PRODUCT MONOGRAPH

PrRAN-CIPROFLOXACIN

Ciprofloxacin Hydrochloride Tablets, USP

250 mg, 500 mg, 750 mg Ciprofloxacin

Antibacterial agent

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Ciprofloxacin Hydrochloride Tablets, USP

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THERAPEUTIC CLASSIFICATION

Antibacterial agent

ACTIONS 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[30].

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.

Ciprofloxacin and metronidazole have been studied in combination and serum levels of ciprofloxacin are not significantly altered by metronidazole at the doses studied. Serum

levels of metronidazole when administered orally at a dose of 500 mg q6h in combination with ciprofloxacin 500 mg PO q12h are: AUC_{0-6} 156.3 mg.h/L, C_{max} 31.3 mg/L and T_{max} 1.71 hours. Serum levels of metronidazole when administered intravenously at a dose of 500 mg i.v. q6h in combination with ciprofloxacin 400 mg i.v. q12h are: AUC_{0-6} 153.0 mg.h/L, C_{max} 33.6 mg/L and T_{max} 1.0 hours (see **HUMAN PHARMACOLOGY**).

BIOAVAILABILITY

A randomized, two-way crossover, single-dose bioavailability study was conducted in fasting healthy, adult male subjects. The bioavailability of**RAN-CIPROFLOXACIN** tablets, 750 mg, relative to Cipro® tablets, 750 mg, was determined following a single 1 x 750 mg dose. The average values of the pharmacokinetic parameters, as well as ratio of means (with 90% confidence intervals) are listed in the following table:

Table 1:

Summary Table of the Comparative Bioavailability Study of **RAN-CIPROFLOXACIN** vs Cipro®, ciprofloxacin hydrochloride 750 mg tablets conducted under fasting conditions in 20 healthy adult male volunteers (from measured data)

Parameter	Geometric Mean Arithmetic Mean (CV%)		Ratio of Geometric Means (%) (90% Confidence Limits)
	ratio-CIPROFLOXACIN	Cipro®**	
AUCt (ng.h/mL)	14289.40 14544.67 (19.1)	13935.71 14354.45 (23.1)	102.5 (98.2 - 107.1)
AUCinf (ng.h/mL)	14760.73 15039.86 (19.7)	14389.27 14836.83 (23.6)	102.6 (98.2 - 107.2)
C_{max} (ng/mL)	2777.73 2817.89 (17.2)	2619.31 2714.28 (25.1)	106.1 (98.9 - 113.8)
T_{max}* (h)	1.41 (35.9)	1.75 (32.1)	---
$T_{½}$* (h)	5.06 (10.5)	5.05 (9.2)	---

**The T_{max} and $t_{½}$ parameters are expressed as the arithmetic means.*
***Cipro® is manufactured by Bayer and was purchased in Canada.*

Conclusion: The 90% confidence intervals for the ln-transformed parameters AUCt, AUCinf and Cmax for ciprofloxacin were within the 80-125% TPD acceptance range both before and after correction for measured content. Based on these results, **RAN-CIPROFLOXACIN** and Cipro® (ciprofloxacin hydrochlroride) 750 mg tablets are considered bioequivalent under single-dose fasting conditions.

INDICATIONS AND CLINICAL USE

Oral administration: RAN-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, **RAN-CIPROFLOXACIN** (ciprofloxacin hydrochloride tablets) 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 *Eschericia Coli.*

Chronic Bacterial Prostatitis: Caused by: *Escherichia coli.*

Skin and Soft Tissue Infections: Caused by: *Enterobacter cloacae, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus 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 *Clamydia trachomatis* is common,

consideration should be given to treating presumptively with an additional regimen that is effective against *Clamydia trachomatis*.

CONTRAINDICATIONS

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

WARNINGS

Children

The safety of **RAN-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, **RAN-CIPROFLOXACIN** (ciprofloxacin hydrochloride tablets) should not be used in prepubertal patients[27]. Experience in pubertal patients below 18 years of age is limited.

Pregnancy

The safety of **RAN-CIPROFLOXACIN**(ciprofloxacin hydrochloride tablets) 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 hydrochloride tablets. 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 tendonitis (i.e., painful swelling), the administration of ciprofloxacin whould 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. Therefore, it is important to consider this diagnosis in patients with diarrhea subsequent to the administration of antibacterial agents. Subsequent to diagnosis of pseudomembranous colitis, therapeutic measures should be initiated. Mild cases will usually respond to discontinuation of drug alone. In moderate to severe cases, consideration should be given to the management with fluids, electrolytes, protein supplementation and treatment with an antibacterial drug effective against *C. difficile.*

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 photosensitisation (ie. sunburn-like skin reactions) occur.

Prolonged use of ciprofloxacin hydrochloride tablets 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 hydrochloride tablets in pregnancy has not yet been established. Ciprofloxacin hydrochloride tablets should not be used in pregnant women unless the likely benefits outweigh the possible risk to the fetus. Ciprofloxacin hydrochloride tablets have 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 hydrochloride, 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.[24]

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 hydrochloride tablets 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 kidneys, ciprofloxacin hydrochloride tablets 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 diarrhea were observed in this patient population.

ADVERSE REACTIONS

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

Adverse events, possibly, probably or highly probably related to ciprofloxacin occurred in 1395 (8.8%) of patients. The adverse reactions according to treatment (oral) show that the incidence of adverse reactions was 8.0% for the group treated orally.

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

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

Blood and Blood Constituents agranulocytosis, anemia, eosinophilia, granulocytopenia, leukocytopenia, leukocytosis, pancytopenia,. Very rarely: altered prothrombin levels, hemolytic anemia, 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, hemorrhagic 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 hydrochloride. In these instances, ciprofloxacin hydrochloride has to be discontinued and the physician 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, hematuria, 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 hydrochloride. 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: tongue discoloration, colitis, gastritis.

Hemic and Lymphatic: coagulation disorder, thrombocythemia.

Skin: fungal dermatitis, pustular rash, sweating.

Metabolic: hypernatremia, healing abnormal.

Nervous: dementia.

Urinary: kidney tumour necrosis, urinary incontinence.

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-defense mechanisms, and the status of renal function.

RAN-CIPROFLOXACIN (ciprofloxacin hydrochloride tablets) 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 dosages of oral **RAN-CIPROFLOXACIN** (ciprofloxacin hydrochloride tablets) are:

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 & Joint** **Skin & Soft Tissue**	Mild/Moderate Severe*/Complicated	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

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

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

Definitive clinical studies have not been completed for severe infections other than in the respiratory tract.

The duration of treatment depends upon the severity of infection. Generally ciprofloxacin should be continued for at least 3 days after the signs and symptoms of infection have disappeared. The usual duration is 7 to 14 days. However for severe and complicated infections more prolonged therapy may be required. Bone and joint infections may require treatment for 4 to 6 weeks or longer.

Sequential I.V./P.O. Therapy

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

Impaired Renal function

Ciprofloxacin is eliminated primarily by renal excretion. However, the drug is also metabolized and partially cleared through the biliary system of the liver and through the intestine (see **HUMAN PHARMACOLOGY**). This alternate pathway of drug elimination appears to compensate for the reduced renal excretion of patients with renal impairment. Nonetheless, some modification of dosage is recommended, particularly for patients with severe renal dysfunction. The following table provides a guideline for dosage adjustment. However, monitoring of serum drug levels provides the most reliable basis for dosage adjustments. Only a small amount of ciprofloxacin (<10%) is removed from the body after hemodialysis or peritoneal dialysis.

Creatinine clearance mL/min/1.73m²	Maximum Daily Dose		Serum Creatinine concentration mg/100 mL
	Oral	I.V.	
31-60	1000 mg	800 mg	1.4-1.9
≤30	500 mg	400 mg	≥2.0

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

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

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 hydrochloride tablets in children has not been established. Ciprofloxacin hydrochloride tablets should not be used in prepubertal patients (see **WARNINGS**).

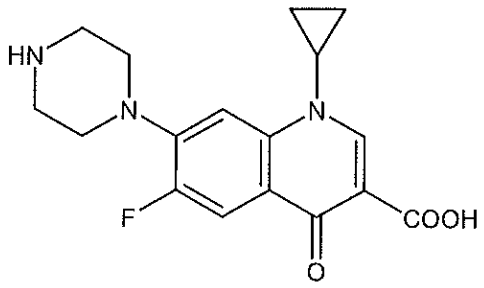
PHARMACEUTICAL INFORMATION

Drug substance

Proper name: Ciprofloxacin hydrochloride

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

Structural formula:



. HCl . H_2O

Molecular formula: $C_{17}H_{18}FN_3O_3HCl\ H_2O$

Molecular weight; 385.8

Description: Ciprofloxacin hydrochloride is a pale yellow crystalline powder. It is soluble in water. Its solubility in aqueous buffer of pH 7.4 at 21°C is 0.19 g/L, while the solubility is considerably higher at slightly acidic or slightly alkaline pH. At 140°C water of crystallisation 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 of 25°C.

COMPOSITION:

RAN-CIPROFLOXACIN 250 mg tablets contain: ciprofloxacin hydrochloride equivalent to 250 mg ciprofloxacin.**Non-medicinal ingredients in alphabetical order:** hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polydextrose, polyethylene glycol, pregelatinized corn starch, silicon dioxide, sodium starch glycolate, titanium dioxide and triacetin.

RAN-CIPROFLOXACIN 500 mg tablets contain: ciprofloxacin hydrochloride equivalent to 500 mg ciprofloxacin**Non-medicinal ingredients in alphabetical order:**hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polydextrose, polyethylene glycol, pregelatinized corn starch, silicon dioxide, sodium starch glycolate, titanium dioxide and triacetin.

RAN-CIPROFLOXACIN 750 mg tablets contain: ciprofloxacin hydrochloride equivalent to 750 mg ciprofloxacin. **Non-medicinal ingredients in alphabetical order:**hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polydextrose, polyethylene glycol, pregelatinized corn starch, silicon dioxide, sodium starch glycolate, titanium dioxide and triacetin.

AVAILABILITY OF DOSAGE FORMS AND STORAGE RECOMMENDATIONS

RAN-CIPROFLOXACIN (ciprofloxacin hydrochloride) 250 mg tablets are white, coated and engraved with C93 on one side and rph on the other side. Packaged in bottles of 100.

RAN-CIPROFLOXACIN (ciprofloxacin hydrochloride) 500 mg tablets are white, coated and engraved with C92 on one side and rph on the other side. Packaged in unit dose packages of 100 and bottles of 100.

RAN-CIPROFLOXACIN (ciprofloxacin hydrochloride) 750 mg tablets are white, coated and engraved with C91 on one side and rph on the other side. Packaged in bottles of 50.

For bottles - Store between 15° and 30°C.

For blisters: Store between 15 and 30°C. Protect from light.

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

		mg/L												
Genera or Species	**(Number of Strains)**	**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												
Enterobacter aerogenes	(5)	50	83		100									
Enterobacter agglomerans	(2)	100												
Enterobacter cloaceac	(49)	61	86	96	100									
Escherichia coli	(203)	84	92	93	96	98	99	100						
Flavobacterium brevie	(3)						66	100						
Fusobacterium spp.	(8)					25.0	50.0		75.0	87.5	100			
Haemophilus ducreyi	(72)	100												
Haemophilus influenzae beta-lactamase positive	(50)		90	100										
Klebsiella oxytoca	(32)	78	97		100									
Klebsiella pneumonia	(40)	21	72	85	90	97	100							
Klebsiella species	(24)	33	88	92		96	100							
Morganella morganii	(12)	92	100											
Moraxella spp.	(5)		20		40	60	80	100						
Neisseria gonorrhoeae beta-lactamase negative	(15)		13	73	87	100								

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Genera or Species	**(Number of Strains)**	**0.015**	**0.03**	**0.06**	**0.12**	**0.25**	**0.5**	**1**	**2**	**4**	**8**	**16**	**32**	**64**
Propionibacterium spp.	(42)				2.4	28.6	88.1	92.9	100					
Proteus mirabilis	(57)	28	88	93	98	100								
Proteus vulgaris	(3)	100												
Providencia alcalifaciens	(6)	33					66		100					
Providencia rettgeri	(5)		80		100									
Providencia stuartii	(16)	6	25	38	50	56	75		100					
Pseudomonas aeruginosa	(187)	1	2	7	41	65	83	89	96		98	100		
Pseudomonas aeruginosa (Fibrocystic mucoid strain)			3	20	43	63	80	100						
Pseudomonas aeruginosa (Fibrocystic non-mucoid strain)	-(30)			13	50	93	100							
Pseudomonas aeruginosa (Bacteremic non-cystic strain)			3	57	88	100								
Pseudomonas cepacia	(10							50	100					
Pseudomonas fluorescens	(8)				50	75	100							
Pseudomonas maltophilia	(11)			9			36	55	64	82	91	100		
Salmonella spp.	(81)		33	68	96	100								
Serratia marcescens	(12)		50	100										
Shigella spp.	(59)		97	98	98	100								
Shigella sonnei	(45)	100												
Staphylococcus aureus	(101)		2	5	15	52	95	100						
Staphylococcus epidermidis	(64)	5		6	28	84	95	100						
Streptococcus faecalis	(39)						31	87	100					
Streptococcus pneumoniae	(51)					9	27	100						
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, *Straphylococcus aureus K734, Straphylococcus 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[3].

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	5×10^3	5×10^6
Staphylococcus aureus K 734	4.0	0.5	0.5	0.25	0.5
Staphylococcus epidermidis H 846	2.0	0.25	0.25	0.125	0.25
Streptococcus faecalis 7149	8.0	1.0	1.0	0.5	2.0
Escherichia coli 2345	0.5	0.016	0.016	0.008	0.016
Proteus mirabilis 2349	1.0	0.03	0.016	0.008	0.03

(a) Mueller Hinton broth (BBL) 5×10^5 cfu/mL.
(b) No difference between the 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[28/29].

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, 10^5cfu/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	$1 \times <10^{-9}$
	8	$1 \times <10^{-9}$
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	$1 \times <10^{-9}$
	8	$1 \times <10^{-9}$
Serratia marcescens (0.2)	4	$1 \times <10^{-9}$
	8	$1 \times <10^{-9}$
Staphylococcus aureus (0.4)	4	1.82×10^{-7}
	8	1.67×10^{-8}
Streptococcus faecalis (0.8)	4	$1 \times <10^{-9}$
	8	$1 \times <10^{-9}$

(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 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 resistant 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 ß-Lactams and Aminoglycosides

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

The MIC's of piperacillin and cefoperazone were >128 mg/L for all organisms. (Clinical isolates from urine – both agar and broth dilution tests were used, 10^5 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

	Number of test strains which the combination was				
	Synergistic	additive – indifferent			antagonistic
Combination	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 Disks 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	Disk Zone Diameter (mm)	MIC (mg/L)
S. aureus (ATCC 25923)	22-30	-
S. aureus (ATCC 29213)	-	0.25-1.0
E. coli (ATCC 25922)	30-40	0.008-0.03
P. aeruginosa (ATCC 27853)	25-33	0.25-1.0
N. gonorrhoeae (ATCC 49226)	48-58	≤ 0.008

PHARMACOLOGY

ANIMAL PHARMACOLOGY

Effects on histamine release

Ciprofloxacin was administered intravenously to 9 anesthetized 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 anesthesia at doses of 0, 10, 20 and 100 mg/kg. No effects were observed on neuromuscular transmission, flexor reflex, or blood pressure.

Gastrointestinal Effects

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

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

Effect on Blood Glucose and Serum Triglycerides

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

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

HUMAN PHARMACOLOGY

Pharmacokinetics

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

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

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

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

An intravenous infusion of 400 mg ciprofloxacin given over 60 minutes every 12 hours, for 6 doses, to 12 healthy male volunteers (18-40 years) has been shown to produce an area under the serum concentration time curve (AUC) equivalent to that produced by a 500 mg oral dose given every 12 hours. The 400 mg iv dose administered over 60 minutes every 12 hours resulted in a C_{max} similar to that observed with a 750 mg oral dose.

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

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

Table 6

Pharmacokinetic Parameters of Ciprofloxacin Following Single Doses in Healthy Volunteers Oral

Dose	250 mg	500 mg	750 mg
C_{max} (mg/L)	1.42	2.60	3.41
T ½ (hr)	4.19	4.87	5.34
$AUC_{0-\infty}$ (mg•h/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

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

Regimen	AUC (mg.h/L)	C_{max} (mg/L)	T_{max} (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

Figure 1

Mean Ciprofloxacin Serum Concentration After Single Oral Doses

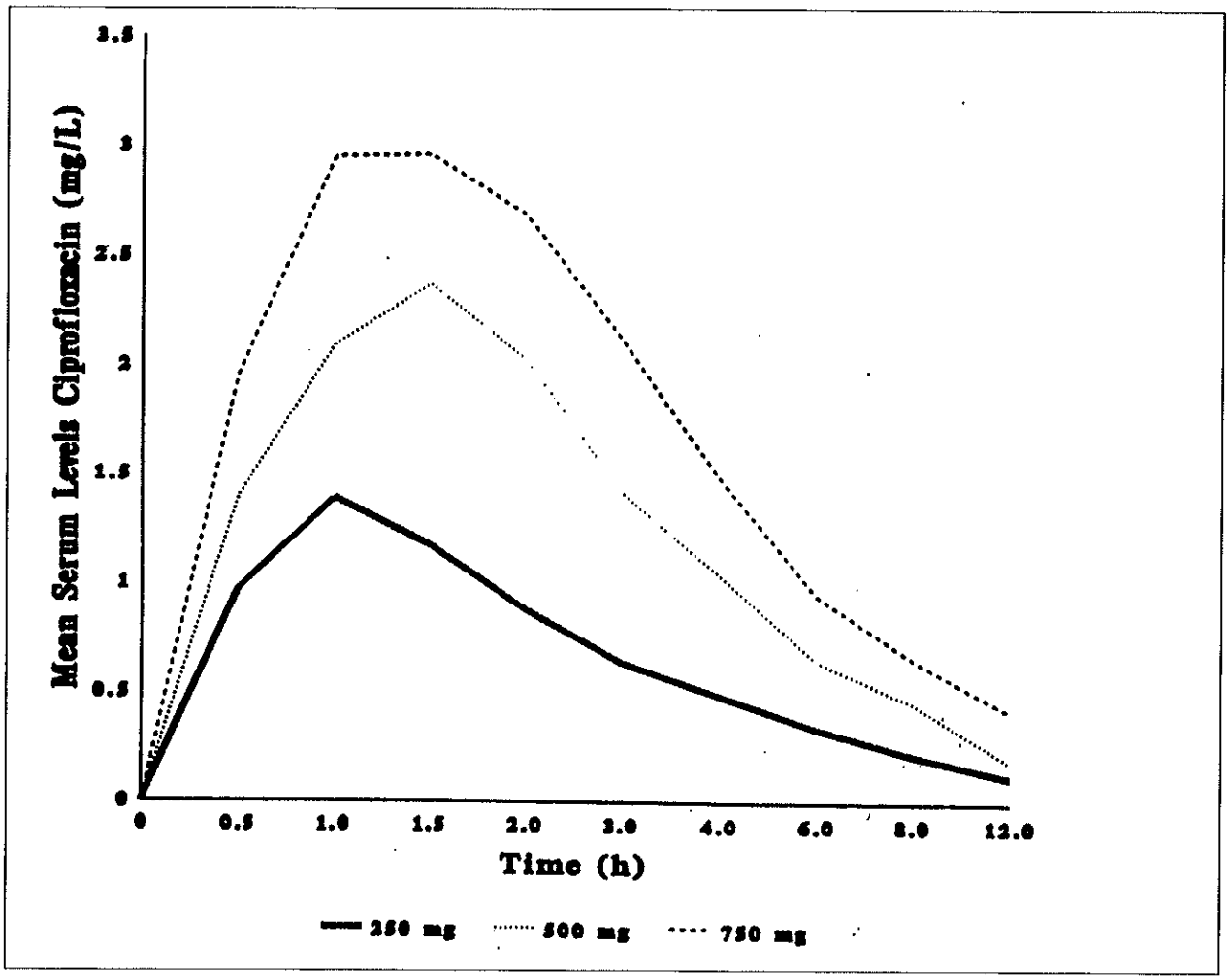

Table 8

Mean Urinary Excretion of Ciprofloxacin

Hours After Administration of a Single Dose				
	0 - 2	2 - 4	4 - 8	8 - 12
Urine Concentration mg/L (± S.D.)				
250 mg po	205 (±89)	163 (±145)	101 (±65)	32 (±28)
500 mg po	255 (±204)	358 (±206)	117 (±86)	26 (±10)
750 mg po	243 (±143)	593 (±526)	169 (±131)	55 (±36)
Amount Excreted mg (± S.D.)				
250 mg dose	54.38 (±36.22)	26.79 (±11.78)	22.84 (±6.79)	8.90 (±4.25)
500 mg dose	64.51 (±25.06)	47.37 (±15.65)	39.54 (±11.17)	15.52 (±5.39)
750 mg dose	68.90 (±41.85)	72.43 (±33.13)	61.07 (±21.68)	28.11 (±7.64)

Metabolism and Excretion

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

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

dose, respectively. Total (urine and feces) excretion of all metabolites was 18.8%.

Direct evidence of biliary excretion of ciprofloxacin was obtained in 12 patients (age 28-58) with T-tube drainage. A peak biliary concentration of 16 mg/L was seen 4 hours after a single oral dose of ciprofloxacin 500 mg.

FACTORS INFLUENCING THE PHARMACOKINETICS

Age (Elderly)

In 4 females and 6 males, (age: 67 ± 4 years, weight: 65 ± 6 kg) with normal renal function for their age, given a single oral dose of 250 mg, maximum ciprofloxacin serum concentrations and areas under the serum concentration time curves were significantly higher than in 10 male younger volunteers (age: 24 ± 3 years, weight: 72 ± 9 kg). The time to peak serum concentrations, overall elimination half-life and urinary recovery of ciprofloxacin were similar in both age groups.

Table 9

Comparison of pharmacokinetic parameters between healthy elderly and healthy younger volunteers

Parameter	Elderly Volunteers (mean ± S.D.)	Younger Volunteers (mean ± S.D.)
C_{max} (mg/L)	1.8 ± 0.5	1.3 ± 0.4
T_{max} (hr)	1.2 ± 0.3	1.2 ± 0.1
T ½ (hr)	3.7 ± 0.9	3.3 ± 0.6
Total AUC (mg.h/L)	7.25 ± 2.45	5.29 ± 1.21
% Dose Urinary Recovery after 24 hours	43	43

Impaired Renal Function

Since ciprofloxacin is eliminated primarily by the kidneys, 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 1, 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 hemodialysis (**see Group III, Table 10**). Patients with renal insufficiency had significantly increased AUCs, prolonged (about 2-fold) elimination half-lives, and decreased renal clearances.

Hemodialysis 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 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)	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 (± 041)	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)		

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

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	1.4	± 0.87	2-4
			to				
			1.6	± 0.97			
Prostatic Tissue	1	500 mg po	3.76		1.84		2.5
Muscle	4	250 mg po	2.4	± 1.0	2.9	± 2.2	2-4
Nasal Secretions	20	500 mg po	1.4	± 0.81	1.8	± 0.48	1-3

TOXICOLOGY

Acute Toxicity

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

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

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

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

Short-term Toxicity

Groups of 10 male and 10 female Wistar rats each, strain Bor: WISW, were given ciprofloxacin hydrochloride in doses of 0, 5, 20, or 80 mg/kg/day intraperitoneally for 4 weeks. After administration of 80 mg/kg/day, evidence of mechanically caused nephropathy was found. This was associated with a slight effect on the kidney function (increased BUN) Crystal-like precipitates were found in the distal tubules and were probably responsible for the mechanical tubule obstruction. The urine sediment was found also to contain crystals. On the basis of morphological criteria, the crystalline precipitates in the tubule lumens and those in the urine sediment were regarded as identical. They were probably caused by the low solubility of the ciprofloxacin at neutral pH values. Groups of 2 male and 2 female beagles each were given ciprofloxacin hydrochloride orally in doses of 0, 40, or 80 mg/kg/day for 4 weeks. Ciprofloxacin was administered orally, in gelatin capsules. Both doses produced swelling of the soft tissue in the region of the head, reddening, and pruritus after the very first dose. This oral intolerability improved substantially after the administration of ciprofloxacin in lacquered capsules. All the other investigations, 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 hematological 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 males and 60 females per group) by a stomach tube, in doses of 0, 10, 30, or 100 mg/kg/day. Treatment was commenced in the males 10 weeks before mating and in the females 3 weeks before mating and was continued in the females up to the 7th day of gestation. Doses up to 100 mg/kg/day ciprofloxacin had no effects on fertility; the intrauterine and postnatal development of the young and the fertility of the 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 had no embryotoxic or teratogenic effects. In a parenteral study on rats, strain Bc-WISW, (25 per group) ciprofloxacin hydrochloride at doses of 0, 3, 10, or 30 mg/kg/day was administered intravenously from day 6 to day 15 of gestation. Caesarean sections were performed on the 20th day of gestation. In addition, 2 groups of animals were given doses of 0 or 30 mg/kg/day for the same period but were allowed to litter normally and to rear their young for a period of 3 weeks. It was found that all the doses tested had neither embryotoxic nor teratogenic effects. No effects on the postnatal development of the reared young were observed.

(c) Rabbits

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

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

Perinatal and Postnatal Studies

Pregnant SPF rats, strain Mura: WIST, (50 per group) were given ciprofloxacin hydrochloride orally in doses of 0, 10, 30 or 100 mg/kg/day. Treatment of the dams commenced on the 16 th day of gestation. Caesarean sections were performed on 50 percent 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 12 for details)**

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

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

***In vivo* (see Table 12 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 12

Mutagenicity Studies Summary

IN VIVO TEST	Strain	Positive Control and Dose	Ciprofloxacin	Dose
Micronucleus Test	Bor: NMR1 Mice	Endoxan-72.5 µg/kg once, oral	4,000 mg/kg ----- 1,000 mg/kg 2,000 mg/kg 4,000 mg/kg	one, oral ----- one, oral one, oral one, oral
Dominant Lethal Test	Bor: NMR1 Mice	Negative Control Only	4,000 mg/kg	one, oral
Rat Hepatocyte DNA Repair Test	F344 Male Fisher rat	2-acetylaminofluorene 10 mg/kg i.v.	30 mg/kg	one, i.v.

IN VITRO TEST	Positive Control and Concentration		Ciprofloxacin Concentration
Salmonella/Microsome Test (Ames)	Endoxan Trypaflavine 2-Aminoanthracene	145µg/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	5×10^{-1} mg/mL to 1.25×10^{-2} mg/mL
Mouse Lymphoma Test	Ethylmethane sulfonate Methylcholanthrene	0.3 µL/mL – 0.4 µL/mL 2 µL/mL – 4 µL/mL	10 µL/mL – 500 µL/mL
Hamster V79 HGPRT Assay	Ethylmethane sulfonate 9,10-dimethyl-1, 2-benzenthracene	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 histopathological eye examinations were performed to assess the possibility of oculotoxicity. Ciprofloxacin induced marginal degenerative damage to the articular cartilage after the administration of the highest dose (500 mg/kg) and only in 1 of the 20 animals used. Doses up to 250 mg/kg/day were tolerated without any harmful effects. Ciprofloxacin caused no discernible ophthalmoscopic or histopathological damage to the eye.

In the dog study, groups of 2 male and 2 female beagles each, aged between 13 and 14 weeks were used. Ciprofloxacin hydrochloride was administered in gastric-juice-resistant gelatin capsules at doses of 0, 30, 70 or 100 mg/kg/day for 4 weeks. Histopathological

examination revealed primary degenerative articular changes in the knee joint and hip joint cartilages at all doses tested. Severity of degenerative changes was dose-related with 100 mg/kg resulting in moderate primary degenerative articular cartilage changes in the knee-joint cartilage while 30 mg/kg resulted in slight focal degenerative change in the tibial knee-joint cartilage. No treatment-related ophthalmological changes were found.

REFERENCES

1. Aigner KR, Dalhoff A. Penetration activities of ciprofloxacin into muscle, skin and fat following oral administration. J. Antimicrob Chemother 1986; 18: 644-645.

2. Aldridge KE, Schiro DD, Tsai L, Janney A, Sanders CV, Marier RL. Ciprofloxacin (BAY o 9867) and *in vitro* comparison with other broad spectrum antibiotics. Curr Ther Res 1985; 37 (4): 754-762.

3. Auckenthaler R, Michea-Hamzehpour M, Pechere JC. *In vitro* activity of newer quinolones against aerobic bacteria. J Antimicrob Chemother 1986; 17 (Suppl. B): 29-39.

4. Barry AL, Fass RJ, Anhalt JP, Neu HC, Thornsberry C, Tilton RC, Painter BG, Washington JA. Ciprofloxacin disk susceptibility tests: interpretive zone size standards for 5 µg disks. J Clin Microbiol 1985; 21 (6): 880-883.

5. Bauernfeind A, Petermuller C. *In vitro* activity of ciprofloxacin, norfloxacin and nalidixic acid. Eur J Clin Microbiol 1983; 2 (2): 111-115.

6. Bayer A, Gajewska A, Stephens M, Marshal-Stark J, Pathy J. Pharmacokinetics of ciprofloxacin in the elderly. Respiration 1987; 51: 292-295.

7. Beermann D, Scholl H, Wingender W, Forster D, Beubler E. Metabolism of ciprofloxacin in man. In Neu HC & Weuta H (Eds) 1 st International Ciprofloxacin Workshop, Leverkusen 1985, pp. 141-146, Excerpta Medica, Amsterdam, 1986.

8. Crump B, Wise R, Dent J. Pharmacokinetics and tissue penetration of ciprofloxacin. Antimicrob Agents Chemother 1983; 24 (5): 784-786.

9. Fass RJ. Efficacy and safety of oral ciprofloxacin for treatment of serious urinary tract infections Antimicrob Agents Chemother 1987; 31: 148-150.

10. Fass RJ. Efficacy and safety of oral ciprofloxacin in the treatment of serious respiratory infections. Am J Med 1987; 82 (Suppl 4A): 202-207.

11. Fass RF. Treatment of skin and soft tissue infections with oral ciprofloxacin. J Antimicrob Chemother 1986; 18 (Suppl. D): 153-157.

12. Fong IG, Ledbetter WH, Van en broucke C, Simbul M, Rahm V. Ciprofloxacin concentrations in bone and muscle after oral dosing. Antimicrob Agents Chemother 1986; 29: 405-408.

13. Gasser TC, Ebert SC, Graversen PHm, Madsen PO. Ciprofloxacin pharmacokinetics with normal and impaired renal function. Antimicrob Agents and Chemother 1987; 31: 709-712.

14. Giamarellou H, Galanakis N, Dendrinos C, Stefanou J, Daphnis E. Evaluation of ciprofloxacin in the treatment of *Pseudomonas aeruginosa* infections. Eur J Clinical Microbiol 1986; 5: 232-235.

15. Gonzalez MA, Moranchel AH, Duran S, Pichardo A, Magana JL. Multiple dose ciprofloxacin dose ranging and kinetics. Clin Pharmacol Ther 1985; 37: 633-637.

16. Greenberg RN, Kennedy DJ, Reilly PM, Luppen KL, Weinandt WJ. Treatment of bone, joint and soft tissue infections with oral ciprofloxacin. Antimicrob Agents Chemother 1987; 31: 151-155.

17. Greenberg RNM, Tice AD, Marsh PK, Craven PC, Reilly PM. Randomized trial of ciprofloxacin compared with other antimicrobial therapy in the treatment of osteomyelitis. Am J Med 1987; 82 (Suppl. 4A): 266-269.

18. Honeybourne D, Wise R, Andrews JM. Ciprofloxacin penetration into lungs. Lancet 1987; 2031: 1040.

19. LeBel M, Bergeron MG, Vallee F, Fiset C, Chasse G. Pharmacokinetics & Pharmacodynamics of ciprofloxacin in cystic fibrosis patients. Antimicrob Agents Chemother 1986; 30: 260-266.

20. Ledergerber B, Bettex JD, Joos B, Flepp M, Luethy R. Effect of standard breakfast on drug absorption and multiple-dose pharmacokinetics of ciprofloxacin. Antimicrob Agents Chemother 1985; 27 (3): 350-352.

21. Licitra CM, Brooks RG, Siegler BE. Clinical Efficacy and levels of ciprofloxacin in tissue in patients with soft tissue infection. Antimicrob Agents Chemother 1987; 31: 805-807.

22. National Committee for Clinical Laboratory Standards 1987. Performance standards for antimicrobial susceptibility testing; Second Informational Supplement. NCCLS document M100-S2. Villanova, Pa.

23. Ramirez-Ronda CH, Saavedra S, Rivera-Vazques CR. Comparative, double-blind study of oral ciprofloxacin and intravenous cefotaxime in skin and skin structure infections. Am J Med 1987; 82 (suppl. 4A): 220-223.

24. Raoof S, Wollschager C, Khan FA. Ciprofloxacin increases serum levels of theophylline. Am J Med 1987; 84 (Suppl. 4A): 115-118.

25. Ratcliffe NT, Smith JT. Effects of magnesium on the activity of 4-quinolone antibacterial agents. J Pharm Pharmacol 1983; 35 (Suppl): 61P.

26. Schacht P, Arcieri G, Branolte J, Bruck H, Chysky V. Worldwide Clinical Data on Efficacy and Safety of Ciprofloxacin. Infection, 1988; (Suppl. 1), 16: 29-43.

27. Schluter G. Toxicology of ciprofloxacin. In Neu HC, Weuta H (Eds) 1st International Ciprofloxacin Workshop, Leverkusen 1985, pp. 291-296, Excerpta Medica, Amsterdam, 1986.

28. Smith JT. The mode of action of 4-quinolones and possible mechanisms of resistance. J Antimicrob Chemother 1986; 18 (Supp. D.): 21-29.

29. Wolfson JS, Hooper DC, The fluoroquinolones: Structures, Mechanisms of Action and Resistance, and Spectra of Activities *in Vitro*. Antimicrob Agents Chemother 1985; 28 (4): 581-586.

30. Zeiler H-J. Evaluation of the *In Vitro* Bactericidal Action of Ciprofloxacin on Cells of Escherichia Coli in the Logarithmic and Stationary Phases of Growth. Antimicrob Agents Chemother 1985; 28 (4): 524-527.

31. Cox CE. Brief Report: Sequential Intravenous and Oral Ciprofloxacin versus Intravenous Ceftazidime in the Treatment of Complicated Urinary Tract Infections. Am J Med 1989; 87 (5a): 157S-159S.

32. Menon L, Ernst JA, Sy ER, Flores D, Pacia A, Lorian V. Brief Report: Sequential Intravenous/Oral Ciprofloxacin Compared with Intravenous Ceftazidime in the

Treatment of Lower Respiratory Tract Infections. Am J Med 1989; 87 (5a): 119S-120S.

33. Thorsteinsson SB, Bergan T, Johannesson G, Thorsteinsson HS, Rohwedder R. Tolerance of Ciprofloxacin at Injection Site, Systemic Safety and Effect of Electroencephalogram. Chemotherapy 1987; 33: 448-451.

34. Honeybourne D, Andrews JM, Ashby JP, Lodwick R, Wise R. Evaluation of the penetration of ciprofloxacin and amoxycillin into the bronchial mucosa. From the Departments of Thoracic Medicine and Microbiology, Dudley Road Hospital, Birmingham, June 1, 1988.

35. Houghton G, thorne PS, Smith J, Templeton R. *et al.* The Pharmacokinetics of Intravenous metronidazole (single and multiple dosing). Royal Society of Medicine International Congress and Symposium Series No. 18.

36. Product Monograph, Cipro®, Cipro® I.V., Cipro® I.V. Minibag, Cipro® Oral Suspension, Antibacterial Agent, Bayer Inc., Date of Revision: March 11, 2003