrhythmia, atrial flutter, bleeding diathesis, bronchospasm, *C. difficile* associated diarrhea, candiduria, cardiac murmur, cardiopulmonary

arrest, cardiovascular collapse, cerebral thrombosis, chills, delirium, drowsiness, dysphasia, edema (conjunctivae, hands, lips, lower extremities, neck), epistaxis, exfoliative dermatitis, fever, gastrointestinal bleeding, gout (flare up), gynecomastia, hearing loss, hemoptysis, hemorrhagic cystitis, hyperpigmentation, joint stiffness, lightheadedness, lymphadenopathy, manic reaction, myoclonus, nystagmus, pain (arm, breast, epigastric, foot, jaw, neck, oral mucosa), paranoia, peripheral neuropathy, phobia, pleural effusion, polyneuropathy, polyuria, postural hypotension, pulmonary embolism, purpura, QT prolongation, renal calculi, respiratory arrest, respiratory distress, restlessness, rhabdomyolysis, torsades de pointes, toxic psychosis, unresponsiveness, urethral bleeding, urination (frequent), ventricular ectopy, ventricular fibrillation, ventricular tachycardia, vesicles, visual acuity (decreased) and visual disturbances (flashing lights, change in color 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

CIPRO[®] XL[™] AND CIPRO[®] (CIPROFLOXACIN) TABLETS (IMMEDIATE RELEASE FORMULATION) ARE NOT INTERCHANGEABLE. CIPRO[®] XL[™] should be administered once daily as described in the table below.

Table 4: Recommended Dosage

Indication	Unit Dose CIPRO [®] XL [™]	Frequency	Recommended Duration
Uncomplicated Urinary Tract Infection (Acute Cystitis) in Females	500 mg	q 24 h	3 Days
Complicated Urinary Tract Infection	1000 mg*	q 24 h	7-14 Days
Acute Uncomplicated Pyelonephritis	1000 mg*	q 24 h	7-14 Days

* For severely renally impaired patients see [Impaired Renal Function](#) below.

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

Although CIPRO[®] XL[™] 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 CIPRO[®] XL[™] be administered at least 2 hours before or 2 hours after substantial calcium intake (>800 mg). CIPRO[®] XL[™] should be swallowed whole. Tablets should not be split, crushed or chewed (see [PRECAUTIONS, Drug Interactions](#)).

Impaired Renal Function

CIPRO[®] XL[™] 500 mg

Based on pharmacokinetic data, no dosage adjustment is required with CIPRO[®] XL[™] 500 mg (see [HUMAN PHARMACOLOGY, Special Populations](#)).

CIPRO[®] XL[™] 1000 mg

For complicated urinary tract infections or acute uncomplicated pyelonephritis, where 1000 mg is the appropriate dose, the dosage of CIPRO[®] XL[™] should be reduced to 500 mg

CIPRO[®] XL[™] once daily in patients with creatinine clearance below 30 mL/min. This recommendation is based on pharmacokinetic modeling. Clinical studies with CIPRO[®] XL[™] have not been performed in patients with impaired renal function. For patients on hemodialysis or peritoneal dialysis, administer CIPRO[®] XL[™] after the dialysis procedure is completed (see [HUMAN PHARMACOLOGY, Special Populations](#)).

Impaired Hepatic Function

Based on pharmacokinetic data, no dosage adjustment is required with CIPRO[®] XL[™] in patients with stable chronic cirrhosis (with mild to moderate hepatic impairment). The kinetics of ciprofloxacin in patients with acute hepatic insufficiency and stable chronic cirrhosis (with severe hepatic impairment), however, have not been elucidated (see [HUMAN PHARMACOLOGY, Special Populations](#)).

Elderly

No dosage adjustment based on age alone is necessary in elderly patients. Since ciprofloxacin is substantially excreted by the kidney, the risk of adverse reactions may be greater in patients with impaired renal function. No significant accumulation of ciprofloxacin is anticipated in elderly subjects with renal impairment who take CIPRO[®] XL[™] 500 mg, therefore, no reductions in dosage are required.

However, in patients with renal impairment, where CIPRO[®] XL[™] 1000 mg once daily is the appropriate dose, dosage may need to be reduced to CIPRO[®] XL[™] 500 mg once daily (see [DOSAGE AND ADMINISTRATION, Impaired Renal Function](#)).

PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE

1) Ciprofloxacin Hydrochloride

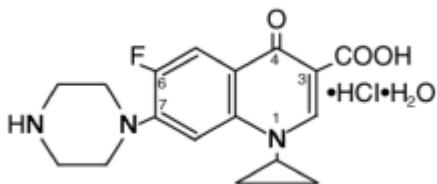
Proper Name

Ciprofloxacin hydrochloride (USP)

Chemical Name

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

Structural Formula



Molecular Formula

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

Molecular Weight

385.8

Description

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

2) Ciprofloxacin

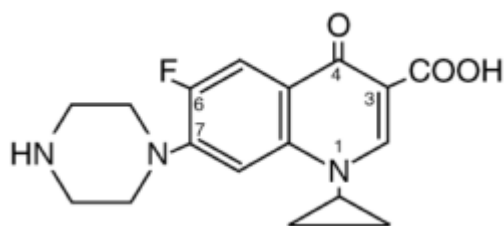
Proper Name

Ciprofloxacin (Bayer standard)

Chemical Name

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

Structural Formula



Molecular Formula

$C_{17}H_{18}FN_3O_3$

Molecular Weight

331.4

Description

Ciprofloxacin is a pale yellow to white crystalline powder which is soluble in dilute (0.1N) 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 3×10^{-4} solution of 25°C.

COMPOSITION

Each CIPRO[®] XL[™] (ciprofloxacin) extended release 500 mg tablet contains 500 mg of ciprofloxacin as ciprofloxacin hydrochloride (287.5 mg, calculated as ciprofloxacin on the dried basis) and ciprofloxacin (212.6 mg, calculated on the dried basis). Each CIPRO[®] XL[™] (ciprofloxacin) extended release 1000 mg tablet contains 1000 mg of ciprofloxacin as ciprofloxacin hydrochloride (574.9 mg, calculated as ciprofloxacin on the dried basis) and

ciprofloxacin (425.2 mg, calculated on the dried basis). The inactive ingredients are hypromellose, succinic acid, crospovidone, magnesium stearate, polyethylene glycol, titanium dioxide, and silical colloidal anhydrous.

STABILITY AND STORAGE RECOMMENDATIONS

Store at 15-30°C (56-86°F).

AVAILABILITY OF DOSAGE FORMS

CIPRO[®] XL[™] (ciprofloxacin) extended release is available as nearly white to slightly yellowish, film-coated, oblong-shaped tablets containing either 500 mg or 1000 mg of ciprofloxacin. The 500 mg tablet is coded with the word “BAYER” on one side and “C500 QD” on the reverse side. The 1000 mg tablet is coded with the word “BAYER” on one side and “C1000 QD” on the reverse side. CIPRO[®] XL[™] 500 mg tablets are supplied in bottles of 50. CIPRO[®] XL[™] 1000 mg tablets are supplied in bottles of 50.

INFORMATION FOR THE CONSUMER

This section contains important patient information about CIPRO[®] XL[™] (ciprofloxacin) extended release tablets and should be read completely before you begin treatment. This does not take the place of discussion with your doctor or health care professional about your medical condition or your treatment. This section does not list all benefits and risks of CIPRO[®] XL[™].

How to obtain your medicine: CIPRO[®] XL[™] can be prescribed only by a licensed physician. Your doctor has prescribed CIPRO[®] XL[™] tablets only for you.

Name of your medicine: The name of your medicine is CIPRO[®] XL[™]. It is manufactured by Bayer.

Purpose of your medicine: CIPRO[®] XL[™] 500 mg is intended to treat bladder infections (also known as cystitis or simple urinary tract infections) in females over 18 years of age. It should not be used to treat infections other than simple urinary tract infections.

CIPRO[®] XL[™] 1000 mg is intended to treat complicated urinary tract infections or acute uncomplicated pyelonephritis (also known as kidney infection).

CIPRO[®] XL[™] should not be used to treat other infections. Do not give it to other people even if they have a similar condition. If you have any concerns about your condition or your medicine, ask your doctor. Only your doctor can determine if CIPRO[®] XL[™] is right for you.

What is CIPRO[®] XL[™]?

CIPRO[®] XL[™] is an antibiotic in the quinolone class that contains the active ingredient ciprofloxacin. CIPRO[®] XL[™] is specifically formulated to be taken just once daily to kill bacteria causing infection in the urinary tract. CIPRO[®] XL[™] has been shown in clinical trials to be effective in the treatment of urinary tract infections. You should contact your doctor if your condition has not improved or if it has worsened while taking CIPRO[®] XL[™].

CIPRO[®] XL[™] tablets are nearly white to slightly yellowish, film-coated, oblong-shaped tablets. CIPRO[®] XL[™] tablets are available in 500 mg and 1000 mg strengths.

How and when should I take CIPRO[®] XL[™]?

- CIPRO[®] XL[™] 500 mg should be taken once a day for three (3) days at approximately the same time each day with food or on an empty stomach for the treatment of simple urinary tract infections.
- CIPRO[®] XL[™] 1000 mg should be taken once a day for 7-14 days at approximately the same time each day with food or on an empty stomach for the treatment of complicated urinary tract infections or acute uncomplicated pyelonephritis. The dosage should be reduced to CIPRO[®] XL[™] 500 mg once a day for patients with severe kidney problems.
- CIPRO[®] XL[™] should not be taken with dairy products (like milk or yogurt) or calcium-fortified juices alone; however, CIPRO[®] XL[™] may be taken with a meal that contains these products.
- You should avoid excessive caffeine consumption while taking CIPRO[®] XL[™].
- Should you forget to take it at the usual time, you may take your dose later in the day. Do not take more than one CIPRO[®] XL[™] tablet per day, even if you missed a dose.
- Swallow the CIPRO[®] XL[™] tablet whole. **DO NOT SPLIT, CRUSH, OR CHEW THE TABLET.**

You should take CIPRO[®] XL[™] for as long as your doctor prescribes it, even after you start to feel better. Stopping an antibiotic too early may result in failure to cure your infection.

Who should not take CIPRO[®] XL[™]?

You should not take CIPRO[®] XL[™] if you have ever had a severe reaction to any of the ingredients contained within this medication or to the group of antibiotics known as “quinolones.” Before taking this medication, tell your doctor if you have a history of convulsions (see [What is in your medicine?](#)).

You should not take CIPRO[®] XL[™] if you are currently taking tizanidine (Zanaflex) for the management of spasticity. Tizanidine concentrations may increase and cause further side effects such as drowsiness, sleepiness and low blood pressure.

CIPRO[®] XL[™] is not recommended for use during pregnancy or nursing, as the effects on the unborn child or nursing infant are unknown. If you are pregnant or plan to become pregnant while taking CIPRO[®] XL[™], talk to your doctor before taking this medication.

CIPRO[®] XL[™] is not recommended for persons less than 18 years of age.

What are the possible side effects of CIPRO[®] XL[™]?

CIPRO[®] XL[™] is generally well-tolerated. In CIPRO[®] XL[™] 500 mg, the most common side effects, which are usually mild, include nausea and headache. In CIPRO[®] XL[™] 1000 mg, the most common side effects, which are usually mild, include nausea and diarrhea. Antibiotics of the quinolone class may also cause vomiting, rash, and abdominal pain/discomfort. If these symptoms persist, call your health care professional.

If you develop severe diarrhea during treatment, contact your doctor.

You should be careful about driving or operating machinery until you are sure CIPRO[®] XL[™] is not causing dizziness.

Rare cases of allergic reactions have been reported in patients receiving quinolones, including ciprofloxacin, even after just one dose. If you develop hives, difficulty breathing, swelling of the tongue, throat, face, itching, serious skin reactions or other symptoms of a severe allergic reaction, seek emergency treatment right away. If you develop a skin rash, you should stop taking CIPRO[®] XL[™] and call your health care professional.

Some patients taking quinolone antibiotics may become more sensitive to sunlight or ultraviolet light such as that used in tanning salons. You should avoid excessive exposure to sunlight or ultraviolet light while you are taking CIPRO[®] XL[™].

Ciprofloxacin has been rarely associated with inflammation of tendons. If you experience pain, swelling or rupture of a tendon, you should stop taking CIPRO[®] XL[™], avoid physical exercise and call your health care professional.

Convulsions have been reported in patients receiving quinolone antibiotics including ciprofloxacin. If you have experienced convulsions in the past, be sure to let your physician know that you have a history of convulsions. Quinolones, including ciprofloxacin, have been rarely associated with other central nervous system events including confusion, tremors,

hallucinations, depression, agitation, insomnia, anxiety, nervousness and rarely, suicidal thoughts.

If you notice any side effects not mentioned in this section, or if you have any concerns about side effects you may be experiencing, please inform your health care professional.

What about other medications I am taking?

It is important to let your health care professional know of all the medicines and supplements that you are using including the following:

- Theophylline or Videx[®] (didanosine) chewable/buffered tablets or pediatric powder.
- Other medications including vitamin K antagonists like warfarin and acenocoumerol, glyburide, phenytoin, duloxetine, tizanidine, methylxanthines, caffeine, sevelamer, sucralfate, clozapine, ropinirole, lidocaine, sildenafil, pentoxifylline and certain heart medications known as antiarrhythmics which may interact with CIPRO[®] XL[™].
- Antacids, multivitamins, and other dietary supplements containing magnesium, calcium, aluminum, iron or zinc, all of which can interfere with the absorption of CIPRO[®] XL[™] and may prevent it from working. You should take CIPRO[®] XL[™] either 2 hours before or 6 hours after taking these products.

What is in your medicine?

Each CIPRO[®] XL[™] tablet contains either 500 mg or 1000 mg of ciprofloxacin as ciprofloxacin hydrochloride and ciprofloxacin. The other ingredients are hypromellose, succinic acid, crospovidone, magnesium stearate, polyethylene glycol, titanium dioxide, and silical colloidal anhydrous.

Remember:

- Take your dose of CIPRO[®] XL[™] once a day.
- Complete the course of CIPRO[®] XL[™] even if you are feeling better.
- Do not use CIPRO[®] XL[™] for another condition or give it to others.
- Keep CIPRO[®] XL[™] and all medications out of the reach of children.

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

MICROBIOLOGY

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

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 known cross-resistance between ciprofloxacin and the mentioned classes of antibiotics.

Ciprofloxacin is slightly less active when tested at acidic pH. The inoculum size has little effect when tested in vitro. The minimal bactericidal concentration (MBC) generally does not exceed the minimal inhibitory concentration (MIC) by more than a factor of 2.

The in vitro activity of ciprofloxacin against various clinical uropathogen isolates is provided in the following table.

Table 5: In Vitro Activity of Ciprofloxacin Against Clinical Isolates (as of 2003)

Organism	Number of Isolates	MIC ($\mu\text{g/mL}$)		
		50%	90%	Range
<i>Staphylococcus aureus</i>	29	0.25	16	0.12 - 16
<i>Staphylococcus saprophyticus</i>	68	0.25	0.5	0.12 - 2
<i>Streptococcus agalactiae</i>	54	1	2	0.15 - 2
<i>Enterococcus faecalis</i>	170	1	2	0.25 - 16
<i>Escherichia coli</i>	1464	0.015	0.03	0.008 - 16
<i>Klebsiella pneumoniae</i>	135	0.03	0.25	0.015 - 16
<i>Klebsiella oxytoca</i>	15	0.03	0.12	0.008 - 0.5
<i>Proteus mirabilis</i>	95	0.03	0.06	0.008 - 16
<i>Enterobacter cloacae</i>	23	0.015	0.03	0.008 - 0.06
<i>Enterobacter aerogenes</i>	34	0.03	0.06	0.015 - 0.5
<i>Citrobacter freundii</i>	16	0.03	0.5	0.008 - 16
<i>Citrobacter koseri</i>	13	0.015	0.03	0.008 - 0.5
<i>Pseudomonas aeruginosa</i>	20	0.25	16	0.03 - 16

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.

In summary, the overall susceptibility to ciprofloxacin of the gram-negative and gram-positive organisms predominantly responsible for urinary tract infections has changed little since the introduction of CIPRO[®].

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 $<10^{-9}$ to 1×10^{-6} . The prevalence of resistance may vary geographically and with time for selected species. Local information on resistance is desirable, particularly when treating severe infections.

Susceptibility Tests

Dilution Techniques: Quantitative methods are used to determine antimicrobial minimal inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method (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, *Pseudomonas aeruginosa*, and *Staphylococcus* species:

<u>MIC (µg/mL)</u>	<u>Interpretation</u>
≤ 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>MIC Range ($\mu\text{g/mL}$)</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
<i>Pseudomonas aeruginosa</i>	ATCC 27853	0.25 - 1

Diffusion Techniques: Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 5- μg ciprofloxacin to test the susceptibility of microorganisms to ciprofloxacin.

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

For testing *Enterobacteriaceae*, *Enterococcus* species, *Pseudomonas aeruginosa*, and *Staphylococcus* species:

<u>Zone Diameter (mm)</u>	<u>Interpretation</u>
≥ 21	Susceptible (S)
16 – 20	Intermediate (I)
≤ 15	Resistant (R)

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

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

<u>Microorganism</u>		<u>Zone Diameter (mm)</u>
<i>Escherichia coli</i>	ATCC 25922	30 - 40
<i>Staphylococcus aureus</i>	ATCC 25923	22 - 30
<i>Pseudomonas aeruginosa</i>	ATCC 27853	25 - 33

PHARMACOLOGY

ANIMAL PHARMACOLOGY

Effects on Histamine Release

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

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

Bronchodilatory Effects

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

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

Absorption:

CIPRO[®] XL[™] (ciprofloxacin) extended release tablets are formulated to release drug at a slower rate compared to CIPRO[®], which are immediate release tablets. Approximately 35% of the ciprofloxacin dose in CIPRO[®] XL[™] is contained within an immediate release component, while the remaining 65% is contained in a slow-release matrix.

CIPRO[®] XL[™] 500 mg

The C_{max} of once daily treatment with 500 mg CIPRO[®] XL[™] is 1.59 mg/L, which is 40% higher than the C_{max} of CIPRO[®] (ciprofloxacin) 250 mg tablets (immediate release formulation) (1.14 mg/L). The mean area under the plasma-concentration time curve (AUC) over 24 hours at steady state following CIPRO[®] XL[™] 500 mg once daily is 7.97 mg*h/L, which is equivalent to

the AUC of CIPRO[®] 250 mg tablets bid (8.25 mg*h/L). Maximum plasma concentrations are attained between 1 and 2.5 hours after dosing of CIPRO[®] XL[™] 500 mg (median t_{\max} = 1.5 h).

The following table (**Table 6**) compares the pharmacokinetic parameters obtained at steady state for CIPRO[®] XL[™] 500 mg tablets and CIPRO[®] 250 mg tablets bid.

Table 6: Ciprofloxacin Pharmacokinetics (Mean ± SD) Following CIPRO[®] (Ciprofloxacin) 250 mg Tablets (Immediate Release Formulation) BID and CIPRO[®] XL[™] (Ciprofloxacin) Extended Release 500 mg Tablets Administration

	C_{\max} (mg/L)	AUC _{0-24h} (mg* h/L)	$t_{1/2}$ (h)	t_{\max} (h) ^a
CIPRO [®] XL [™] (ciprofloxacin) extended release 500 mg tablets	1.59 ± 0.43	7.97 ± 1.87	6.6 ± 1.4	1.5 (1.0-2.5)
CIPRO [®] (ciprofloxacin) 250 mg tablets (immediate release formulation) bid	1.14 ± 0.23	8.25 ± 2.15	4.8 ± 0.6	1.0 (0.5-2.5)

a Median (range)

CIPRO[®] XL[™] 1000 mg

The C_{\max} of once daily treatment with 1000 mg CIPRO[®] XL[™] is 3.11 mg/L, which is 51% higher than the C_{\max} of CIPRO[®] (ciprofloxacin) 500 mg tablets (immediate release formulation) (2.06 mg/L). The mean area under the plasma-concentration time curve (AUC) over 24 hours at steady state following CIPRO[®] XL[™] 1000 mg once daily is 16.83 mg*h/L, which is equivalent to the AUC of CIPRO[®] 500 mg tablets bid (17.04 mg*h/L). Maximum plasma concentrations are attained between 1 and 4 hours after dosing (median t_{\max} = 2.0 h). The following table (**Table 7**) compares the pharmacokinetic parameters obtained at steady state for CIPRO[®] XL[™] 1000 mg and CIPRO[®] 500 mg bid.

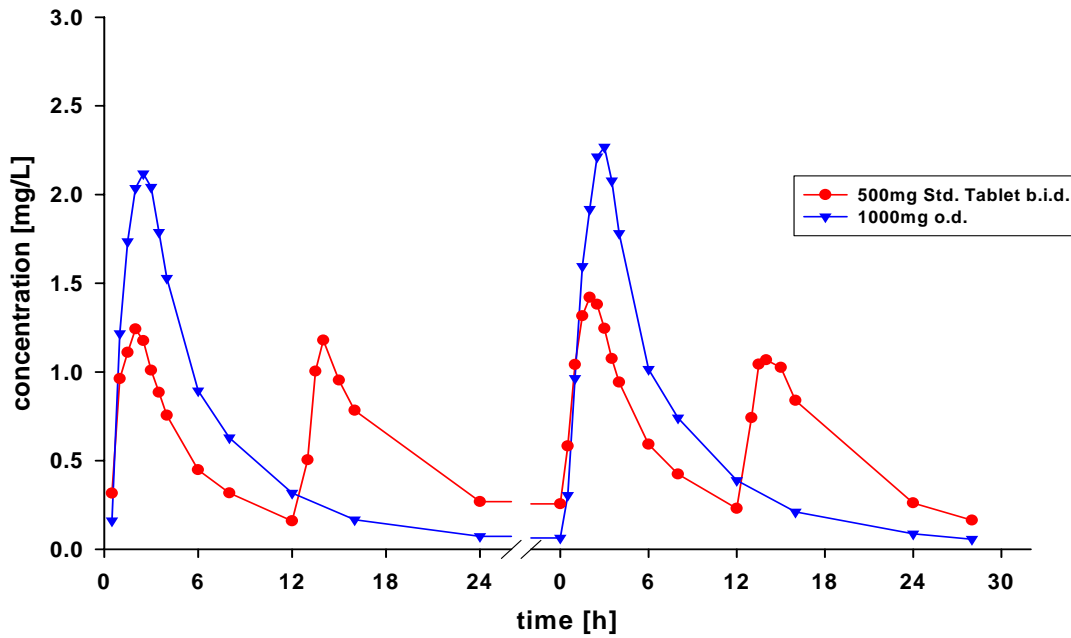
Table 7: Ciprofloxacin Pharmacokinetics (Mean ± SD) Following CIPRO[®] (Ciprofloxacin) 500 mg Tablets (Immediate Release Formulation) BID and CIPRO[®] XL[™] (Ciprofloxacin) Extended Release 1000 mg Tablets Administration

	C_{\max} (mg/L)	AUC _{0-24h} (mg* h/L)	$t_{1/2}$ (h)	t_{\max} (h) ^a
CIPRO [®] XL [™] (ciprofloxacin) extended release 1000 mg tablets	3.11 ± 1.08	16.83 ± 5.65	6.31 ± 0.72	2.0 (1 - 4)
CIPRO [®] (ciprofloxacin) 500 mg (immediate release formulation) bid	2.06 ± 0.41	17.04 ± 4.79	5.66 ± 0.89	2.0 (0.5 - 3.5)

a Median (range)

The relative bioavailability of CIPRO[®] XL[™] 1000 mg compared to CIPRO[®] 500 mg bid was examined in a crossover study of 20 healthy male volunteers under fasted conditions. Mean concentrations for Day 1 are shown in **Figure 2**.

Figure 2: Relative Bioavailability of CIPRO[®] XL[™] 1000 mg versus CIPRO[®] 500 mg BID



The pharmacokinetics of the CIPRO[®] XL[™] tablets are not altered by co-administration with food. AUC values were comparable following administration of CIPRO[®] XL[™] with a high-fat meal, a low-fat meal, or under fasted conditions (see **Table 8**).

Table 8: Pharmacokinetics of CIPRO[®] XL[™] (Ciprofloxacin) Extended Release 500 mg Tablets Under Fed and Fasted Conditions

Parameter	Fed	Fasted	Ratio (Fed/Fasted)	90% CI
AUC (mg* ^a h/L) ^a	7.12 (21%)	7.05 (36%)	1.01	0.89 - 1.15
C _{max} (mg/L) ^a	1.30 (26%)	1.34 (42%)	0.97	0.79 - 1.18
t _{max} (h) ^b	3.5 (1.5 - 4.0)	1.5 (0.5 - 3.5)	Not evaluated	

a Geometric mean (% CV)

b Median (range)

Distribution

In one study, the apparent volume of distribution ($V_{d_{area}}$) of CIPRO[®] was estimated from kinetic data recorded after oral doses and found to be approximately 3.5 L/kg. Studies with the oral and intravenous forms of CIPRO[®] have demonstrated penetration of ciprofloxacin into a variety of tissues. A single dose study in healthy subjects has demonstrated penetration of ciprofloxacin into prostate tissue following administration of CIPRO[®] XL[™] 1000 mg. One and three hours after dosing, mean ciprofloxacin concentrations in the prostate were $4.75 \pm 1.3 \mu\text{g/g}$ and $4.29 \pm 1.61 \mu\text{g/g}$, respectively. The binding of ciprofloxacin to serum proteins is 20% to 40%, which is not likely to be high enough to cause significant protein binding interactions with other drugs. Following administration of a single dose of CIPRO[®] XL[™] (500 mg or 1000 mg), ciprofloxacin concentrations in urine, collected up to 4 hours after dosing, averaged over 300 mg/L and over 500 mg/L, respectively; in urine excreted from 12 to 24 hours after dosing, ciprofloxacin concentration averaged 27 mg/L for CIPRO[®] XL[™] 500 mg and 58 mg/L for CIPRO[®] XL[™] 1000 mg.

The following table (**Table 9**) compares the mean concentrations in urine at steady state during different collection intervals for CIPRO[®] XL[™] and CIPRO[®] bid.

Table 9: Concentration of Ciprofloxacin in Urine at Steady State

Collection Interval	Mean Concentration (Range) (mg/L)	
	CIPRO [®] XL [™] 500 mg	CIPRO [®] bid 250 mg
0 - 4 h	368 (73 - 968)	196 (49 - 371)
4 - 8 h	166 (30 - 298)	82 (19 - 231)
8 - 12 h	53 (15 - 143)	31 (6 - 77)
12 - 24 h	30 (8 - 71)	128 (43 - 231)
Collection Interval	CIPRO [®] XL [™] 1000 mg	CIPRO [®] bid 500 mg
0 - 4 h	589 (108 - 3030)	272 (98 - 762)
4 - 8 h	359 (26 - 1991)	136 (34 - 288)
8 - 12 h	160 (36 - 843)	59 (20 - 151)
12 - 24 h	65 (5 - 204)	231 (80 - 864)

Metabolism

Four metabolites of ciprofloxacin were identified in human urine. The primary metabolites are oxociprofloxacin (M3) and sulfociprofloxacin (M2), each accounting for roughly 3% to 8% of the total dose. Other minor metabolites are desethylene ciprofloxacin (M1), and formylciprofloxacin (M4). The relative proportion of drug and metabolite in serum corresponds to the composition found in urine. Excretion of these metabolites was essentially complete by 24 hours after dosing.

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

Elimination

The elimination kinetics of ciprofloxacin are similar for CIPRO[®] XL[™] and CIPRO[®] (immediate release formulation). The mean serum elimination half-life ($t_{1/2}$) of CIPRO[®] XL[™] (ciprofloxacin) extended release is 6.6 (± 1.4) hours, and 6.3 (± 0.7) hours for the 500 mg and 1000 mg tablets, respectively. The major route of elimination of ciprofloxacin in humans is as unchanged drug in urine.

In studies comparing the CIPRO[®] XL[™] and CIPRO[®] bid regimens (CIPRO[®] XL[™] 500 mg vs CIPRO[®] 250 mg bid and CIPRO[®] XL[™] 1000 mg vs CIPRO[®] 500 mg bid), approximately 35% of an orally administered dose was excreted in the urine as unchanged drug for both formulations. The urinary excretion of ciprofloxacin is virtually complete within 24 hours after dosing. The renal clearance of ciprofloxacin, which is approximately 300 mL/minute, exceeds the normal glomerular filtration rate of 120 mL/minute. Thus, active tubular secretion would seem to play a significant role in its elimination. Co-administration of probenecid with immediate release ciprofloxacin results in about a 50% reduction in the ciprofloxacin renal clearance and a 50% increase its concentration in the systemic circulation.

Although bile concentrations of ciprofloxacin are several fold higher than serum concentrations after oral dosing with the immediate release tablet, only a small amount of the dose administered is recovered from the bile as unchanged drug. An additional 1% to 2% of the dose is recovered from the bile in the form of metabolites. Approximately 20% to 35% of an oral dose of immediate release ciprofloxacin is recovered from the feces within 5 days after dosing. This may arise from either biliary clearance or transintestinal elimination.

Special Populations

Renal Impairment

Ciprofloxacin is eliminated primarily by renal excretion; however, the drug is also metabolized and partially cleared through the biliary system of the liver and through the intestine. These alternate pathways of drug elimination appear to compensate for the reduced renal excretion in patients with renal impairment. In patients with reduced renal function, the half-life of ciprofloxacin is slightly prolonged. Since the total drug exposure attained with CIPRO[®] XL[™] 500 mg does not exceed that achieved with CIPRO[®] 500 mg (immediate release formulation) which is approved as a total daily dose for use in renally impaired patients, no dosage adjustment for renal disease is required for CIPRO[®] XL[™] 500 mg.

For complicated urinary tract infections or acute uncomplicated pyelonephritis, where 1000 mg is the appropriate dose, the dosage of CIPRO[®] XL[™] should be reduced to 500 mg CIPRO[®] XL[™] once daily in patients with creatinine clearance below 30 mL/min.

Since ciprofloxacin is eliminated primarily by the kidney, a change in pharmacokinetics is to be expected depending on the degree of impairment of renal function.

The pharmacokinetics of ciprofloxacin following a single oral dose of 250 mg in 6 patients (5 male, 1 female, age: 51 ± 9 years) with normal renal function (see Group I, **Table 10**) were compared to 6 patients (3 male, 3 female, age: 63 ± 6 years) with renal impairment (see Group II, **Table 10**) and to 5 patients (2 male, 3 female, age: 63 ± 6 years) with end-stage renal failure, treated by haemodialysis (see Group III, **Table 10**). Patients with renal insufficiency had significantly increased AUCs, prolonged (about 2-fold) elimination half-lives, and decreased renal clearances.

Haemodialysis resulted in a minimal decrease in plasma levels. From the dialysate concentrations, it can be estimated that no more than 2% of the dose was removed by dialysis over 4 hours, which was less than the amount lost in the urine over 24 hours in patients of Group II (see [Table 10](#)).

Table 10: Mean Pharmacokinetic Parameters for CIPRO[®] Following a Single 250 mg Oral Dose in Healthy Volunteers and in Patients With Renal Insufficiency

Group	Creatinine Clearance (mL/min/1.73 m ²)	Parameter					
		C _{max} (mg/L)	t _{max} (h)	Half-life (h)	Total AUC (mg*h/mL)	Renal Clearance (mL/min)	% Dose Urinary Recovery 0-24 h
I	> 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	< 20	1.70 (± 0.41)	1.7 (± 0.5)	8.7 (±0.9)	14.36 (± 3.5)	18.3 (± 3.5)	5.3 (± 1.7)
III	End-Stage Renal Failure Treated by Hemodialysis	2.07 (± 0.23)	1.6 (± 0.2)	5.8 (± 0.9)	15.87 (± 2.0)		

Hepatic Impairment

In preliminary studies in patients with stable chronic liver cirrhosis (with mild to moderate hepatic impairment), no significant changes in ciprofloxacin pharmacokinetics have been observed. No dosage adjustment is required with CIPRO[®] XL[™] in patients with stable chronic cirrhosis (with mild to moderate hepatic impairment). The kinetics of ciprofloxacin in patients with acute hepatic insufficiency and stable chronic cirrhosis (with severe hepatic impairment), however, have not been elucidated.

In a study of 7 cirrhotic patients and healthy volunteers given CIPRO[®] 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[®] 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.

Elderly

No dosage adjustment based on age alone is necessary for elderly patients. Pharmacokinetic studies of immediate release oral tablet (single dose) and intravenous (single and multiple dose) forms of ciprofloxacin indicate that plasma concentrations of ciprofloxacin are higher in elderly subjects (> 65 years) as compared to young adults. C_{max} is increased 16% to 40% and mean AUC is increased approximately 30%, which can be at least partially attributed to decreased renal clearance in the elderly. Elimination half-life is only slightly (~20%) prolonged in the elderly.

Since, ciprofloxacin is substantially excreted by the kidney and the risk of adverse reactions may be greater in patients with impaired renal function. No significant accumulation of ciprofloxacin is anticipated in elderly subjects with renal impairment who take CIPRO[®] XL[™] 500 mg, therefore, no reductions in dosage are required.

However, in patients with renal impairment, where CIPRO[®] XL[™] 1000 mg once daily is the appropriate dose, dosage may need to be reduced to CIPRO[®] XL[™] 500 mg once daily (see **DOSAGE AND ADMINISTRATION, Impaired Renal Function**).

In 4 females and 6 males, (age: 67 ± 4 years, weight: 65 ± 6 kg) with normal renal function for their age, given a single oral dose of CIPRO[®] 250 mg, maximum ciprofloxacin serum

concentrations and areas under the serum concentration time curves were significantly higher than in 10 male younger volunteers (age: 24 ± 3 years, weight: 72 ± 9 kg). The time to peak serum concentrations, overall elimination half-life and urinary recovery of ciprofloxacin were similar in both age groups (see [Table 11](#)).

Table 11: Comparison of Pharmacokinetic Parameters Between Healthy Elderly and Healthy Younger Volunteers With CIPRO[®] 250 mg

Parameter	Elderly Volunteers (Mean \pm SD)	Younger Volunteers (Mean \pm SD)
C_{\max} (mg/L)	1.8 ± 0.5	1.3 ± 0.4
t_{\max} (h)	1.2 ± 0.3	1.2 ± 0.1
$t_{1/2}$ (h)	3.7 ± 0.9	3.3 ± 0.6
Total AUC (mg•h/L)	7.25 ± 2.45	5.29 ± 1.21
% Dose Urinary Recovery after 24 hours	43	43

Serum Protein Binding

Serum protein binding of ciprofloxacin is between 20% to 40%.

Tissue Concentrations

In one study, the apparent volume of distribution ($V_{d\text{area}}$) 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.

Drug Interactions

Theophylline

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

Caffeine and Other Xanthine Derivatives

Ciprofloxacin has also been shown to interfere with the metabolism of caffeine. This may lead to reduced clearance of caffeine and a prolongation of its serum half-life.

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

Class IA or III antiarrhythmics

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

Multivalent Cations

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

When CIPRO[®] XL[™], given as a single 1000 mg dose, was administered two hours before or four hours after a magnesium/aluminum-containing antacid (900 mg aluminum hydroxide and 600 mg magnesium hydroxide as a single oral dose) to 18 healthy volunteers, there was a 4% and 19% reduction, respectively, in the mean C_{max} of ciprofloxacin. The reduction in the mean AUC was 24% and 26%, respectively. CIPRO[®] XL[™] should be administered at least 2 hours before or 6 hours after antacids containing magnesium or aluminum, as well as sucralfate, Videx[®] (didanosine) chewable/buffered tablets or pediatric powder, metal cations such as iron, and multivitamin preparations with zinc. Although CIPRO[®] XL[™] may be taken with meals that include milk, concomitant administration with dairy products or with calcium-fortified juices alone should be avoided, since decreased absorption is possible.

Omeprazole

When CIPRO[®] XL[™], given as a single 1000 mg dose, was administered concomitantly with omeprazole (40 mg once daily for three days) to 18 healthy volunteers, the mean AUC and C_{max} of ciprofloxacin were reduced by 20% and 23%, respectively. These differences are not considered clinically significant.

Probenecid

Probenecid interferes with renal tubular secretion of ciprofloxacin and produces an increase in the level of ciprofloxacin in the serum. This should be considered if patients are receiving both drugs concomitantly.

Clozapine

Following concomitant administration of 250 mg ciprofloxacin for 7 days, serum concentrations of clozapine and n-desmethyleclozapine 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.

Sildenafil

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

Vitamin K Antagonists

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

Clinical Studies:

Uncomplicated Urinary Tract Infections (acute cystitis)

CIPRO[®] XL[™] was evaluated for the treatment of uncomplicated urinary tract infections (acute cystitis) in females in a prospective, randomized, double-blind, multicentre, clinical trial. This study compared CIPRO[®] XL[™] (500 mg once daily for three days) with CIPRO[®] (250 mg bid for three days). Of the 905 patients enrolled, 452 were randomly assigned to the CIPRO[®] XL[™] treatment group and 453 were randomly assigned to the control group. The primary efficacy variable was bacteriologic eradication at Test of Cure (TOC; Day 4-11 Post Therapy).

The bacteriologic eradication and clinical success rates were similar between CIPRO[®] XL[™] and the control group. The eradication and clinical success rates and their corresponding 95% confidence intervals for the differences between rates (CIPRO[®] XL[™] minus control CIPRO[®] group) are given in **Table 12** below:

Table 12: Clinical and Bacteriologic Response at Test of Cure

	CIPRO[®] XL[™] 500 mg Once Daily x 3 Days	CIPRO[®] 250 mg bid x 3 Days
Randomized Patients	452	453
Per Protocol Patients ^a	199	223
Clinical Success at TOC (n/N) ^b	189/199 (95.0%)	204/ 223 (91.5%)
	CI [-1.6%, 7.1%]	
Bacteriologic Eradication at TOC (n/N) ^b	188/199 (94.5%)	209/223 (93.7%)
	CI [-3.5%, 5.1%]	
Bacteriologic Eradication (by organism) at TOC (n/N) ^b		
<i>E coli</i>	156/160 (97.5%)	176/181 (97.2%)
<i>E faecalis</i>	10/11 (90.9%)	17/21 (81.0%)
<i>P mirabilis</i>	11/12 (91.7%)	7/7 (100%)
<i>S saprophyticus</i>	5/6 (83.3)	7/7 (100%)
<i>K pneumoniae</i>	7/9 (77.8%) ^c	11/14 (78.6%) ^c

a The presence of a pathogen at a level of $\geq 10^5$ CFU/mL was required for microbiological evaluability criteria.

b n/N = patients with pathogen eradicated/total number of patients

c Eradication rate at Follow-up was 3/6 (50%) for CIPRO[®] XL[™] and 6/10 (60%) for CIPRO[®]. This was due primarily to eradication with recurrence for this organism in both treatment groups.

Complicated Urinary Tract Infections and Acute Uncomplicated Pyelonephritis

CIPRO[®] XL[™] 1000 mg was evaluated for the treatment of complicated urinary tract infections and acute uncomplicated pyelonephritis in a large, randomized, double-blind, controlled clinical trial. This study compared CIPRO[®] XL[™] (1000 mg once daily for 7 to 14 days) with CIPRO[®] (500 mg twice daily for 7 to 14 days). Of the 1,042 patients enrolled, 521 were randomly assigned to the CIPRO[®] XL[™] treatment group and 521 were randomly assigned to the control group. The primary efficacy variable was bacteriological eradication at Test of Cure (TOC; Day 5-11 Post Therapy).

The bacteriological eradication and clinical success rates were similar between CIPRO[®] XL[™] 1000 mg and the control group. The eradication and clinical success rates and their corresponding 95% confidence intervals for the differences between rates (CIPRO[®] XL[™] 1000 mg minus control CIPRO[®] group) are given in **Table 13**.

Table 13: Clinical and Bacteriologic Response at Test of Cure

	CIPRO[®] XL[™] 1000 mg Once Daily x 7-14 Days	CIPRO[®] 500 mg bid x 7-14 Days
Randomized Patients	521	521
Per Protocol Patients ^a	206	229
Clinical Success at TOC in cUTI and AUP combined (n/N) ^b	198/206 (96.1%)	211/ 229 (92.1%)
	CI [-1.2%, 6.9%]	
Bacteriologic Eradication at TOC in cUTI and AUP combined (n/N) ^c	183/206 (88.8%)	195/229 (85.2%)
	CI [-2.4%, 10.3%]	
cUTI		
Clinical Success in cUTI at TOC (n/N) ^b	159/166 (95.8%)	161/177 (91.0%)
Bacteriologic Eradication (by organism) in cUTI at TOC (n/N) ^d		
<i>E coli</i>	91/94 (96.8%)	90/92 (97.8%)
<i>K pneumoniae</i>	20/21 (95.2%)	19/23 (82.6%)
<i>E faecalis</i>	17/17 (100%)	14/21 (66.7%)
<i>P mirabilis</i>	11/12 (91.6%)	10/10 (100%)
<i>P aeruginosa</i>	3/3 (100%)	3/3 (100%)
Bacteriologic Eradication Overall in cUTI at TOC ^e	148/166 (89.2%)	144/177 (81.4%)
AUP		
Clinical Success in AUP at TOC (n/N) ^b	39/40 (97.5%)	50/52 (96.2%)
Bacteriologic Eradication of <i>E coli</i> in AUP at TOC (n/N) ^d	35/36 (97.2%)	41/41 (100%)

a Patients excluded from the Per Protocol population were primarily those with no causative organism(s) at baseline or no organism present at 105 CFU/mL at baseline, inclusion criteria violation, no valid test-of-cure urine culture within the TOC window, an organism resistant to study drug, premature discontinuation due to an adverse event, lost to follow-up, or noncompliance with dosage regimen (among other criteria).

b n/N - patients with clinical success or pathogen eradicated/total number of patients

c n/N - patients with bacteriological eradication and no new infection /total number of patients

d n/N - patients with specified baseline organism eradicated/patients with specified baseline organism

e n/N - patients with specified baseline organism(s) eradicated and no new infections or superinfections/total number of patients

TOXICOLOGY

Acute Toxicity

<u>Species</u>	<u>Mode of Administration</u>	<u>LD₅₀ (mg/kg)</u>
Mouse	PO	approx. 5000
Rat	PO	approx. 5000
Rabbit	PO	approx. 2500
Mouse	IV	approx. 290
Rat	IV	approx. 145
Rabbit	IV	approx. 125
Dog	IV	approx. 250

Chronic Toxicity

Subacute Tolerability Studies over 4 Weeks

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

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

Subchronic Tolerability Studies Over 3 Months

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

Parenteral administration: Although the changes in the renal tubules observed in rats were in some cases very slight, they were present in every dose group. In monkeys they were found only in the highest-dose group (18 mg/kg) and were associated with slightly reduced erythrocyte counts and hemoglobin values.

Chronic Tolerability Studies Over 6 Months

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

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

Carcinogenicity

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

Reproduction Toxicology

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

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

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

Mutagenicity

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

Salmonella: Microsome Test (Negative)

E. coli: DNA Repair Assay (Negative)

Mouse Lymphoma Cell Forward Mutation Assay (Positive)

Chinese Hamster V₇₉ Cell HGPRT Test (Negative)

Syrian Hamster Embryo Cell Transformation Assay (Negative)

Saccharomyces cerev.: 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

Although two of the eight in vitro assays (ie, the Mouse Lymphoma Cell Forward Mutation Assay and the Rat Hepatocyte Primary Culture DNA Repair Assay [LIDS]) were positive, all of the in vivo test systems covering all relevant endpoints gave negative results.

Special Tolerability Studies

It is known from comparative studies in animals, both with the older gyrase inhibitors (eg, nalidixic and pipemidic acid) and the more recent ones (eg, norfloxacin and ofloxacin), 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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