PRODUCT MONOGRAPH

Pr CIPROFLOXACIN INJECTION

Ciprofloxacin 0.2 % Intravenous Infusion

Ciprofloxacin 0.2 % (as lactate) in 5 % dextrose solution

Sterile

Antibacterial Agent

SteriMax Inc.
2770 Portland Drive
Oakville, Ontario
L6H 6R4

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PART I: HEALTH PROFESSIONAL INFORMATION SUMMARY PRODUCT INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
Intravenous	Intravenous Infusion Solution (2 mg/mL)	Lactic Acid Dextrose Hydrochloric Acid Water for injection

INDICATIONS AND CLINICAL USE

CIPROFLOXACIN INJECTION (Ciprofloxacin 0.2% Intravenous Infusion) may be indicated for the treatment of patients with the following infections caused by susceptible strains of the indicated microorganisms:

Respiratory Tract Infections

Acute pneumonia caused by:
Enterobacter cloacae
Escherichia coli
Haemophilus influenzae
Haemophilus parainfluenzae
Klebsiella pneumonia
Proteus mirabilis
Pseudomonas aeruginosa
Staphylococcus aureus
Streptococcus pneumoniae

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

subsequent courses of therapy, 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.

Septicemia
Caused by:
Escherichia coli
Salmonella typhi

Bone
Caused by: *Enterobacter cloacae*
Pseudomonas aeruginosa

Complicated intra-abdominal infections only when used in combination with metronidazole:
(See DOSAGE AND ADMINISTRATION)

Caused by:
Escherichia coli
Pseudomonas aeruginosa
Klebsiella pneumoniae
Bacteroides fragilis

Note: Most anaerobic bacteria, including *Bacteroides fragilis*, are resistant to ciprofloxacin. Therefore, ciprofloxacin should not be used as single agent therapy for complicated intra- abdominal infections. Efficacy against *Enterococcus* sp. in clinical trials has been shown to be only 75%.

Empiric Therapy in Febrile Neutropenic Patients (in combination with piperacillin sodium)
(see DOSAGE AND ADMINISTRATION)

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

Geriatrics (> 65 years of age):
Ciprofloxacin is known to be substantially excreted by kidney, and the risk of adverse reactions may be greater in patients with impaired renal function. No alteration of dosage is necessary for patients greater than 65 years of age with normal renal function. However, since some older individuals experiences reduced renal function by virtue of their advanced age, care should be taken in dose selection for elderly patients, and renal function monitoring may be useful in these patients **(See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION)**

Pediatrics:
The safety of CIPROFLOXACIN INJECTION (Ciprofloxacin 0.2% Intravenous Infusion) in pediatric patients 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 pediatric patients and adolescents.

CONTRAINDICATIONS
CIPROFLOXACIN INJECTION (Ciprofloxacin 0.2% Intravenous Infusion) is contraindicated in patients who have shown hypersensitivity to ciprofloxacin or other quinolone antibacterial agents or any of the excipients.

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

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- **The safety of CIPROFLOXACIN INJECTION in pediatric patients and adolescents (under the age of 18 years), pregnant women and nursing women has not been established.**
- **Serious and fatal reactions have been reported in patients receiving concurrent administration of Ciprofloxacin Injection and theophylline.**
- **Damage to juvenile weight-bearing joints and lameness were observed both in rats 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**

<u>Cardiac Disorders</u>
Ciprofloxacin has been shown to prolong the QT interval of the electrocardiogram in some

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

Central Nervous System (CNS) and Psychiatric Effects

Seizures and toxic psychoses may occur with quinolone therapy. Convulsions, increased intracranial pressure (including pseudotumor cerebri), and toxic psychoses have been reported in patients receiving quinolones, including Ciprofloxacin. Cases of status epilepticus have also been reported. Ciprofloxacin Injection may also cause central nervous system (CNS) stimulation which may lead to dizziness, tremors, restlessness, lightheadedness, confusion, hallucinations, depression, nervousness, agitation, insomnia, anxiety, paranoia, nightmares and rarely, suicidal thoughts or acts. In some cases, depression or psychotic reactions can progress to suicidal ideations/thoughts and self-injurious behavior, such as attempted suicide or completed suicide. These reactions may occur even following the first dose of ciprofloxacin. If any of these reactions occur in patients receiving ciprofloxacin, the drug should be discontinued and appropriate measures instituted. CIPROFLOXACIN INJECTION should be used with caution in patients with known or suspected CNS disorders which may predispose to seizures or lower the seizure threshold (eg, severe cerebral arteriosclerosis, epilepsy), or in the presence of other risk factors that may predispose to seizures or lower the seizure threshold (eg, certain drug therapy, renal dysfunction) (see **ADVERSE REACTIONS**).

Cytochrome P450

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

Hypersensitivity

Serious hypersensitivity and/or anaphylactic reactions have been reported in patients receiving quinolone therapy, including ciprofloxacin (see **ADVERSE REACTIONS**). These reactions may occur within the first 30 minutes following the first dose and may require epinephrine and other emergency measures. Some reaction have been accompanied by cardiovascular collapse, hypotension/shock, seizure, loss of consciousness, tingling, angioedema (including tongue, laryngeal, throat or facial edema/swelling), airway obstruction (including bronchospasm, shortness of breath and acute respiratory distress), dyspnea, urticaria, itching and other serious skin reactions. Ciprofloxacin should be discontinued at the first appearance of a skin rash or any other sign of

hypersensitivity. Serious acute hypersensitivity reactions may require treatment with epinephrine and other resuscitative measures, including oxygen, intravenous fluids, antihistamines, corticosteroids, pressor amines and airway management, as clinically indicated.

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

Gastrointestinal

Clostridium difficile-associated disease

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

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

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

Endocrine and Metabolism

Disturbances of Blood Glucose

Disturbances of blood glucose, including symptomatic hyper- and hypoglycemia, have been reported with the use of quinolones, including Ciprofloxacin (see **ADVERSE REACTIONS**).

Hepatic/Biliary/Pancreatic

Cases of hepatic necrosis and life-threatening hepatic failure have been reported with ciprofloxacin. In the event of any signs and symptoms of hepatic disease (such as anorexia, jaundice, dark urine, pruritus, or tender abdomen), treatment should be discontinued (see **ADVERSE REACTIONS**). There can be an increase in transaminases, alkaline phosphatase, or cholestatic jaundice, especially in patients with previous liver damage, who are treated with ciprofloxacin (**see ADVERSE REACTIONS**).

Interaction With Tests

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

Musculoskeletal

Myasthenia Gravis

Fluoroquinolone including Ciprofloxacin has neuromuscular blocking activity and may exacerbate muscle weakness in persons with myasthenia gravis. Post marketing serious adverse events, including deaths and requirement for ventilatory support, have been associated with fluroquinoline use in persons with myasthenia gravis. Avoid Ciprofloxacin in patients with known history of myasthenia gravis (see ADVERSE EVENTS)

Tendinitis

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

their healthcare provider regarding changing to a non-quinolone antimicrobial drug.

Ciprofloxacin Injection should not be used in patients with a history of tendon disease/disorder related to previous quinolone treatment.

Peripheral Neuropathy

Cases of sensory or sensorimotor axonal polyneuropathy affecting small and/or large axons resulting in paresthesias, hypoesthesias, dysesthesias and/or weakness have been reported in patients receiving quinolones, including Ciprofloxacin.

Ciprofloxacin should be discontinued if the patient experiences symptoms of neuropathy including pain, burning, tingling, numbness, and/or weakness, or is found to have deficits in light touch, pain, temperature, position sense, vibratory sensation, and/or motor strength in order to prevent the development of an irreversible condition (see **ADVERSE REACTIONS**).

Skin

Phototoxicity

Moderate to severe phototoxicity reactions have been observed in patients exposed to direct sunlight or ultraviolet light while receiving drugs in this class. Excessive exposure to sunlight or ultraviolet light should be avoided. Therapy should be discontinued if phototoxicity occurs.

***Streptococcus pneumoniae* Infections**

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

PRECAUTIONS

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

Tendon rupture (generally achilles tendon) has been reported predominantly in the elderly on prior systemic treatment with glucocorticoids. At any sign of tendonitis (i.e., painful swelling, inflammation), a physician should be consulted and the antibiotic treatment should be discontinued. Care should be taken to keep the affected extremity at rest and avoid any inappropriate exercise (as the risk for tendon rupture might increase otherwise). Ciprofloxacin should not be used in patients

with a clear history of tendon disorders related to quinolone treatment because they may be at risk of developing tendon disorders again when re-exposed to a fluoroquinolone.

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

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

Intravenous infusion should be administered by slow infusion over a period of 60 minutes. Local I.V. reactions have been reported with the intravenous administration of ciprofloxacin. These reactions are more frequent if infusion time is 30 minutes or less, or if small veins of the hand are used.

Prolonged use of CIPROFLOXACIN INJECTION (Ciprofloxacin 0.2% Intravenous Infusion) 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.

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

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

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

Salmonella: Microsome Test (Negative)
E.Coli: DNA Repair Assay (Negative)
Mouse Lymphoma Cell Forward Mutation Assay (Positive)
Chinese Hamster V_{79} Cell HGPRT Test (Negative)
Syrian Hamster Embryo Cell Transformation Assay (Negative)
Saccharomyces cerevisiae: Point Mutation Assay (Negative)

Mitotic Crossover and Gene Conversion Assay (Negative)
Rat Hepatocyte Primary Culture DNA Repair Assay (LIDS) (Positive)

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

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

Cardiovascular

In 1% or less of patients treated with oral or I.V. ciprofloxacin during clinical trials and subsequent post-marketing surveillance, the following events were reported rarely (<0.1 %): hypotension. The following have been reported very rarely (<0.01 %): angina pectoris, atrial fibrillation, cardiac arrest, cerebrovascular disorder, electrocardiogram abnormality, hot flashes, hypertension, kidney vasculitis, myocardial infarct, pericarditis, pulmonary embolus, substernal chest pain, syncope (fainting), vasodilation (hot flashes).

Ear/Nose/Throat

In 1% or less of patients treated with oral or I.V. ciprofloxacin during clinical trials and subsequent post-marketing surveillance, the following events were reported: abnormal vision (visual disturbances), taste perversion, tinnitus. The following have been reported very rarely: chromatopsia, colour blindness, conjunctivitis, corneal opacity, diplopia, ear pain, eye pain, parosmia (impaired smell), anosmia (usually reversible on discontinuation).

Endocrine and Metabolism

In 1% or less of patients treated with oral or I.V. ciprofloxacin during clinical trials and subsequent post-marketing surveillance, the following events were reported: creatinine increased. The following have been reported rarely: edema (face) and hyperglycemia.

Gastrointestinal

In 1% or less of patients treated with oral or I.V. ciprofloxacin during clinical trials and subsequent post-marketing surveillance, the following events were reported: abdominal pain, anorexia, dry mouth, dyspepsia, dysphagia, enlarged abdomen, flatulence, gastrointestinal moniliasis, jaundice, stomatitis, vomiting, abnormal liver function test. The following have been reported rarely: moniliasis (oral) cholestatic jaundice, and pseudomembranous colitis. The following have been reported very rarely: constipation, esophagitis, gastrointestinal hemorrhage, glossitis, hepatomegaly, ileus, increased appetite, intestinal perforation, life-threatening pseudomembranous colitis with possible fatal outcome, liver damage, melena, pancreatitis, tenesmus, tooth discoloration, toxic

megacolon, ulcerative stomatitis.

Genitourinary

In 1% or less of patients treated with oral or I.V. ciprofloxacin during clinical trials and subsequent post-marketing surveillance, the following events were reported: albuminuria, hematuria. The following have been reported rarely: abnormal kidney function, acute kidney failure, dysuria, leucorrhea, nephritis interstitial, urinary retention, vaginitis, vaginal moniliasis.

Hematologic

In 1% or less of patients treated with oral or I.V. ciprofloxacin during clinical trials and subsequent post-marketing surveillance, the following events were reported: agranulocytosis, anaemia, eosinophilia, granulocytopenia, leukocytopenia, leukocytosis, pancytopenia. The following have been reported very rarely: altered prothrombin levels, haemolytic anaemia, marrow depression (life threatening), pancytopenia (life threatening), thrombocytopenia, thrombocytosis.

Neurologic

In 1% or less of patients treated with oral or I.V. ciprofloxacin during clinical trials and subsequent post-marketing surveillance, the following events were reported: agitation, confusion, convulsion, dizziness, hallucinations, headache, hypesthesia, increased sweating, insomnia, somnolence, tremor (trembling). The following have been reported rarely: paresthesia (peripheral paralgesia). The following have been reported very rarely: abnormal dreams (nightmares), anxiety, apathy, ataxia, depersonalization, depression, diplopia, hemiplegia, hyperesthesia, hypertonia, increase of intracranial pressure, meningism, migraine, nervousness, neuritis, paresthesia, polyneuritis, sleep disorder, twitching, grand mal convulsions, abnormal (unsteady) gait, psychosis, intracranial hypertension. In some instances these reactions occurred after the first administration of Ciprofloxacin. In these instances, Ciprofloxacin has to be discontinued and the doctor should be informed immediately.

Musculoskeletal

In 1% or less of patients treated with oral or I.V. ciprofloxacin during clinical trials and subsequent post-marketing surveillance, the following events were reported rarely: achiness, arthralgia (joint pain), joint disorder (joint swelling), pain in the extremities, partial or complete tendon rupture (predominantly achilles tendon), tendonitis (predominantly achillotendonitis), myalgia (muscular pain). The following have been reported very rarely: myasthenia (exacerbation of symptoms of myasthensia gravis).

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.

Peri-Operative Considerations

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

Dextrose load for intravenous solution formulation

Ciprofloxacin Injection infusion solution (bags) contain dextrose. This should be taken into account in patients with diabetes mellitus. Dextrose content is 5 g for the 100 mL bag and 10 g for the 200 mL bag. (See **PHARMACEUTICAL INFORMATION**).

Psychiatric

See NEUROLOGIC subsections of **ADVERSE REACTIONS**.

Renal Impairment

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

Hepatic Impairment

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

Respiratory

In 1% or less of patients treated with oral or I.V. ciprofloxacin during clinical trials and subsequent post-marketing surveillance, the following events were reported: dyspnea. The following have been reported very rarely: hiccup, hyperventilation, increased cough, larynx edema, lung edema, lung hemorrhage, pharyngitis, stridor, voice alteration.

Sensitivity/Resistance

The *in vitro* activity of ciprofloxacin was investigated against clinical isolates of gram-positive and gram-negative aerobic and anaerobic bacteria. The results indicated *m*ost 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 (**See MICROBIOLOGY**).

Development of resistance to ciprofloxacin *in vitro* can also occurred slowly via multiple-step

mutation. Resistance to ciprofloxacin due to mutations occurs at general frequency of between $<1x10^{-9}$ to $1x10^{-6}$.

Skin

In 1% or less of patients treated with oral or I.V. ciprofloxacin during clinical trials and subsequent post-marketing surveillance, the following events were reported: pruritus, rash. The following have been reported rarely: photosensitivity reaction. The following have been reported very rarely: alopecia, angioedema, fixed eruption, photosensitive dermatitis, urticaria.

Special Populations

Pregnancy

The safety of CIPROFLOXACIN INJECTION (Ciprofloxacin 0.2% Intravenous Infusion) in pregnancy has not yet been established. CIPROFLOXACIN INJECTION (Ciprofloxacin 0.2% Intravenous Infusion) should not be used in pregnant women unless the likely benefits outweigh the possible risk to the fetus **(see WARNINGS)**. Ciprofloxacin has been shown to be non-embryotoxic and non-teratogenic in animal studies.

Nursing Women

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

Pediatric Use

The safety and efficacy of Ciprofloxacin in the pediatric population less than 18 years of age have not been established. Quinolones, including ciprofloxacin, cause arthropathy and osteochondrosis in juvenile animals of several species (**See TOXICOLOGY**).

Geriatrics

CIPROFLOXACIN INJECTION (Ciprofloxacin 0.2% Intravenous Infusion) is substantially excreted by the kidney, and the risk of adverse reactions may be greater in patients with impaired renal function (**SEE HUMAN PHARMACOLOGY**).

Monitoring and Laboratory Tests

In 1% or less of patients treated with oral or I.V. ciprofloxacin during clinical trials and subsequent post-marketing surveillance, the following events were reported: increased alkaline phosphatase, ALT increased, AST increased, BUN (urea) increased, cholestatic parameters increased, Gamma-GT increased, lactic dehydrogenase increased, NPN increased, transaminases increased, decreased albuminuria, bilirubinemia, creatinine clearance decreased, hypercholesteremia, hyperuricemia, increased sedimentation rate. The following have been reported rarely: acidosis, increased amylase,

crystalluria, electrolyte abnormality, haematuria, hypercalcemia, hypocalcemia and lipase increased.

ADVERSE REACTIONS

CIPROFLOXACIN INJECTION (Ciprofloxacin 0.2% Intravenous Infusion) is generally well tolerated. During worldwide clinical investigation (1991), 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 Ciprofloxacin intravenous infusion 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.

Clinical Trial Adverse Drug Reactions

In patients treated with ciprofloxacin injection, the most frequently reported events, possibly, probably drug-related were: rash (1.8%), diarrhea (1.0%), and injection site pain (1.0%).
Local I.V. site reactions have been reported. These reactions are more frequent if the infusion time is 30 minutes or less. These may appear as local skin reactions which resolve rapidly upon completion of the infusion. Subsequent I.V. administration is not contraindicated unless the reactions recur or worsen.

Abnormal Hematologic and Clinical Chemistry Findings

See **WARNINGS AND PRECAUTIONS** Section: MONITORING AND LABORATORY TESTS Subsection.

Post-Market Adverse Drug Reactions

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

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

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

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

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

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

I.V. Infusion Site: thrombophlebitis, injection site reaction (e.g. edema, hypersensitivity, inflammation, pain). The following have been reported very rarely: burning, erythema, pain, paresthesia, and swelling.

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

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

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.

Nervous System: agitation, confusion, convulsion, dizziness, hallucinations, headache, hypesthesia, increased sweating, insomnia, somnolence, tremor (trembling). The following has been reported rarely: paresthesia (peripheral paralgesia), abnormal dreams (nightmares), anxiety, seizures (including status epilepticus), depression (potentially culminating in self- injurious behavior, such as suicidal ideations/thoughts and attempted or completed suicide) (see **WARNINGS**). The following have been reported very rarely: apathy, ataxia, depersonalization, diplopia, hemiplegia, hyperesthesia, hypertonia, increase of intracranial pressure, meningism, migraine, nervousness, neuritis, paresthesia, polyneuritis, sleep disorder, twitching, grand mal convulsions, abnormal (unsteady) gait, psychotic reactions (potentially culminating in self- injurious behavior, such as suicidal ideations / thoughts and attempted or completed suicide), intracranial hypertension (including pseudotumor cerebri). In some instances these reactions occurred after the first administration of ciprofloxacin. In these instances, ciprofloxacin has to be discontinued and the doctor should be informed immediately.

Other: the following have been reported rarely: asthenia (general feeling of weakness, tiredness), death.

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

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

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

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

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

abnormality, haematuria, hypercalcemia, hypocalcemia and lipase increased.
Most of the adverse events reported were described as only mild or moderate in severity.
Adverse reactions noted during therapy with ciprofloxacin and metronidazole in clinical trials were similar to those already noted during therapy with ciprofloxacin alone with the following additions:

Cardiovascular: peripheral edema

Digestive: colitis, gastritis, tongue discoloration

Hemic and Lymphatic: coagulation disorder, thrombocythemia

Skin: fungal dermatitis, pustular rash, sweating **Metabolic:** healing abnormal, hypernatremia

Nervous: dementia

Urinary: kidney tumour necrosis, urinary incontinence.
The following additional adverse events, in alphabetical order, regardless of incidence or relationship to drug, have been reported during clinical trials and/or from worldwide postmarketing experience in patients given ciprofloxacin (includes all formulations, all dosages, all drug-therapy durations, and in all indications): acute generalized exanthematous pustulosis (AGEP), arrhythmia, atrial flutter, bleeding diathesis, bronchospasm, C. difficile associated diarrhea, candiduria, cardiac murmur, cardiopulmonary arrest, cardiovascular collapse, cerebral thrombosis, chills, delirium, drowsiness, dysphasia, edema (conjunctivae, hands, lips, lower extremities, neck), epistaxis, exfoliative dermatitis, fever, gastrointestinal bleeding, gout (flare up), gynecomastia, hearing loss, hemoptysis, hemorrhagic cystitis, hyperpigmentation, joint stiffness, lightheadedness, lymphadenopathy, manic reaction, myoclonus, nystagmus, pain (arm, breast, epigastric, foot, jaw, neck, oral mucosa), paranoia, peripheral neuropathy, phobia, pleural effusion, polyneuropathy, polyuria, postural hypotension, pulmonary embolism, purpura, QT prolongation, renal calculi, respiratory arrest, respiratory distress, restlessness, rhabdomyolysis, torsades de pointes, toxic psychosis, unresponsiveness, urethral bleeding, urination (frequent), ventricular ectopy, ventricular fibrillation, ventricular tachycardia, vesicles, visual acuity (decreased) and visual disturbances (flashing lights, change in colour perception, overbrightness of lights).
The following has been reported at an unknown frequency: international normalized ratio (INR) increased (in patients treated with Vitamin K antagonists).

DRUG INTERACTIONS

Antidiabetic Agents
Disturbances of blood glucose, including symptomatic hyperglycemia and hypoglycemia, have been reported with quinolones, including ciprofloxacin, usually in diabetic patients receiving concomitant

treatment with an oral antidiabetic agent (mainly sulfonylureas such as glyburide/glibenclamide, glimepiride) or with insulin.

In diabetic patients, careful monitoring of blood glucose is recommended. If a hypoglycemic reaction occurs in a patient receiving ciprofloxacin, discontinue the drug immediately and an appropriate therapy should be instituted (see **ADVERSE REACTIONS**).

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

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

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

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

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

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

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

Food and Dairy Products
Although, ciprofloxacin may be taken with meals that include milk, simultaneous administration with dairy products alone, or with calcium-fortified products should be avoided, since decreased

absorption is possible. It is recommended that ciprofloxacin be administered at least 2 hours before or 2 hours after substantial calcium intake (>800 mg). (See DOSAGE AND ADMINISTRATION.).

Histamine H_2-receptor Antagonists
Histamine H_2-receptor antagonists appear to have no significant effect on the bioavailability of ciprofloxacin.

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

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

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

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

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

Oral Anticoagulants
Simultaneous administration of ciprofloxacin with an oral anticoagulant (eg, vitamin K antagonist) may augment its anticoagulant effects. There have been many reports of increases in oral anticoagulant activity in patients receiving antibacterial agents, including quinolones. The risk may vary with the underlying infection, age, and general status of the patient so that the contribution of ciprofloxacin to the increase in INR (international normalized ratio) is difficult to assess. INR

and/or prothrombin time should be monitored frequently during and shortly after coadministration of ciprofloxacin with an oral anticoagulant (eg, warfarin, acenocoumarol).

Phenytoin
Altered (decreased or increased) serum levels of phenytoin were observed in patients receiving ciprofloxacin and phenytoin simultaneously. Monitoring of phenytoin therapy is recommended, including phenytoin serum concentration measurements,during and shortly after coadministration of ciprofloxacin with phenytoin to avoid the loss of seizure control associated with decreased phenytoin levels and to prevent phenytoin overdose-related undesirable effects when ciprofloxacin is discontinued in patients receiving both agents.

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

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

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

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

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

Drug-Herb Interactions

The drug-herb interaction of Ciprofloxacin has not been established.

Drug-Laboratory Interactions
See MONITORING AND LABORATORY TESTS Subsection under PRECAUTIONS or LABORATORY VALUES Subsection under ADVERSE REACTIONS.

Drug-Lifestyle Interactions
No information is available.

DOSAGE AND ADMINISTRATION

Dosing Considerations
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.

Recommended Dose and Dosage Adjustment
CIPROFLOXACIN INJECTION (Ciprofloxacin 0.2% Intravenous Infusion) should be administered by intravenous infusion over a period of 60 minutes. Slow infusion into a large vein will minimize patient discomfort and reduce the risk of venous irritation.

Adults
The recommended adult dosages of Ciprofloxacin injection are:

Table 1: Recommended Adult Dosages of CIPROFLOXACIN INJECTION (Ciprofloxacin 0.2% Intravenous Infusion)

Location of Infection	Type/Severity	Unit Dose	Frequency	Daily Dose
Urinary Tract	Moderate/ Severe/ Complicated	200 mg to 400 mg	q12h	400 mg to 800 mg
Respiratory Tract	Moderate/ Severe	400 mg	q8h to q12h	800 mg to 1200 mg
Skin or Skin Structure	Moderate	400 mg	q12h	800 mg
Intra-abdominal	Complicated	400 mg	q12h	400 mg q12h only when used in combination with metronidazole 500 mg IV q6h*

Empiric Therapy in Febrile Neutropenic Patients	Severe Ciprofloxacin + Piperacillin Sodium	400 mg 50 mg/kg	q8h q4h	1200 mg Not to exceed 24 g/day

* (1) Clinical success was demonstrated with a limited number of patients switched to oral therapy: (Ciprofloxacin 500 mg p.o..q 12h plus metronidazole 500 mg P.O. q6h) during day 3, 4 or 5 of therapy when able to take oral medication and having shown an initial clinical response to the intravenous therapy.
(2) See Metronidazole Product Monograph for Prescribing Information including cautionary statements.
(3) For information on Ciprofloxacin plus metronidazole combination therapy, see Action and Clinical Pharmacology, Human Pharmacology, and Adverse Reaction sections of the CIPROFLOXACIN INJECTION Product Monograph.

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

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

Sequential I.V./P.O. Therapy

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

Impaired Renal Function

Ciprofloxacin is eliminated primarily by renal excretion. However, the drug is also metabolized and partially cleared through the biliary system of the liver and through the intestine (**See HUMAN PHARMACOLOGY**). This alternate pathway of drug elimination appears to compensate for the reduced renal excretion of patients with renal impairment. Nonetheless, some modification of dosage is recommended, particularly for patients with severe renal dysfunction. The following table provides a guideline for dosage adjustment. However, monitoring of serum drug levels provides the most reliable basis for dosage adjustments.

Table 2: Maximum Daily Dose with Stated Creatinine Clearance or Serum Creatinine

Creatinine Clearance mL/min/1.73 m^2	Maximum Daily Dose	Serum Creatinine Concentration mg/100 mL
	I.V.	
31 – 60	800 mg	1.4 – 1.9

≤ 30	400 mg	≥ 2.0

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

Hemodialysis
Only a small amount of ciprofloxacin (< 10%) is removed from the body after hemodialysis or peritoneal dialysis. For hemodialysis patients, please follow dosing recommendations as described in **Table 2**. On dialysis days, the dose should be administered after dialysis.

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

Creatinine Clearance mL/sec =

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

Females: 0.85 x the above value

In traditional units mL/min =

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

Females: 0.85 x the above value

Impaired Hepatic Function
No dosage adjustment is required.

Pediatric Use
The safety and efficacy of Ciprofloxacin in individuals less than 18 years of age has not been established. Ciprofloxacin should not be used in pediatric patients and adolescents (**see WARNINGS**).

Missed Dose
Not Applicable.

Administration

CIPROFLOXACIN INJECTION should be administered by I.V. infusion over a period of 60 minutes. The drug should not be given by rapid injection. Slow infusion into a large vein will minimize patient discomfort and reduce the risk of venous irritation.
If CIPROFLOXACIN INJECTION (Ciprofloxacin 0.2% Intravenous Infusion) is to be given concomitantly with another drug, each drug should be given separately in accordance with the recommended dosage and route of administration for each drug. CIPROFLOXACIN INJECTION (Ciprofloxacin 0.2% Intravenous Infusion) contains ciprofloxacin at 2.0 mg/mL and should be administered "as is".

OVERDOSAGE

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

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

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

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action
Ciprofloxacin, a synthetic fluoroquinolone, has *in vitro* activity against a wide range of gram-negative and gram-positive microorganisms. Its bactericidal action is achieved through inhibition of topoisomerase II (DNA gyrase) and topoisomerase IV (both Type II topoisomerase), which are required for bacterial DNA replication, transcription, repair, and recombination.

Ciprofloxacin retained some of its bactericidal activity after inhibition of RNA and protein synthesis by rifampin and chloramphenicol, respectively. These observations suggest ciprofloxacin may possess two bactericidal mechanisms, one mechanism resulting from the inhibition of DNA gyrase and a second mechanism which may be independent of RNA and protein synthesis.

The mechanism of action of fluoroquinolones, including ciprofloxacin, is different from that of penicillins, cephalosporins, aminoglycosides, macrolides, and tetracyclines. Therefore,

microorganisms resistant to these classes of drugs may be susceptible to ciprofloxacin. Conversely, microorganisms resistant to fluoroquinolones may be susceptible to these other classes of antimicrobial agents (**See MICROBIOLOGY**). There is no cross-resistance between ciprofloxacin and the mentioned classes of antibiotics.

Pharmacodynamics

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

Following infusion of 400 mg IV Ciprofloxacin every eight hours in combination with 50 mg/kg IV piperacillin sodium every 4 hours, mean serum ciprofloxacin concentrations were 3.02 µg/mL at 30 minutes and 1.18 µg/mL between 6-8 hours after the end of infusion. The mean serum ciprofloxacin concentration given alone at 400 mg IV every eight hours was 3.67 µg/mL at 30 minutes and 1.16 µg/mL at 6 hours after the end of infusion.

Pharmacokinetics

The pharmacokinetics of ciprofloxacin were linear over the dose range of 200 to 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 1^{st} and 5^{th} I.V. 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 I.V. dose administered over 60 minutes every 12 hours resulted in a C_{max} similar to that observed with a 750 mg oral dose.

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

Pharmacokinetics were dose proportioned with no significant changes in clearance or half-life occurring over this dose range (**See DETAILED PHARMACOLOGY: Human Pharmacology subsections**).

Absorption:
Following an intravenous infusion of ciprofloxacin the mean maximum serum concentrations were achieved at the end of infusion. Pharmacokinetics of ciprofloxacin was linear over the dose range up to 400 mg administered intravenously.

Comparison of the pharmacokinetic parameters for a b.i.d. and t.i.d. I.V. dose regimen indicated no evidence of drug accumulation for ciprofloxacin and its metabolites.

A 60-minute I.V. infusion of 200 mg ciprofloxacin or the oral administration of 250 mg ciprofloxacin both given every 12 hours produced an equivalent area under the serum concentration time curve (AUC).

A 60-minute infusion of 400 mg ciprofloxacin every 12 hours were bioequivalent to a 500 mg oral dose every 12 hours with regard to AUC.

The 400 mg I.V. dose administered over 60 minutes every 12 hours resulted in a C_{max} similar to that observed with a 750 mg oral dose.

A 60-minute infusion of 400 mg ciprofloxacin every 8 hours is equivalent with respect to AUC to 750 mg oral regimen given every 12 hours.

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

Metabolism:
Small concentrations of four metabolites have been reported. They were identified as desethyleneciprofloxacin (M 1), sulphociprofloxacin (M 2), oxociprofloxacin (M 3) and formylciprofloxacin (M 4). M 1 to M 3 display antibacterial activity comparable to or inferior to that of nalidixic acid. M 4, with the smallest quantity, is largely equivalent to norfloxacin in its antimicrobial activity.

Elimination:
Ciprofloxacin is largely excreted unchanged both renally and to a smaller extent non-renally. Renal clearance is between 0.18 – 0.3 L/h/kg and the total body clearance between 0.48 – 0.6 L/h/kg. Ciprofloxacin undergoes both glomerular filtration and tubular secretion.
Non-renal clearance of ciprofloxacin is mainly due to active transintestinal secretion as well as metabolization. 1 % of the dose is excreted via the biliary route. Ciprofloxacin is present in the bile

in high concentrations.

Table 3: Pharmacokinetic Parameters of Ciprofloxacin Following Single Doses in Healthy Volunteers (I.V.)

Dose	200 mg*	400 mg*
C_{max} (mg/L)	2.14	4.60
$t_{1/2}$ (hr)	3.4	3.5
$AUC_{0-\infty}$ (mg•h/L)	5.24	11.69
T_{max} (hr)	0.95	1.00

*I.V. parameters following a 60-minute infusion period

Table 4: 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 400 mg I.V. q12h	12.7 (AUG_{0-12})	4.56	1.0
(ii) When administered as Ciprofloxacin 400 mg I.V. q12h in combination with Metronidazole 500 mg I.V. q6h			
Ciprofloxacin	15.9 (AUC_{0-12})	5.21	1.0
Metronidazole	153.0 (AUC_{0-6})	33.6	1.0

Note: Following the repeated dosing of metronidazole 500 mg I.V. t.i.d., the peak and minimum mean plasma metronidazole concentrations, at steady-state, were 26 µg/mL and 12 µg/ml respectively.

Table 5: 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.)				
200 mg I.V.	335.2 (±61.5)	99.9 (±16.0)	71.7 (±10.9)	31.24 (±4.06)
400 mg I.V.	706.0 (±99.0)	181.3 (±25.9)	127.1 (±18.9)	63.5 (±7.4)
Amount Excreted mg (± S.D.)				
200 mg I.V.	58.8 (±9.3)	13.6 (±3.2)	14.1 (±9.0)	7.5 (±2.5)
400 mg I.V.	125.0 (±7.2)	24.1 (±4.7)	35.1 (±12.7)	15.7 (±3.9)

Note: I.V. dose administered over 30 minutes

Special Populations and Conditions

Geriatrics: 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. (**See FACTORS INFLUENCING THE PHARMACOKINETICS Subsection under HUMAN PHARMACOLOGY Section**).

Gender: No information is available.

Race: No information is available.

Hepatic Insufficiency: In studies in patients with stable chronic cirrhosis (with mild to moderate hepatic impairment), no significant changes in ciprofloxacin pharmacokinetics have been observed. In a study of 7 cirrhotic patients and healthy volunteers given ciprofloxacin 750 mg every 12 hours for a total of nine doses followed by a 1 week washout and then a 30 minute infusion of Ciprofloxacin Intravenous Infusion 200 mg, there was no difference in pharmacokinetics between patients with stable chronic cirrhosis (with mild to moderate hepatic impairment) and healthy volunteers.

Renal Insufficiency: Ciprofloxacin is eliminated primarily by renal excretion. However, the drug is also metabolized and partially cleared through the biliary system of the liver and through the intestine. This alternate pathway of drug elimination appears to compensate for the reduced renal excretion of patients with renal impairment. Nonetheless, some modification of dosage is recommended, particularly for patients with severe renal dysfunction.

The pharmacokinetics of ciprofloxacin following a single oral dose of 250 mg in 6 patients (5 male, 1 female, age: 51± 9 years) with normal renal function were compared to 6 patients (3 male, 3 female, age: 63 ± 6 years) with renal impairment and to 5 patients (2 male, 3 female, age: 63 ± 6 years) with end-stage renal failure, treated by haemodialysis. 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.
The pharmacokinetics of ciprofloxacin following multiple I.V. doses were compared in subjects with

normal renal function and in subjects with various degrees of renal impairment. Patients with renal insufficiency had significantly increased concentrations of ciprofloxacin, MI and M2 metabolites and decreased renal clearances.

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

An open-label crossover study was conducted in eight peritoneal dialysis patients. Patients received a single dose of I.V. ciprofloxacin on two separate occasions, once with frequent dialysis (fluid exchange done at 4,8,12 and 24 hours) and once with delayed dialysis (fluid exchange at 12 and 24 hours). Pharmacokinetic parameters for ciprofloxacin, M1 and M2 metabolites were not significantly different for frequent versus delayed dialysis, except that dialysate clearances for ciprofloxacin and M2 were higher when dialysis was done frequently.

In an open-label crossover study, seven hemodialysis patients received a single dose of I.V. ciprofloxacin on two separate occasions, once immediately after hemodialysis, and once 2 hours before hemodialysis. The results demonstrated that the pharmacokinetic parameters were not significantly different between the two treatments for ciprofloxacin, M1 and M2 metabolites.

STORAGE AND STABILITY

Protect from light, excessive heat and freezing.

Store at controlled room temperature 15-25 °C (56-77 °F).

SPECIAL HANDLING INSTRUCTIONS

Protect from light, excessive heat and freezing.

Use promptly when pouch is opened.

DOSAGE FORMS, COMPOSITION AND PACKAGING

CIPROFLOXACIN INJECTION (Ciprofloxacin 0.2% Intravenous Infusion) is an aqueous infusion for intravenous administration.

COMPOSITION:

Name of Ingredient	Quantity per Container of	
	100 mL	**200 mL**
Ciprofloxacin Lactate	254.4 mg eq. to 200.0 mg of Ciprofloxacin	508.8 mg eq. to 400.0 mg of Ciprofloxacin

Lactic acid	10.0 mg	20.0 mg
Dextrose	5 g	10 g
Hydrochloric acid	q.s. to adjust pH*	q.s. to adjust pH*
Water for Injections	q.s. to 100 mL	q.s. to 200 mL

*q.s. of Hydrochloric Acid to adjust pH to 3.50 to 4.60

Ciprofloxacin Injection is supplied in a clear 100 mL & 200 mL plastic bag with the twist off port (TOP) and the Extra Medication Port (EMP).

PART II: SCIENTIFIC INFORMATION
PHARMACEUTICAL INFORMATION

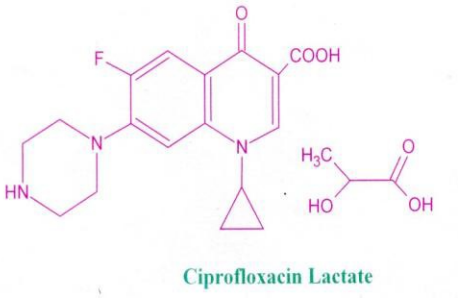
Drug Substance

Proper name: CIPROFLOXACIN LACTATE

Chemical name: 1-Cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinoline carboxylic acid lactate.

Molecular formula and molecular mass: $C_{17}H_{18}FN_3O_3 \bullet C_3O_3H_6$; MW = 421 g/mol

Structural formula:



Ciprofloxacin Lactate

Physicochemical properties:

Description : White to yellowish coloured powder.

Solubility : Freely soluble in water, slightly soluble in 90% ethanol.

DETAILED 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**.**

Effects on Blood Dextrose 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 dextrose 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 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

An intravenous infusion of 400 mg ciprofloxacin given over 60 minutes every 12 hours, for 6 doses, to 12 healthy male volunteer (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 I.V. dose administered over 60 minutes every 12 hours resulted in a C_{max} similar to that observed with a 750 mg oral dose. 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.

Following a 60-minute intravenous infusion of 200 mg and 400 mg ciprofloxacin to 13 healthy male volunteers (18-40 years), the mean maximum serum concentrations achieved were 2.14 and 4.60 mg/L respectively; the concentrations at 12.0 hours were 0.11, 0.23 mg/L respectively (**see figure 1**).

The pharmacokinetics of ciprofloxacin were linear over the dose range of 200 mg and 400 mg administered intravenously (**see Table 6**). 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 I.V. dose on a 12 h regimen indicated no evidence of drug accumulation.

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

Table 6: Pharmacokinetics Parameters of Ciprofloxacin Following Single Doses In Healthy Volunteers I.V.

Dose	**200 mg I.V.***	**400 mg I.V.***
C_{max} (mg/L)	2.14	4.60
$t_{1/2}$ (hr)	3.40	3.50
$AUC_{0-\infty}$ (mg•h/mL)	5.24	11.69
T_{max} (hr)	0.95	1.00

*I.V. parameters following a 60-minute infusion period

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 400 mg I.V. q12h	12.7 (AUC_{0-12})	4.56	1.0
(ii) When administered as Ciprofloxacin 400 mg I.V. q12h in combination with Metronidazole 500 mg I.V. q6h			
Ciprofloxacin	15.9 (AUC_{0-12})	5.21	1.0
Metronidazole	153.0 (AUC_{0-6})	33.6	1.0

Note: Following the repeated dosing of metronidazole 500 mg I.V. t.i.d., the peak and minimum mean plasma metronidazole concentrations, at steady-state, were 26 µg/mL and 12 µg/mL respectively.

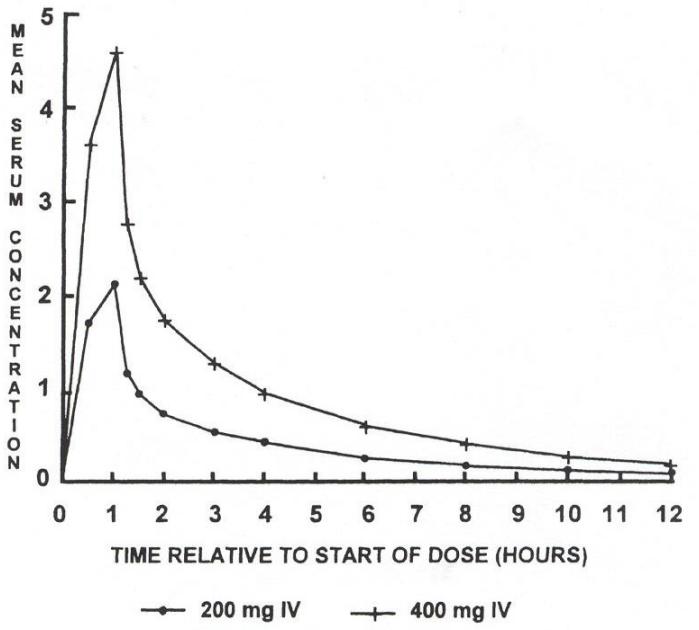


Figure 1: Mean Serum Ciprofloxacin Concentration (mg/L) vs Time After a Single Intravenous Dose Administered Over 60 Minutes

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.)				
200 mg I.V.	335.2 (± 61.5)	99.9 (± 16.0)	71.7 (± 10.9)	31.24 (± 4.06)
400 mg I.V.	706.0 (± 99.0)	181.3 (± 25.9)	127.1 (± 18.9)	63.5 (± 7.4)
Amount Excreted mg (± S.D.)				
200 mg I.V.	58.8 (±9.3)	13.6 (± 3.2)	14.1 (± 9.0)	7.5 (± 2.5)
400 mg I.V.	125.0 (± 7.2)	24.1 (± 4.7)	35.1 (± 12.7)	15.7 (± 3.9)

Note: I.V. dose administered over 30 minutes

Metabolism and Excretion

Ciprofloxacin is largely excreted unchanged both renally and, to a small extent, extra- renally. Small concentrations of 4 metabolites have been reported: Desethyleneciprofloxacin (M1)(1.8 %), sulphociprofloxacin (M2)(5.0%), oxociprofloxacin (M3)(9.6%) and formylciprofloxacin (M4)(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%.

Following the intravenous administration of a single 107 mg dose of ^{14}C-labelled ciprofloxacin to six healthy male volunteers (age: 23.7 ± 1.89 years, weight: 80.2 ± 3.45 kg), 15% of unchanged ciprofloxacin was recovered in the feces, suggesting that hepatic extraction and biliary excretion is an extra-renal clearance pathway for ciprofloxacin. Direct evidence of biliary excretion of ciprofloxacin was obtained in 12 patients (age 28-58) with T-tube drainage. A peak biliary concentration of 16 mg/L was seen 4 hours after a single oral dose of ciprofloxacin 500 mg. After intravenous administration to a group of 9 healthy male volunteers (age 26.8 ± 9.7 years, weight: 63.9 ± 6.4 kg), approximately 50% to 70% of the dose is excreted in the urine as unchanged drug. After a 200 mg I.V. dose, urine concentrations of ciprofloxacin usually exceed 200 µg/mL during the first two hours after dosing, and are generally greater than 10 µg/mL at 8 to 12 hours after dosing. The urinary excretion of ciprofloxacin is virtually complete by 24 hours after dosing.

Approximately 15% of an I.V. dose is recovered from the feces within 5 days after dosing, which

may arise from either biliary clearance or transintestinal elimination. Following intravenous administration, approximately 10% of the dose is recovered in the urine in the form of metabolites.

FACTORS INFLUENCING THE PHARMACOKINETICS

Age (Elderly)

In 4 females and 6 males, (age: 67 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 following oral administration of a single 250 mg tablet

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
$t_{1/2}$ (hr)	3.7 0.9	3.3 0.6
Total AUC (mg h/L)	7.25 2.45	5.29 1.21
% Dose Urinary Recovery after	43	43

Impaired Renal Function

Ciprofloxacin is eliminated primarily by renal excretion. However, the drug is also metabolized and partially cleared through the biliary system of the liver and through the intestine. This alternate pathway of drug elimination appears to compensate for the reduced renal excretion of patients with renal impairment. Nonetheless, some modification of dosage is recommended, particularly for patients with severe renal dysfunction.

The pharmacokinetics of ciprofloxacin following a single oral dose of 250 mg in 6 patients (5 male, 1 female, age: 51 9 years) with normal renal function (see Group 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 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 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 Oral Administration of 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)	1.7 (0.41)	1.7 (0.5)	8.7 (0.9)	14.36 (3.5)	18.3 (3.5)	5.3 (1.7)
III	End-Stage Renal Failure Treated by Hemodialysis	2.07 (0.23)	1.6 (0.2)	5.8 (0.9)	15.87 (2.0)	-	

The pharmacokinetics of ciprofloxacin following multiple I.V. doses were compared in subjects with normal renal function and in subjects with various degrees of renal impairment (**see Table 11, Groups 1-4**). Patients with renal insufficiency had significantly increased concentrations of ciprofloxacin, MI and M2 metabolites and decreased renal clearances.

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

An open-label crossover study was conducted in eight peritoneal dialysis patients. Patients received a single dose of I.V. ciprofloxacin on two separate occasions, once with frequent dialysis (fluid exchange done at 4,8,12 and 24 hours) and once with delayed dialysis (fluid exchange at 12 and 24 hours). Pharmacokinetic parameters for ciprofloxacin, M1 and M2 metabolites were not significantly different for frequent versus delayed dialysis, except that dialysate clearances for ciprofloxacin and M2 were higher when dialysis was done frequently. Group 5 in **Table 11** shows the pharmacokinetic results for the frequent dialysis group.

In an open-label crossover study, seven hemodialysis patients received a single dose of I.V. ciprofloxacin on two separate occasions, once immediately after hemodialysis, and once 2 hours before hemodialysis. The results demonstrated that the pharmacokinetic parameters were not significantly different between the two treatments for ciprofloxacin, M1 and M2 metabolites. Group 6 in **Table 11** shows the pharmacokinetic results for the group dosed two hours before hemodialysis.

Table 11: Mean Pharmacokinetic Parameter for Ciprofloxacin and Metabolites M1 and M2 Following I.V. Dosing in Healthy Volunteers, Patients with Renal Insufficiency, Peritoneal Dialysis Patients, and Hemodialysis Patients.

Group	Creatinine Clearance mL/min/1.73m^2	IV Ciprofloxacin Dose	Parameter								
			Ciprofloxacin			M1 (desethylene ciprofloxacin)			M2 (sulfociprofloxacin)		
			AUC $_{0-\infty}$ (mg·hr/L)	Cl_r (L/hr)	$t_{1/2}$ (hr)	AUC $_{0-\infty}$ (µg·h/mL)	Cl_r (L/hr)	$t_{1/2}$ (hr)	AUC $_{0-\infty}$ (µg·h/mL)	Cl_r (L/hr)	$t_{1/2}$ (hr)
1	> 90	400 mg q8h x 11	10.2	20.3	4.59	0.19	19.9	5.04	0.98	19.5	2.33
2	61 - 90	400 mg q8h x 11	15.4	10.9	5.23	0.34	10.8	8.14	1.5	10.7	3.12
3	31-60	400 mg q12h x 8	21.5	6.91	5.72	0.57	7.1	9.1	4.21	6.52	5.25
4	≤30	300 mg q12h x 8	30.1	1.36	8.33	1.09	1.7	15.2	13.0	1.09	13.8
5	Chronic renal failure patients on peritoneal dialysis	400 mg single dose	38.7	0.098	8.39	4.49	0.074	28.6	54.8	0.08	22.6
6	Chronic renal failure patients on hemodialysis	400 mg single dose	38.4	0.11	11.4	2.05	0.087	11.6	29.9	0.073	13.1

Hepatic Impairment

In studies in patients with stable chronic cirrhosis (with mild to moderate hepatic impairment), no significant changes in ciprofloxacin pharmacokinetics have been observed. In a study of 7 cirrhotic patients and healthy volunteers given ciprofloxacin 750 mg every 12 hours for a total of nine doses followed by a 1 week washout and then a 30 minute infusion of ciprofloxacin 200 mg, there was no difference in pharmacokinetics between patients with stable chronic cirrhosis (with mild to moderate hepatic impairment) and healthy volunteers.

Food

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

Drug Interaction

Theophylline

Studies with immediate-release ciprofloxacin have shown that concomitant administration of ciprofloxacin with theophylline decrease the clearance of theophylline, resulting in elevated serum

theophylline levels and increased risk of a patient developing CNS or other adverse reactions.

Caffeine and Other Xanthine Derivatives

Ciprofloxacin decreases caffeine clearance and inhibits the formation of paraxanthine after caffeine administration.Upon concurrent administration of ciprofloxacin and pentoxifylline (oxpentifylline)-containing products, raised serum concentrations of this xanthine derivative were reported.

Class IA or III Antiarrhythmics

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

Multivalent Cations

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

Probenecid

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

Clozapine

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

Lidocaine

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

Ropinirole

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

Sildenafil

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

used when prescribing ciprofloxacin concomitantly with sildenafil, taking into consideration the risks and the benefits.

Oral Anticoagulants

Simultaneous administration of ciprofloxacin with an oral anticoagulant (eg, vitamin K antagonist) may augment its anticoagulant effects. There have been many reports of increases in oral anticoagulant activity in patients receiving antibacterial agents, including quinolones. The risk may vary with the underlying infection, age, and general status of the patient so that the contribution of ciprofloxacin to the increase in INR (international normalized ratio) is difficult to assess. INR and/or prothrombin time should be monitored frequently during and shortly after coadministration of ciprofloxacin with an oral anticoagulant (eg, warfarin, acenocoumarol).

Serum Protein Binding

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

Tissue Concentrations

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

The distribution of ciprofloxacin was observed to be rapid in healthy volunteers receiving various single and multiple intravenous doses. Fitting the serum profile to a two-compartment model provides a distribution phase with a half-life between 0.2 and 0.4 hours. The volume of the distribution at steady state (Vd_{ss}) and Vd_{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 the pharmacokinetic parameters.
Analysis with a three-compartment 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 the 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 I.V.

The results of this study were as follows:

Volume of distribution at a 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 12** summarizes the results of tissue and fluid penetration of ciprofloxacin in man.

Table 12: Distribution of Ciprofloxacin in Human Tissue/Fluid

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

MICROBIOLOGY

Mechanism of Action

The bactericidal action of ciprofloxacin results from inhibition of enzymes topoisomerase II (DNA gyrase) and topoisomerase IV, which are required for bacterial DNA replication, transcription, repair, and recombination.

Drug Resistance

The mechanism of action of fluoroquinolones, including ciprofloxacin, is different from that of penicillins, cephalosporins, aminoglycosides, macrolides, and tetracyclines; therefore, microorganisms resistant to these classes of drugs may be susceptible to ciprofloxacin and other fluoroquinolones. There is no known cross-resistance between ciprofloxacin and other classes of antimicrobials. *In vitro* resistance to ciprofloxacin develops slowly by multiple step mutations. Resistance to ciprofloxacin due to spontaneous mutations occurs at a general frequency of between $<10^{-9}$ to $1x10^{-6}$.

Activity *in vitro* and *in vivo*

Ciprofloxacin has *in vitro* activity against a wide range of gram-positive and gram-negative microorganisms. Ciprofloxacin is slightly less active when tested at acidic pH. The inoculum size has little effect when tested *in vitro*. The minimal bactericidal concentration (MBC) generally does not exceed the minimal inhibitory concentration (MIC) by more than a factor of 2. Ciprofloxacin has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections:

Aerobic gram-positive microorganisms

Enterococcus faecalis (Many strains are only moderately susceptible.)
Staphylococcus aureus (methicillin-susceptible strains only)
Staphylococcus epidermidis (methicillin-susceptible strains only)
Staphylococcus saprophyticus
Streptococcus pyogenes

Aerobic gram-negative microorganisms

Campylobacter jejuni	*Proteus mirabilis*
Citrobacter diversus	*Proteus vulgaris*
Citrobacter freundii	*Providencia rettgeri*
Enterobacter cloacae	*Providencia stuartii*
Escherichia coli	*Pseudomonas aeruginosa*
Haemophilus influenzae	*Salmonella typhi*
Haemophilus parainfluenzae	*Serratia marcescens*
Klebsiella pneumoniae	*Shigella boydii*
Moraxella catarrhalis	*Shigella dysenteriae*
Morganella morganii	*Shigella flexneri*
Neisseria gonorrhoeae	*Shigella sonnei*

The following *in vitro* data are available, **but their clinical significance is unknown**. Ciprofloxacin exhibits *in vitro* minimum inhibitory concentrations (MICs) of 1 µg/mL or less against most (≥90%) strains of the following microorganisms; however, the safety and effectiveness of ciprofloxacin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Aerobic gram-positive microorganisms

Staphylococcus haemolyticus
Staphylococcus hominis

Aerobic gram-negative microorganisms

Acetinobacter iwoffii	*Salmonella enteritidis*
Aeromonas hydrophila	*Vibrio cholerae*
Edwardsiella tarda	*Vibrio parahaemolyticus*
Enterobacter aerogenes	*Vibrio vulnificus*
Legionella pneumophila	*Yersinia enterocolitica*
Pasteurella multocida	

Most strains of *Burkholderia cepacia* and some strains of *Stenotrophomonas maltophilia* are resistant to ciprofloxacin as are most anaerobic bacteria, including *Bacteroides fragilis* and *Clostridium difficile*.

Susceptibility Tests

Dilution Techniques: Quantitative methods are used to determine antimicrobial minimal inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method (1) (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of ciprofloxacin powder. The MIC values should be interpreted according to the criteria outlined in Table 13.

Diffusion Techniques: Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure (2) requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 5 µg ciprofloxacin to test the susceptibility of microorganisms to ciprofloxacin.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 5 µg ciprofloxacin disk should be interpreted according to the criteria outlined in Table 13. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for ciprofloxacin.

Table 13: Susceptibility Interpretative Criteria for Ciprofloxacin

	MIC (µg/mL)			Zone Diameter (mm)		
Species	**S**	**I**	**R**	**S**	**I**	**R**
Enterobacteriacae	≤1	2	≥4	≥21	16-20	≤15
Enterococcus faecalis	≤1	2	≥4	≥21	16-20	≤15

Methicillin susceptible *Staphylococcus* species	≤1	2	≥4	≥21	16-20	≤15
Pseudomonas aeruginosa	≤1	2	≥4	≥21	16-20	≤15
Haemophilus influenzae	≤1[a]	g	g	≥21[b]	g	g
Haemophilus parainfluenzae	≤1[a]	g	g	≥21[b]	g	g
Streptococcus pyogenes	≤1[c]	2[c]	≥4[c]	≥21[d]	16-20[d]	≤15[d]
Neisseria gonorrhoeae	≤0.06[e]	0.12-0.5[e]	≤1[e]	≥41[f]	28-40[f]	≤27[f]

Abbreviations: I = Intermediate; MIC = minimum inhibitory concentration; µg = microgram; mL = milliliter; mm = millimeter; R = Resistant; S = Susceptible

[a] This interpretive standard is applicable only to broth microdilution susceptibility tests with *Haemophilus influenzae* and *Haemophilus parainfluenzae* using *Haemophilus* Test Medium (HTM). (1)

[b] This zone diameter standard is applicable only to tests with *Haemophilus influenzae* and *Haemophilus parainfluenzae* using *Haemophilus* Test Medium (HTM). (2)

[c] These interpretive standards are applicable only to broth microdilution susceptibility tests with streptococci using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.

[d] These zone diameter standards are applicable only to tests performed for streptococci using Mueller-Hinton agar supplemented with 5% sheep blood incubated in 5% CO_2.

[e] This interpretive standard is applicable only to agar dilution test with GC agar base and 1% defined growth supplement.

[f] This zone diameter standard is applicable only to disk diffusion tests with GC agar base and 1% defined growth supplement.

[g] The current absence of data on resistant strains precludes defining any results other than "Susceptible". Strains

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Quality Control: Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. For dilution technique, standard ciprofloxacin powder should provide the MIC values according to criteria outlined in Table 14. For diffusion technique, the 5 µg ciprofloxacin disk should provide the zone diameters outlined in Table 14.

Table 14: Quality Control for Susceptibility Testing

Strains	MIC range (µg/mL)	Zone Diameter (mm)
Enterococcus faecalis ATCC 29212	0.25 - 2	-
Escherichia coli ATCC 25922	0.004 - 0.015	30 - 40
Haemophilus influenzae ATCC 49247	0.004 - 0.03[a]	34 - 42[d]
Pseudomonas aeruginosa ATCC 27853	0.25 - 1	25 - 33
Staphylococcus aureus ATCC 29213	0.12 - 0.5	-
Staphylococcus aureus ATCC 25923	-	22 - 30
Neisseria gonorrhoeae ATCC 49226	0.001 - 0.008[b]	48 - 58[e]
C. jejuni ATCC 33560	0.06 - 0.25 and 0.03- 0.12[c]	-

Abbreviations: ATCC = American Type Culture Collection; MIC = minimum inhibitory concentration; µg = microgram; mL = milliliter; mm = millimeter

[a] This quality control range is applicable to only *H. influenzae* ATCC 49247 tested by a broth microdilution procedure using *Haemophilus* Test Medium (HTM). (1)

[b] *N. gonorrhoeae* ATCC 49226 tested by agar dilution procedure using GC agar and 1% defined growth supplement in a 5% CO_2 environment at 35-37°C for 20-24 hours.(2)

[c] *C. jejuni* ATCC 33560 tested by broth microdilution procedure using cation adjusted Mueller Hinton broth with 2.5-5% lysed horse blood in a microaerophilic environment at 36-37°C for 48 hours and for 42°C at 24 hours, respectively.

[d] These quality control limits are applicable to only *H. influenzae* ATCC 49247 testing using *Haemophilus* Test Medium (HTM). (2)

[e] These quality control limits are applicable only to tests conducted with *N. gonorrhoeae*

TOXICOLOGY

Acute Toxicity

Species	Mode of Administration	LD_{50} mg/kg
Mouse	p.o.	approx 5000
Rat	p.o.	approx 5000
Rabbit	p.o.	approx 2500
Mouse	I.V.	approx 290
Rat	I.V.	approx 145

Rabbit	I.V.	approx 125
Dog	I.V.	approx 250

Chronic Toxicity

Subacute Tolerability Studies over 4 weeks

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

Subchronic Tolerability Studies over 3 months

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

Chronic Tolerability Studies over 6 months

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

Carcinogenicity

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

Reproduction Toxicology

Fertility studies in rats: Fertility, the intrauterine and postnatal development of the young, and the fertility of F1 generation were not affected by ciprofloxacin.
Embryotoxicity studies: These yielded no evidence of any embryotoxic or teratogenic action of ciprofloxacin.

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

Mutagenicity

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

below:

Salmonella: Microsome Test (Negative)
E.Coli: DNA Repair Assay (Negative)
Mouse Lymphoma Cell Forward Mutation Assay (Positive)
Chinese Hamster V_{79} Cell HGPRT Test (Negative)
Syrian Hamster Embryo Cell Transformation Assay (Negative)
Saccharomyces cerevisiae: Point Mutation Assay (Negative)
Mitotic Crossover and Gene Conversion Assay (Negative)
Rat Hepatocyte Primary Culture DNA Repair Assay (LIDS) (Positive)

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

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

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

Renal Tolerability: The crystallization observed in the animal studies occurred preferentially under pH conditions that do not apply in man.

Compared to rapid infusion, a slow infusion of ciprofloxacin reduces the danger of crystal precipitation. The precipitation of crystals in renal tubules does not immediately and automatically lead to kidney damage. In the animal studies, damage occurred only after high doses, with correspondingly high levels of crystalluria. For example, although they always caused crystalluria, even high doses were tolerated over 6 months without damage and without foreign-body reactions occurring in individual distal renal tubules.

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

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

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

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

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PART III: INFORMATION FOR THE CONSUMER

This section contains important patient information about CIPROFLOXACIN INJECTION (Ciprofloxacin 0.2% Intravenous Infusion) and should be read completely before you begin treatment. This does not take the place of discussion with your doctor or health care professional about your medical condition or your treatment. This section does not list all benefits and risks of CIPROFLOXACIN INJECTION.

How to obtain your medicine: CIPROFLOXACIN INJECTION can be prescribed only by a licensed physician. Your doctor has prescribed CIPROFLOXACIN INJECTION only for you.

Name of your medicine: The name of your medicine is CIPROFLOXACIN INJECTION. It is manufactured by SteriMax Inc.

Purpose of your medicine: CIPROFLOXACIN INJECTION is intended to treat bacterial infections in males or females over 18 years of age and is administered by the healthcare professional.

What is CIPROFLOXACIN INJECTION?

CIPROFLOXACIN INJECTION is an antibiotic in the quinolone class that contains the active ingredient ciprofloxacin. CIPROFLOXACIN INJECTION is formulated to kill bacteria causing infection. You should contact your doctor if your condition has not improved or if it has worsened while taking CIPROFLOXACIN INJECTION.

CIPROFLOXACIN INJECTION is available in one strength: ciprofloxacin 2 mg/mL solution in 5% dextrose.

How and when should CIPROFLOXACIN INJECTION be administered?

CIPROFLOXACIN INJECTION will be administered according to your doctor's instructions, usually for 7-14 days, depending on the infection.

Stopping an antibiotic too early may result in failure to cure your infection.

Who should not take CIPROFLOXACIN INJECTION?

CIPROFLOXACIN INJECTION should not be taken if you have ever had a severe reaction to any of the ingredients contained within this medication or to the group of antibiotics known as "quinolones". Before taking this medication, tell your doctor if you have a history of seizures (see: What is in your medicine?).

You should not take CIPROFLOXACIN INJECTION if you are currently taking tizanidine for the management of spasticity. Tizanidine concentrations may increase and cause further side effects

such as drowsiness, sleepiness and low blood pressure.

As CIPROFLOXACIN INJECTION contains dextrose, you should not use this product if you have hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase- isomaltase deficiency.

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

CIPROFLOXACIN INJECTION is not recommended for persons less than 18 years of age.

What are the possible side effects of CIPROFLOXACIN INJECTION?
CIPROFLOXACIN INJECTION is generally well-tolerated. The most common side effects, which are usually mild, include nausea and diarrhea. Antibiotics of the quinolone class may also cause vomiting, rash, and abdominal pain/discomfort. If these symptoms persist, call your health care professional.

If you experience symptoms such as severe diarrhea (watery or bloody), with or without fever or abdominal pain, you may have C*lostridium difficile* colitis (bowel inflammation). If this happens, administration of CIPROFLOXACIN INJECTION should stop and you should contact your healthcare professional immediately.

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

Some patients taking quinolone antibiotics may become more sensitive to sunlight or ultraviolet light such as that used in tanning salons. You should avoid excessive exposure to sunlight or ultraviolet light while you are taking CIPROFLOXACIN INJECTION.

Quinolones, a class of antibiotics including ciprofloxacin, have been rarely associated with inflammation of the tendons. If you experience pain, swelling or rupture of a tendon, administration of CIPROFLOXACIN INJECTION should stop, and you should rest, avoid physical exercise and call your health care professional.

Treatment with a quinolone antibiotic, including CIPROFLOXACIN INJECTION, may worsen

muscle weakness in persons with myasthenia gravis. If you have myasthenia gravis, CIPROFLOXACIN INJECTION should not be administered.

Neuropathy (problems in the nerves) has been reported in patients receiving quinolones, including ciprofloxacin. If neuropathy symptoms occur such as pain, burning, tingling, numbness or weakness, administration of CIPROFLOXACIN INJECTION should stop and you should contact your doctor immediately.

Seizures have been reported in patients receiving quinolone antibiotics including ciprofloxacin. If you have experienced seizures in the past, be sure to let your physician know that you have a history of seizures. Quinolones, including ciprofloxacin, have been rarely associated with other central nervous system events including confusion, tremors, headache, hallucinations, depression, agitation, insomnia, anxiety, nervousness and rarely, suicidal thoughts.

In some cases, depression or psychotic reactions can lead to attempted or completed suicide, even after one dose of ciprofloxacin. If reactions such as depression, suicidal thoughts or psychotic reactions occur, administration of CIPROFLOXACIN INJECTION should stop.

Cases of severe liver problems and liver failure have been reported with ciprofloxacin. If symptoms of liver problems occur, such as yellowing of the skin or eyes, dark urine, nausea, vomiting, abdominal pain, or itching, administration of CIPROFLOXACIN INJECTION should stop and you should contact a doctor immediately.

Other side effects include: cramping, disturbed coordination (unsteady walk), dizziness, fainting, feeling unwell, gas, increased muscle tone, inflammation of joints, irregular heart rhythm, loss of appetite, loss of hearing (tinnitus), migraine, muscle pain, pustular rash, sleeping problems, sweating and taste disorders.

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

What about other medications I am taking?
It is important to let your health care professional know of all the medicines and supplements that you are using including the following:

Theophylline or didanosine chewable/buffered tablets or pediatric powder.

Other medications including oral anticoagulants (like warfarin and acenocoumerol), phenytoin, duloxetine, tizanidine, methylxanthines, caffeine, sevelamer, sucralfate, clozapine, ropinirole, lidocaine, sildenafil, pentoxifylline, probenacid, methotrexate, metoclopramide, cyclosporine,

lanthanum carbonate, and certain heart medications known as antiarrhythmics which may interact with ciprofloxacin.

Antidiabetic agents (e.g. glyburide, glibenclamide, glimepiride, insulin) as the combination of these agents with ciprofloxacin may cause lower blood sugar.

Avoid excessive caffeine intake (e.g. coffee).

What is in your medicine?
Each mL of CIPROFLOXACIN INJECTION contains 2 mg of ciprofloxacin. The other ingredients are dextrose, lactic acid, hydrochloric acid to adjust pH and water for injection.

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

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