

PRODUCT MONOGRAPH

PRO-CIPROFLOXACIN
(ciprofloxacin hydrochloride tablets, USP)

ciprofloxacin 250 mg
ciprofloxacin 500 mg
ciprofloxacin 750 mg

Antibacterial Agent

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Control # 125176

PRODUCT MONOGRAPH

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THERAPEUTIC CLASSIFICATION

Antibacterial Agent

ACTION AND CLINICAL PHARMACOLOGY

Ciprofloxacin, a synthetic fluoroquinolone, has a bactericidal mode of action. This action is achieved through inhibition of DNA gyrase, an essential component of the bacterial DNA replication system. Inhibition of the alpha subunit of the DNA gyrase blocks the resealing of the nicks on the DNA strands induced by this alpha subunit, leading to the degradation of the DNA by exonucleases. This bactericidal activity persists not only during the multiplication phase, but also during the resting phase of the bacterium.

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.

Bioavailability and Bioequivalence:

Two bioequivalence studies of Ciprofloxacin Tablets USP have been conducted and compared to the reference product, Cipro® of Bayer Inc. purchased in the USA.

The first study was a randomized, 2-way cross-over study comparing the single-dose relative bioavailability of the test and reference drugs products (750 mg ciprofloxacin) under fasting conditions in healthy volunteers. The results of the study in terms of the pharmacokinetic parameters measured are tabulated below.

Analyte Name - ciprofloxacin
Single dose of 750 mg Ciprofloxacin Tablet
From measured and log transformed data uncorrected for potency
Geometric Mean
Arithmetic Mean (CV %)

PARAMETER	TEST Generic Product Ciprofloxacin Tablet Batch D001	REFERENCE Cipro® of Bayer Inc. purchased in USA Batch 7JGAT	% RATIO OF GEOMETRIC MEANS
AUC _T (ng.h/mL)	12293.64 12759.1 (25.4)	12354.25 12572.8 (19.4)	99.5
AUC _I (ng.h/mL)	12735.39 13217.9 (25.6)	12792.03 13022.0 (19.6)	99.6
C _{MAX} (ng/mL)	2348.850 2432.12 (22.5)	2396.964 2426.88 (16.0)	98.0
T _{MAX} [*] (h)	1.594 (36.4)	1.458 (44.8)	-
T _½ [*] (h)	5.182 (11.9)	5.158 (8.5)	-

* expressed as arithmetic mean (CV%) only.

The second study was a randomized, 3-way cross-over study comparing the single-dose relative bioavailability of the test and reference drugs products (750 mg ciprofloxacin) under fed conditions and under fed/fasting conditions in healthy volunteers. The results of the study in terms of the pharmacokinetic parameters measured are tabulated below.

Analyte Name - ciprofloxacin
 Single dose of 750 mg Ciprofloxacin Tablet from measured and log transformed data
uncorrected for potency
 Geometric Mean
 Arithmetic Mean (CV %)

PARAMETER	TEST Generic Product Ciprofloxacin Tablet Batch D001	REFERENCE Cipro® of Bayer Inc. purchased in USA Batch 7JGAT	% RATIO OF GEOMETRIC MEANS
AUC _T (ng.h/mL)	9620.83 9690.8 (12.9)	9678.23 9806.9 (17.0)	103.4
AUC _I (ng.h/mL)	10054.27 10137.1 (13.9)	10117.90 10262.9 (17.8)	103.2
C _{MAX} (ng/mL)	1963.155 2033.54 (27.1)	1982.802 2030.99 (23.5)	104.8
T _{MAX} [*] (h)	1.792 (48.9)	1.667 (34.9)	-
T _½ [*] (h)	5.397 (12.8)	5.354 (9.7)	-

* expressed as arithmetic mean (CV%) only.

The bioequivalence study met the Report A requirements of the Therapeutic Products Programme when performed under fed and fasted conditions. The generic product, Ciprofloxacin Tablets USP was deemed to be bioequivalent to the Bayer Inc. reference product.

Ciprofloxacin and metronidazole have been studied in combination and serum levels of ciprofloxacin are not significantly altered by metronidazole at the doses studied. Serum levels of metronidazole when administered orally at a dose of 500 mg q6h in combination with ciprofloxacin 500 mg PO q12h are: AUC_{0-6} 156.3 mg/h/L, C_{max} 31.3 mg/L and T_{max} 1.71 hours.

INDICATIONS AND CLINICAL USES

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

Respiratory tract infections

Acute exacerbation of chronic bronchitis caused by:

Haemophilus influenzae

Moraxella catarrhalis

Streptococcus pneumoniae

Acute pneumonia caused by:

Enterobacter cloacae

Escherichia coli

Haemophilus influenzae

Klebsiella pneumoniae

Proteus mirabilis

Pseudomonas aeruginosa

Staphylococcus aureus

Streptococcus pneumoniae

Acute sinusitis caused by:

Haemophilus influenzae

Moraxella catarrhalis

Streptococcus pneumoniae

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

Urinary tract infections

Upper and lower urinary tract infections, such as complicated and uncomplicated cystitis, pyelonephritis, and pyelitis caused by:

Citrobacter diversus

Citrobacter freundii

Enterobacter cloacae

Escherichia coli

Klebsiella pneumoniae

Klebsiella oxytoca

Morganella morganii

Proteus mirabilis

Pseudomonas aeruginosa

Serratia marcescens

Staphylococcus aureus

Staphylococcus epidermidis

Staphylococcus saprophyticus

Streptococcus faecalis

Acute uncomplicated cystitis in females caused by Escherichia coli.

Chronic bacterial prostatitis

Caused by: Escherichia coli

Skin and soft tissue infection

Caused by:

Enterobacter cloacae

Escherichia coli

Klebsiella pneumoniae

Proteus mirabilis

Proteus vulgaris

Pseudomonas aeruginosa

Staphylococcus aureus

Staphylococcus epidermidis

Streptococcus pyogenes

Bone and joint infections

Caused by:

Enterobacter cloacae

Pseudomonas aeruginosa

Serratia marcescens

Staphylococcus aureus

Infectious diarrhea (when antibacterial therapy is indicated)

Caused by:

Campylobacter jejuni

Escherichia coli (enterotoxigenic strains)

Shigella dysenteriae

Shigella flexneri

Shigella sonnei

Meningococcal carriers

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

Typhoid fever (enteric fever)

Caused by:

Salmonella paratyphi

Salmonella typhi

Uncomplicated gonorrhea

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

CONTRAINDICATIONS

PRO-CIPROFLOXACIN (ciprofloxacin hydrochloride) tablets are contraindicated in patients who have shown hypersensitivity to ciprofloxacin or other quinolone antibacterial agents.

WARNINGS

Children

The safety of PRO-CIPROFLOXACIN (ciprofloxacin hydrochloride tablets) in children has not yet been established. 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.

Consequently, ciprofloxacin should not be used in prepubertal patients. Experience in pubertal patients below 18 years of age is limited.

Pregnancy

The safety of ciprofloxacin in the treatment of infections in pregnant women has not yet been established. (See **PRECAUTIONS**).

General

Convulsions have been reported in patients receiving ciprofloxacin. Convulsions, increased intracranial pressure, and toxic psychosis have been reported in patients receiving drugs in this

class. Quinolones may also cause central nervous system (CNS) stimulation which may lead to tremors, restlessness, lightheadedness, confusion and hallucinations. 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 (See **ADVERSE REACTIONS**).

PRECAUTIONS

General

Anaphylactic reactions including cardiovascular collapse have occurred rarely in patients receiving therapy with ciprofloxacin. These reactions may occur within the first 30 minutes following the first dose and may require epinephrine and other emergency measures.

Severe hypersensitivity reactions characterized by rash, fever, eosinophilia, jaundice, and hepatic necrosis with fatal outcome have also been reported to occur very rarely in patients receiving ciprofloxacin in combination with other drugs. The possibility that these reactions were related to ciprofloxacin cannot be excluded. Ciprofloxacin should be withdrawn at the first appearance of a skin rash or other signs of hypersensitivity.

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

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

Pseudomembranous colitis has been reported with virtually all antibacterial agents, including ciprofloxacin, and may range in severity from mild to life-threatening. It is important to consider this

diagnosis in patients with diarrhoea subsequent to the administrations of antibacterial agents. Subsequent to diagnosis of pseudomembranous colitis, therapeutic measures should be initiated.

Mild cases will usually respond to discontinuation of drug alone. In moderate to severe cases, consideration should be given to the management with fluids, electrolytes, protein supplementation and treatment with an antibacterial drug effective against *Clostridium difficile*.

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

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

Pregnancy

The safety of ciprofloxacin in pregnancy has not yet been established. Ciprofloxacin should not be used in pregnant women unless the likely benefits outweigh the possible risk to the fetus. Ciprofloxacin has been shown to be non-embryotoxic and non-teratogenic in animal studies.

Nursing mothers

Ciprofloxacin is excreted in human milk. A decision should be made to discontinue nursing or to discontinue the administration of ciprofloxacin, taking into account the importance of the drug to the mother and the possible risk to the infant.

Drug interactions

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

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

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

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

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

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

Antacids containing aluminum or magnesium hydroxide have been shown to reduce the absorption of ciprofloxacin. Concurrent administration with these agents should be avoided.

Administration of sucralfate prior to ciprofloxacin resulted in a 30% reduction in absorption of ciprofloxacin. Concurrent administration with ciprofloxacin should be avoided.

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

The use of calcium supplement and highly buffered drugs such as antiretrovirals reduces the absorption of ciprofloxacin, therefore concomitant administration is not advised.

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

Renal impairment

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

Hepatic impairment

In preliminary studies in patients with stable chronic liver cirrhosis, no significant changes in ciprofloxacin pharmacokinetics were observed. The kinetics of ciprofloxacin in patients with acute hepatic insufficiency, however, have not been fully elucidated. An increased incidence of nausea, vomiting, headache and diarrhoea were observed in this patient population.

ADVERSE REACTIONS

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

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

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

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

Blood and Blood Constituents: agranulocytosis, anaemia, eosinophilia, granulocytopenia, leukocytopenia, leukocytosis, pancytopenia. Very rarely: altered prothrombin levels, haemolytic anaemia, marrow depression (life threatening), pancytopenia (life threatening), thrombocytopenia, thrombocytosis.

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

Cardiovascular System: palpitation, phlebitis, tachycardia. The following have been reported very rarely: 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, vasodilation.

Gastro-Intestinal: abdominal pain, anorexia, dry mouth, dyspepsia, dysphagia, enlarged abdomen, flatulence, gastrointestinal moniliasis, jaundice, stomatitis, vomiting. 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.

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

Musculoskeletal: the following have been reported rarely: achiness, arthralgia (joint pain), joint swelling, pain in the extremities, partial or complete tendon rupture (predominantly achilles tendon), tendonitis (predominantly achillotendonitis), and very rarely, myasthenia.

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

Other: very rarely, asthenia, death.

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

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

Special Senses: abnormal vision, taste perversion, tinnitus. The following have been reported very rarely: chromatopsia, colour blindness, conjunctivitis, corneal opacity, diplopia, ear pain, eye pain.

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

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

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

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

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

Cardiovascular: peripheral edema

Digestive: colitis, gastritis, tongue discoloration

Hemic and Lymphatic: coagulation disorder, thrombocytopenia

Skin: fungal dermatitis, pustular rash, sweating

Metabolic: healing abnormal, hypernatremia

Nervous: dementia

Urinary: kidney tumour necrosis, urinary incontinence.

SYMPTOMS AND TREATMENT OF OVERDOSE

In the event of acute, excessive oral overdosage, reversible renal toxicity, arthralgia, myalgia and CNS symptoms have been reported. Therefore, apart from routine emergency measures, it is recommended to monitor renal function and to administer magnesium- or calcium-containing antacids which reduce the absorption of ciprofloxacin and to maintain adequate hydration. Based on information obtained from subjects with chronic renal failure, only a small amount of ciprofloxacin (< 10%) is removed from the body after hemodialysis or peritoneal dialysis.

DOSAGE AND ADMINISTRATION

The determination of dosage for any particular patient must take into consideration the severity and nature of the infection, the susceptibility of the causative organism, the integrity of the patient's host-defence mechanisms, and the status of renal function.

PRO-CIPROFLOXACIN (ciprofloxacin) may be taken before or after meals. Absorption is faster on an empty stomach. Patients should be advised to drink fluids liberally and not take antacids containing magnesium or aluminum.

Adults:

The recommended dosage of PRO-CIPROFLOXACIN is:

Location of infection	Type / severity	Unit dose	Frequency	Daily dose
Urinary tract	Mild / moderate	250 mg	q 12 h	500 mg
	Severe / complicated	500 mg	q 12 h	1000 mg
Chronic bacterial prostatitis	Asymptomatic / mild / moderate	500 mg	q 12 h	1000 mg

Respiratory tract Bone and joint Skin and soft tissue	Mild / moderate Severe* / uncomplicated	500 mg 750 mg	q 12 h q 12 h	1000 mg 1500 mg
Infectious diarrhea	Mild / moderate / severe	500 mg	q 12 h	1000 mg
Urogenital and extragenital gonorrhea	Uncomplicated	500 mg	once	500 mg
Typhoid fever	Mild / moderate	500 mg	q 12 h	1000 mg
Neisseria meningitidis Nasopharyngeal colonization	Carrier state	750 mg	once	750 mg
Acute sinusitis	Moderate	500 mg	q 12 h	1000 mg

* eg. hospital-acquired pneumonia, osteomyelitis

Depending on the severity of the infections, as well as the clinical and bacteriological responses, the average treatment period should be approximately 7 to 14 days. Generally, treatment should last 3 days beyond the disappearance of clinical symptoms or until cultures are sterile. Patients with osteomyelitis may require treatment for a minimum of 6 to 8 weeks and up to 3 months. With acute cystitis in females a 3 to 5 day treatment may be sufficient. With infectious diarrhea, a five day treatment may be sufficient. Typhoid fever should be treated for 14 days. Acute sinusitis should be treated for 10 days with 500 mg q 12h. Chronic bacterial prostatitis should be treated for 28 days with 500 mg q 12h.

Sequential I.V. / P.O. Therapy

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

Impaired renal function:

Ciprofloxacin is eliminated primarily by renal excretion. However, the drug is also metabolized and partially cleared through the biliary system of the liver and through the intestine (see **HUMAN PHARMACOLOGY**). This alternate pathway of drug elimination appears to compensate for the reduced renal excretion of patients with renal impairment. Nonetheless, some modification of

dosage is recommended, particularly for patients with severe renal dysfunction. The following table provides a guideline for dosage adjustment. However, monitoring of serum drug levels provides the most reliable basis for dosage adjustments. Only a small amount of ciprofloxacin (<10%) is removed from the body after hemodialysis or peritoneal dialysis.

Creatinine clearance mL/min/1.73m ²	Maximum daily oral dose	Serum creatinine concentration mg/100 mL
31 - 60 ≤ 30	1000 mg 500 mg	1.4 - 1.9 ≥ 2.0

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

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

Creatinine clearance mL/sec =

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

Females: 0.85 x the above value

In traditional units mL/min. =

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

Females: 0.85 x the above value

Children:

The safety and efficacy of ciprofloxacin in children has not been established. Ciprofloxacin should not be used in prepubertal patients (see **WARNINGS**).

PHARMACEUTICAL INFORMATION

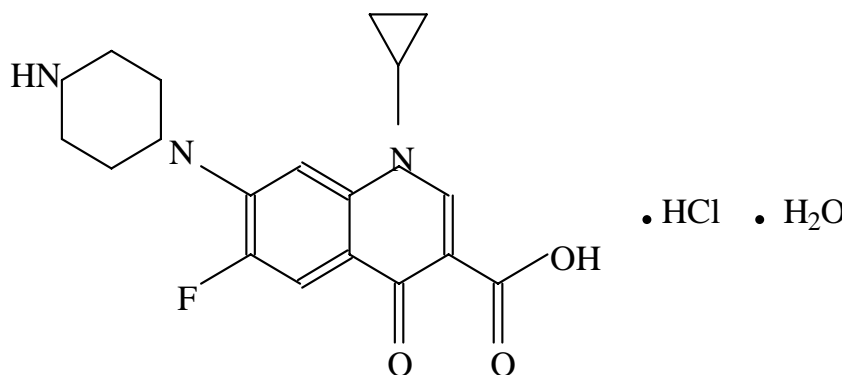
DRUG SUBSTANCE

Proper name: ciprofloxacin hydrochloride

Chemical name:

- (1) 3-Quinolinecarboxylic acid, 1-cyclo-propyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-, monohydrochloride, monohydrate
- (2) 1-Cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid, monohydrochloride, monohydrate

Structural formula:



Molecular formula: C₁₇H₁₈FN₃O₃HCl · H₂O

Molecular weight: 385.8

Description: Ciprofloxacin hydrochloride is a pale yellow crystalline powder. It is sparingly soluble in water, slightly soluble in acetic acid and methanol; very soluble in dehydrated alcohol. It is practically insoluble in acetone, acetonitrile, ethyl acetate, hexane and methylene chloride. Its solubility in aqueous buffer of pH 7.4 at 21°C is 0.19 g/L, while the solubility is considerably higher at slightly acidic or slightly

alkaline pH. At 140°C water of crystallization is lost. At 307°C decomposition takes place. The pH of ciprofloxacin hydrochloride is between 3 and 4.5 in a solution (1 in 40). The pK_{a1} is 6.5 and pK_{a2} is 8.9 determined using a 3×10^{-4} M solution at 25°C.

COMPOSITION

PRO-CIPROFLOXACIN - 250 mg

PRO-CIPROFLOXACIN (ciprofloxacin hydrochloride tablets, USP) 250 mg, are white, oval, film-coated tablets imprinted R on one side and 126 on the other side. Each tablet contains ciprofloxacin (as the hydrochloride) 250 mg as the medicinal ingredient with the following non-medicinal ingredients: microcrystalline cellulose, sodium starch glycolate, corn starch, colloidal silicon dioxide, magnesium stearate, hydroxypropyl methylcellulose, titanium dioxide and polyethylene glycol.

PRO-CIPROFLOXACIN - 500 mg

PRO-CIPROFLOXACIN (ciprofloxacin hydrochloride tablets, USP) 500 mg, are white, oval, film-coated tablets imprinted R on one side and 127 on the other side. Each tablet contains ciprofloxacin (as the hydrochloride) 500 mg as the medicinal ingredient with the following non-medicinal ingredients: microcrystalline cellulose, sodium starch glycolate, corn starch, colloidal silicon dioxide, magnesium stearate, hydroxypropyl methylcellulose, titanium dioxide and polyethylene glycol.

PRO-CIPROFLOXACIN - 750 mg

PRO-CIPROFLOXACIN (ciprofloxacin hydrochloride tablets, USP) 750 mg, are white, modified capsule shaped, film-coated tablets imprinted R on one side and 128 on the other side. Each tablet contains ciprofloxacin (as the hydrochloride) 750 mg as the medicinal ingredient with the following non-medicinal ingredients: microcrystalline cellulose, sodium starch glycolate, corn starch, colloidal silicon dioxide, magnesium stearate, hydroxypropyl methylcellulose, titanium dioxide and polyethylene glycol.

STABILITY AND STORAGE RECOMMENDATIONS

Store PRO-CIPROFLOXACIN at controlled room temperature between 15° C and 25° C.

AVAILABILITY OF DOSAGE FORMS

PRO-CIPROFLOXACIN 250 mg, 500 mg, and 750 mg are each supplied in high density polyethylene (HDPE) plastic bottles with polypropylene caps containing 50, 100 and 500 tablets, and in polyvinyl chloride / aluminum (PVC/Al) unit dose blister strips containing 100 tablets per carton (10 strips of 10 tablets).

MICROBIOLOGY

The *in vitro* activity of ciprofloxacin against clinical isolates of gram-positive and gram-negative aerobic and anaerobic bacteria is shown in Table 1. Susceptibility was determined by both agar and broth dilution tests, pH 7.1 - 7.4, using inoculum sizes ranging from 10^4 to 10^5 colony forming units per mL.

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

Table 1. Cumulative percent of strains inhibited at the indicated concentration of ciprofloxacin

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

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

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

The minimum inhibitory concentrations (MICs) of ciprofloxacin against aerobic bacteria are not significantly affected by changes in inoculum size in the range of 5×10^3 to 5×10^6 cfu/spot. Five bacterial species, *Staphylococcus aureus* K734, *Staphylococcus epidermidis* H846, *Streptococcus faecalis* 7149, *Escherichia coli* 2345 and *Proteus mirabilis* 2349 were tested for MICs with inoculum size of 5×10^3 to 5×10^6 . *Streptococcus faecalis* showed a four-fold increase while the remainder showed only a two to three-fold increase (Table 2). There were no differences between MICs determined in Mueller Hinton and Isosensitest broth.

MIC values 8 to 16 fold higher were seen when these organisms were tested in Mueller Hinton broth at pH 4.8 compared to values obtained at pH 7.3 (Table 2). This reduction in antibacterial activity suggests a significant pH effect.

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

Table 2. Effect of culture medium composition, pH and inoculum size on antibacterial activity of ciprofloxacin.

Organism / strain	MIC (mg/L)				
	pH ^(a)			Inoculum size (cfu) ^(b)	
	4.8	7.3	8.8	5 x 10 ³	5 x 10 ⁶
Staphylococcus aureus K734	4.0	0.5	0.5	0.25	0.5
Staphylococcus epidermidis H846	2.0	0.25	0.25	0.125	0.25
Streptococcus faecalis 7149	8.0	1.0	1.0	0.5	2.0
Escherichia coli 2345	0.5	0.016	0.016	0.008	0.016
Proteus mirabilis 2349	1.0	0.03	0.016	0.008	0.03

(a) Mueller Hinton broth (BBL) 5 x 10⁵ cfu/mL

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

Development of resistance

The mechanism of resistance development to ciprofloxacin is unclear. Plasmid-mediated resistance does not occur. Chromosomal mutation influencing DNA gyrase and / or the cell membrane may confer resistance.

A progressive increase in MIC of ciprofloxacin was demonstrated in a bacterial strain of *E. coli* Neuman by daily passage in subinhibitory concentrations of the drug. MICs were determined by Isosensitest Broth Dilution Test, 10^5 cfu.mL inoculum. The MIC of the parent strain of *E. coli* was 0.03 mg/L. After three passages, the MIC increased to 0.25 mg/L and with five passages resulted in an MIC of 0.50 mg/L.

Mutants having reduced susceptibility to ciprofloxacin emerge at a relatively low incidence *in vitro* (see Table 3).

Table 3: Frequency of resistance to ciprofloxacin*

Organism (MIC µg/mL)	Fold above MIC	Resistance frequency at 48 h
Enterobacter cloacae (0.025)	4	1×10^{-9}
	8	1×10^{-9}
Escherichia coli (0.025)	4	2.92×10^{-7}
	8	3.33×10^{-8}
Klebsiella pneumoniae (0.025)	4	1.06×10^{-7}
	8	3.33×10^{-8}
Providencia stuartii (0.1)	4	1.78×10^{-7}
	8	1.48×10^{-7}
Pseudomonas aeruginosa (0.8)	4	1×10^{-9}
	8	1×10^{-9}
Serratia marcescens (0.2)	4	1×10^{-9}
	8	1×10^{-9}
Staphylococcus aureus (0.4)	4	1.82×10^{-7}
	8	1.67×10^{-8}
Streptococcus faecalis (0.8)	4	1×10^{-9}
	8	1×10^{-9}

* 2 clinical isolates of eight species from human urine - 0.1 mL of an overnight culture in Trypticase Soy Broth plated onto Trypticase Soy Agar containing ciprofloxacin at concentrations 4 and 8 times the MIC, incubated at 35°C for 18 hours.

Cross-resistance:

Cross-resistance with other quinolones has been observed. Although limited data shows that nalidixic-resistant organisms are less susceptible to ciprofloxacin, achievable serum levels of ciprofloxacin are generally above the increased MICs seen in these less susceptible organisms.

A study of the activity of ciprofloxacin against selected organisms which were resistance to antimicrobial agents having other mechanisms of action (e.g. beta-lactam and aminoglycoside antibiotics) showed that they were sensitive to ciprofloxacin (see Table 4) and that their MICs were generally within the range observed for other microorganisms of the same species (compared to Table 1). Similarly, organisms resistant to ciprofloxacin might be sensitive to antimicrobial agents having other mechanisms of action.

Table 4: Activity of ciprofloxacin against selected bacteria resistant to β -lactams and aminoglycosides

MIC mg/L of				
Organism	Ciprofloxacin	Amikacin	Cefotaxime	Moxalactam
<i>Acinetobacter anitratus</i>	0.4	>16	>128	>128
<i>Bacteroides thetaiotaomicron</i>	0.8	>128	>128	>128
<i>Citrobacter freundii</i> 1	0.1	>16	>128	>128
<i>Citrobacter freundii</i> 2	0.05	>16	>128	>128
<i>Enterobacter aerogenes</i>	0.5	>16	>128	>64
<i>Enterobacter cloacae</i> 1	0.05	>16	>128	>128
<i>Enterobacter cloacae</i> 2	0.05	>16	128	64
<i>Klebsiella pneumoniae</i>	0.5	>16	4	4
<i>Proteus vulgaris</i>	0.02	>4	128	32
<i>Pseudomonas aeruginosa</i> 1	0.8	>16	>128	>128
<i>Pseudomonas aeruginosa</i> 2	0.8	>16	>128	>128
<i>Pseudomonas cepacia</i>	0.8	>16	>128	>128
<i>Pseudomonas maltophilia</i>	0.8	>16	>128	>128
<i>Serratia marcescens</i> 1	0.4	>16	>128	64
<i>Serratia marcescens</i> 2	0.4	>16	>128	>32
<i>Staphylococcus aureus</i>	0.8	>16	>128	>128

The MICs of piperacillin and cefoperazone were >128 mg/L for all organisms. Clinical isolates from urine - both agar and broth dilution tests were used, 10^8 inoculum on Mueller Hinton Agar or broth.

Combination with other anti-infectives

In general, combinations of ciprofloxacin with beta-lactam or aminoglycoside antibiotics were neither antagonistic nor synergistic when evaluated by the microdilution checkerboard method. The few instances of synergy that were observed did not show any predictable pattern (Table 5).

Table 5: Combination of ciprofloxacin with aminoglycosides - Checkerboard assay

Combination	synergistic	Number of test strains which the combination was additive - indifferent			antagonistic
	FIC index = <0.5	2 x FIC index >0.5 - 0.625	intermediate	2 x FIC index 2.0 - <4.0	FIC index = >4.0
Ciprofloxacin Gentamicin	1	33	172	14	0
Ciprofloxacin Sisomicin	1	31	177	11	0
Ciprofloxacin Netilmicin	2	33	174	11	0
Ciprofloxacin Amikacin	0	33	177	10	0
Ciprofloxacin Tobramycin	1	32	178	8	1

FIC = Fraction Inhibitory Concentration

Susceptibility testing:

The standard Kirby-Bauer disc susceptibility test (using 5 µg ciprofloxacin discs) and the dilution susceptibility test should be interpreted using the following criteria:

Sensitivity discs Zone diameter (mm)	Interpretation	Broth / agar dilution MIC level breakpoints
≥ 21	(S) susceptible	≥ 1.0 mg/L
16 - 20	(I) intermediate	> 1.0 - ≤ 2.0 mg/L
≤ 15	(R) resistant	> 2.0 mg/L

A report of “intermediate susceptibility” suggests that the organism may be susceptible if the infection is confined to tissues and fluids (e.g urine), in which high antibiotic levels are attained.

The Quality Control strains should have the following assigned daily ranges for ciprofloxacin:

QC strains	Disc zone diameter (mm)	MIC (mg/L)
<i>S. aureus</i> (ATCC 25923)	22 - 30	-
<i>S. aureus</i> (ATCC 29213)	-	0.25 - 1.0
<i>E. coli</i> (ATCC 25922)	30 - 40	0.008 - 0.03
<i>P. aeruginosa</i> (ATCC 27853)	25 - 33	0.25 - 1.0
<i>N. gonorrhoeae</i> (ATCC 49226)	48 - 58	≤ 0.008

PHARMACOLOGY

ANIMAL PHARMACOLOGY

Effects on histamine release

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

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

Bronchodilatory Effects

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

CNS Effects

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

Gastrointestinal Effects

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

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

Effect on Blood Glucose and Serum triglycerides

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

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

HUMAN PHARMACOLOGY

Pharmacokinetics and absorption

Following oral administration of single doses of 250 mg, 500 mg and 750 mg of ciprofloxacin respectively to groups of 3 healthy male volunteers (age: 22.8 ± 3.5 years, weight 68.5 ± 9.4 kg), ciprofloxacin was absorbed rapidly and extensively from the gastrointestinal tract (Figure 1).

Maximum serum concentrations (C_{max}) increased dose-proportionally and were attained 1 to 2

hours after oral dosing. The total areas under the serum concentration - time curves (AUC) were also increased in proportion to dose (Figure 1). Mean concentrations 12 hours after dosing with 250 mg, 500 mg, or 750 mg were 0.1, 0.2, and 0.4 mg/L, respectively. The serum elimination half-lives ($t_{1/2}$) were between 4 and 6 hours. (Table 6).

Pharmacokinetics were dose proportional with no significant changes in clearance or half-life occurring over this dose range (see Table 6 below).

Table 6

Pharmacokinetic parameters of Ciprofloxacin Following Single Oral Doses In Healthy Volunteers

Dose	250 mg	500 mg	750 mg
C _{max} (mg/L)	1.42	2.60	3.41
T _{1/2} (hr)	4.19	4.87	5.34
AUC(mg•L)	5.43	10.60	15.03
T _{max} (hr)	1.11	1.11	1.56

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

Table 7

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

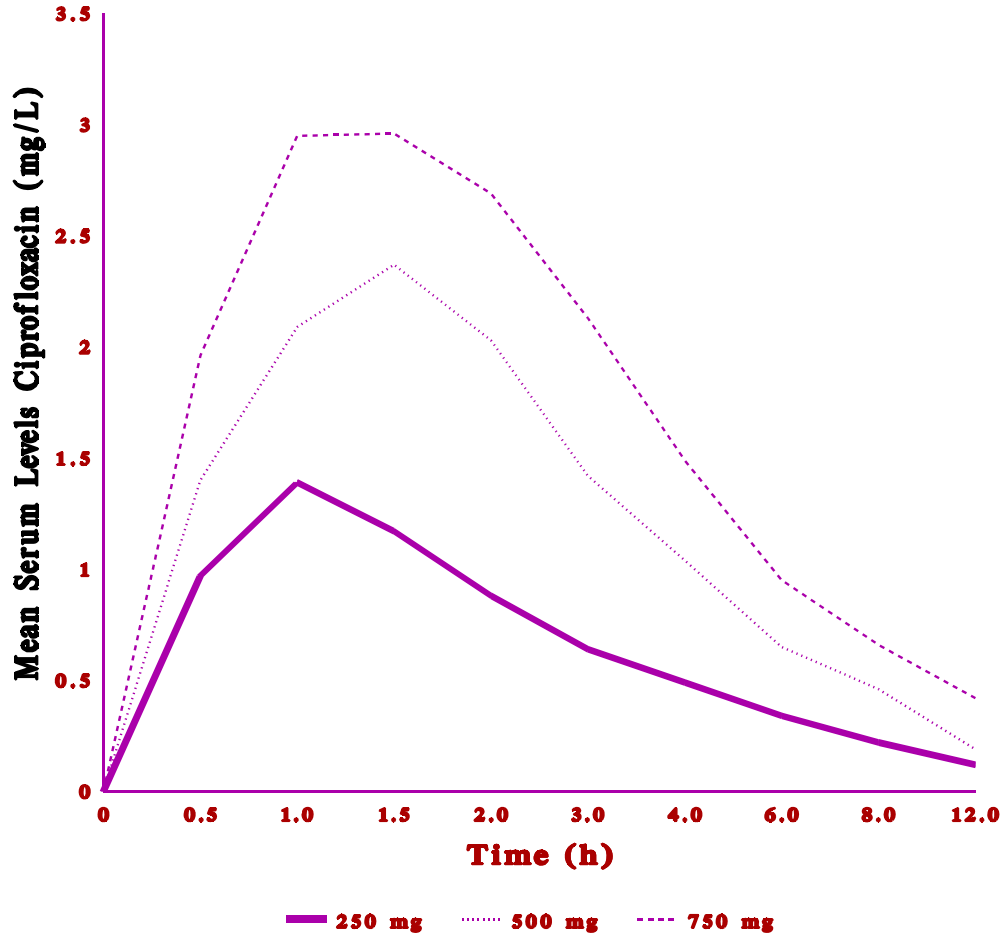
REGIMEN	AUC (mg.h/L)	Cmax (mg/L)	Tmax (h)
(I) When administered alone			
Ciprofloxacin 500 mg PO q12h	13.7 (AUC 0-12)	2.97	1.23

(ii) When administered as Ciprofloxacin 500 mg PO q12h in combination with Metronidazole 500 mg PO q6h*			
Ciprofloxacin	12.6 (AUC 0-12)	2.73	1.3
Metronidazole	156.3 (AUC 0-6)	31.3	1.71

* Following the repeated dosing of metronidazole 55 mg IV tid, the peak and minimum mean plasma metronidazole concentrations, at steady-state, were 26 µg/mL and 12 µg/mL respectively.

Figure 1

Mean Ciprofloxacin Serum Concentration After Single Oral Doses



Metabolism and Excretion

Ciprofloxacin is largely excreted unchanged both renally and to a small extent, extrarenally (Table 8).

Table 8

Mean Urinary Excretion of Ciprofloxacin

Hours After administration of a Single Dose				
	0-2	2-4	4-8	8-12
Urine Concentration mg/L (\pm S.D.)				
250 mg po	205 (\pm 89)	163 (\pm 145)	101 (\pm 65)	32 (\pm 28)
500 mg po	255 (\pm 204)	358 (\pm 86)	117 (\pm 86)	26 (\pm 10)
750 mg po	243 (\pm 143)	593 (\pm 526)	169 (\pm 131)	55 (\pm 36)
Amount excreted mg (\pm S.D.)				
250 mg dose	54.38 (\pm 36.22)	26.79 (\pm 11.78)	22.84 (\pm 6.79)	8.90 (\pm 4.25)
500 mg dose	64.51 (\pm 25.06)	47.37 (\pm 15.65)	39.54 (\pm 11.17)	15.52 (\pm 5.39)
750 mg dose	68.90 (\pm 41.85)	72.43 (\pm 33.13)	61.07 (\pm 21.68)	28.11 (\pm 7.64)

Small concentrations of 4 metabolites have been reported: Desethyleneciprofloxacin (M_1) (1.8%), sulphociprofloxacin (M_2) (5.0%), oxociprofloxacin (M_3) (9.6%) and formylciprofloxacin (M_4) (0.1%).

Following the oral administration of a single 259 mg dose of ^{14}C -labelled ciprofloxacin to six healthy male volunteers (age: 25.0 ± 1.46 years, weight 70.0 ± 3.39 kg), approximately 94% of the dose was recovered in the urine and faeces 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 faeces, accounting for 45% and 25% of the dose, respectively. Total (urine and faeces) excretion of all metabolites was 18.8%.

FACTORS INFLUENCING THE PHARMACOKINETICS

Age (Elderly)

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

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

Table 9

Comparison of pharmacokinetic parameters between healthy elderly and healthy younger volunteers

Parameter	Elderly Volunteers (mean \pm S.D.)	Younger Volunteers (mean \pm S.D.)
C _{max} (mg/L)	1.8 \pm 0.5	1.3 \pm 0.4
T _{max} (hr)	1.2 \pm 0.3	1.2 \pm 0.1
t _{1/2} (hr)	3.7 \pm 0.9	3.3 \pm 0.6
Total AUC (mg•h/L)	7.25 \pm 2.45	5.29 \pm 1.21
% Dose Urinary Recovery after 24 hours	43	43

Impaired renal Function

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).

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

Table 10

Mean pharmacokinetic Parameters for Ciprofloxacin
Following a Single 250 mg Oral Dose in Healthy
Volunteers and in Patients with Renal Insufficiency

Group	Creatinine Clearance (mL/s/1.73 m ²) (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	>1.0 (> 60)	1.52 (± 0.21)	1.0 (± 0.0)	4.4 (± 0.2)	6.94 (± 0.97)	232.9 (± 44.8)	37.0 (± 3.7)
II	< 0.33 (< 20)	1.70 (± 0.41)	1.7 (± 0.5)	8.7 (± 0.9)	14.36 (± 3.5)	18.3 (± 3.5)	5.3 (± 1.7)
III	End- Stage Renal Failure Treated by Hemodialysis	2.07 (± 0.2)	1.6 (± 0.2)	5.8 (± 0.9)	15.87 (± 2.0)		

Food

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

Probenecid

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

Serum Protein Binding

Serum protein binding of ciprofloxacin is between 19 to 40%.

Tissue Concentrations

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

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

Single intravenous doses of 100, 150 and 200 mg ciprofloxacin were administered to nine healthy volunteers to determine the excretion and distribution of ciprofloxacin following intravenous administration and to assess the effect of dose size on pharmacokinetic parameters.

Analysis with a three-compartmental pharmacokinetic model quantified approximate sizes and kinetics of distribution into two peripheral compartments. A rapidly equilibrating compartment (V_2) with a high intercompartmental clearance rate, accounting for the rapid decline in ciprofloxacin concentrations in serum immediately following drug infusion, and a third, slowly equilibrating tissue

compartment with relatively slow intercompartmental clearance. This would contribute to the prolonged terminal half-life (4 to 5 h) of ciprofloxacin IV.

The results of this study were as follows:

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

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

Table 11**Distribution of Ciprofloxacin in Human Tissue/Fluid**

Tissue/Fluid	No. Of patients	Single Dose of Ciprofloxacin	Peak Concentration(mg/kg or mg/L)	Mean Serum Concentration(mg/L)	Time after Dose (hr)
Skin Blister Fluid	6	500 mg po	1.4 ± 0.36	2.3 ± 0.7	1-6
Bone	4	750 mg po	1.4 ± 1.0	2.9 ± 2.2	2-4
Gynecological Tissue	18	500 mg po	1.3 ± 0.66 To 1.6 ± 0.97	1.4 ± 0.87	2-4
Prostatic Tissue	1	500 mg po	3.76	1.84	2.5
muscle	4	250 mg po	2.4 ± 1.0	2.9 ± 2.2	2-4
Nasal Secretions	20	500 mg po	1.4 ± 0.81	1.88 ± 0.48	1-3

TOXICOLOGY

Acute Toxicity

Table 12
Single Dose Toxicity of Ciprofloxacin

Species	Sex	Route of Administration	LD₅₀* mg/kg	95% confidence interval
Mouse	M	p.o.	5000	
Mouse	F	p.o.	Approx 5000	
Mouse	M	i.v.	296.5	275 - 321
Mouse	F	i.v.	291.5	278 - 315
Rat	M	p.o.	5000	
Rat	F	p.o.	5000	
Rat	M	i.v.	147	130 - 164
Rat	F	i.v.	144	130 - 157
Rabbit	M	p.o.	Approx 2500	
Rabbit	F	i.v.	Approx 125	
Dog	M/F	p.o.	Not determinable, vomiting and regurgitating of the test substance	
Dog	M/F	i.v.	Approx 250	

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

The dog regurgitated the substances to a large extent after high oral doses, so that neither symptoms of intoxication nor the LD₅₀ could be determined.

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

Short-term Toxicity

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

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

Long-term toxicity

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

REPRODUCTIVE TOXICITY

Fertility studies

Ciprofloxacin hydrochloride was administered to rats, strain Bor:WISW, (24 male and 60 females per group) by a stomach tube, in doses of 0, 10, 30 or 100 mg/kg/day. Treatment was commenced in the males 10 weeks before mating and in the females 3 weeks before mating and was continued in the females up to the 7th day of gestation. doses up to 100 mg/kg/day ciprofloxacin had no effects on fertility; the intrauterine and postnatal development of the young and the fertility of the F1 generation were likewise unimpaired by ciprofloxacin.

Embryotoxicity studies

(a) Mouse

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

(b) Rats

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

(c) Rabbits

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

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

Perinatal and Postnatal studies

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

Female SPF rats, strain BOR:WIST, (50 per group) were given ciprofloxacin hydrochloride subcutaneously in doses of 0, 3, 10, or 30 mg/kg/day. Ciprofloxacin had no effect either on the late intrauterine development of the fetuses, the course of birth, postnatal development, or the fertility of the F1 generation. The histological examination of the joints of the young, performed at the end of the weaning period, did not reveal any damage to the articular cartilage.

MUTAGENICITY STUDIES

In-vitro (See Table 13 for details)

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

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

In-vivo (See Table 13 for details)

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

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

Table 13 - Mutagenicity Studies Summary

IN-VIVO TEST	Strain	Positive Control and Dose	Ciprofloxacin Dose
Micronucleus test	BOR:NMRI mice	Endoxan 72.5 µg/kg once, oral	4000 mg/kg one, oral ----- 1000 mg/kg one, oral 2000 mg/kg one, oral 4000 mg/kg one, oral
Dominant lethal test	BOR:NMRI mice	Negative control only	4000 mg/kg one, oral
Rat hepatocyte DNA repair test	F-344 male Fisher rat	2-acetylaminofluorene 10 mg/kg i.v.	30 mg/kg one, i.v.
IN-VITRO TEST	Positive control and concentration		Ciprofloxacin concentration
Salmonella / microsome test (Ames)	Endoxan Trypaflavine 2-aminoanthracene	145 µg/plate 50 µg/plate 3 µg/plate	0.016 µg - 10.0 µg/plate
Unscheduled DNA synthesis test (UDS)	2-amino fluorene Fluorene	10 ⁻⁵ M 10 ⁻⁵ M	5 x 10 ⁻¹ mg/mL to 1.25 x 10 ⁻² mg/mL
Mouse lymphoma test	Ethylmethane sulfonate Methylcholanthrene	0.3 µL/mL - 0.4 µL/mL 2 µg/mL - 4 µg/mL	10 µg/mL - 500 µg/mL
Hamster V79 HGPRT assay	Ethylmethane sulfonate 9, 10-Dimethyl-1, 2-benzanthracene	8 mM 15 µg/mL	70 µg/mL - 700 µg/mL

Joint and oculotoxicity

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

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

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

In a dog study, groups of 2 male and 2 female beagles each aged between 13 and 14 weeks were used. Ciprofloxacin hydrochloride was administered in gastric-juice-resistant gelatin capsules at doses of 0, 30, 70, or 100 mg/kg/day for 4 weeks. Histopathological examination revealed primary degenerative articular changes in the knee joint and hip joint cartilages at all doses tested. Severity of degenerative changes was dose-related with 100 mg/kg resulting in moderate primary degenerative articular cartilage changes in the knee-joint cartilage while 30 mg/kg resulted in slight

focal degenerative change in the tibial knee-joint cartilage. No treatment-related ophthalmological changes were found.

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