PRODUCT MONOGRAPH
WITH PATIENT MEDICATION INFORMATION

Pr CIPROFLOXACIN INTRAVENOUS INFUSION, BP

Ciprofloxacin 2 mg/mL in 5.5 % Dextrose

Sterile

Antibacterial Agent

Apotex Inc. 150 Signet Drive Weston, Ontario M9L 1T9	Date of Preparation: July 8, 2019

Submission Control No: 226595

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CIPROFLOXACIN INTRAVENOUS INFUSION, BP

Ciprofloxacin Injection

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
I.V.	Solution for Injection 2 mg/mL	none

INDICATIONS AND CLINICAL USE

Ciprofloxacin Intravenous Infusion is indicated for:

- treatment of patients with the following infections caused by susceptible strains of the indicated microorganisms:

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

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

Urinary Tract Infections
Upper and lower complicated urinary tract infections including pyelonephritis caused by:
Citrobacter diversus
Escherichia coli
Klebsiella pneumoniae
Proteus mirabilis
Pseudomonas aeruginosa

Skin or Skin Structure Infections
Caused by:
Enterobacter cloacae
Escherichia coli
Klebsiella pneumoniae
Morganella morganii
Proteus mirabilis
Proteus vulgaris
Pseudomonas aeruginosa
Staphylococcus aureus
Streptococcus pyogenes

Septicemia
Caused by:
Escherichia coli
Salmonella typhi

Bone
Caused by:
Enterobacter cloacae
Pseudomonas aeruginosa

Complicated Intra-abdominal Infections only when used in Combination with Metronidazole
(See **DOSAGE AND ADMINISTRATION**)
Caused by:
Escherichia coli
Pseudomonas aeruginosa
Klebsiella pneumoniae
Bacteroides fragilis

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

Empiric Therapy in Febrile Neutropenic Patients (in Combination with Piperacillin Sodium) (See **DOSAGE AND ADMINISTRATION**)

Appropriate culture and susceptibility tests should be performed prior to initiating treatment in order to isolate and identify organisms causing the infection and to determine their susceptibilities to ciprofloxacin. Therapy with ciprofloxacin 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.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Ciprofloxacin I.V. and other antibacterial drugs, Ciprofloxacin I.V. should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

CONTRAINDICATIONS

- Ciprofloxacin 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

Fluoroquinolones, including CIPROFLOXACIN INTRAVENOUS INFUSION, BP, have been associated with disabling and potentially persistent adverse reactions which to date include, but are not limited to: tendonitis, tendon rupture, peripheral neuropathy and neuropsychiatric effects.

General

SERIOUS AND FATAL REACTIONS HAVE BEEN REPORTED IN PATIENTS RECEIVING CONCURRENT ADMINISTRATION OF CIPROFLOXACIN 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 (predominantly achilles tendon) has been reported predominantly in the elderly on prior systemic treatment with glucocorticoids. At any sign of tendonitis (i.e., painful swelling), the administration of ciprofloxacin should be discontinued, physical exercise avoided, and a physician consulted.

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

Intravenous infusion should be administered by slow infusion over a period of 60 minutes. Local IV 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 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

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

Blood Glucose Disturbances

Fluoroquinolones, including CIPROFLOXACIN INTRAVENOUS INFUSION, BP, have been associated with disturbances of blood glucose, including symptomatic hyperglycemia and hypoglycemia, usually in diabetic patients receiving concomitant treatment with an oral hypoglycemic agent (e.g., glyburide) or with insulin. In these patients, careful monitoring of blood glucose is recommended. SEVERE CASES OF HYPOGLYCEMIA RESULTING IN COMA OR DEATH HAVE BEEN REPORTED. If a hypoglycemic reaction occurs, discontinue CIPROFLOXACIN INTRAVENOUS INFUSION, BP immediately and initiate appropriate therapy.

Cardiovascular

Aortic Aneurysm and Aortic Dissection

Epidemiologic studies report an increased risk of aortic aneurysm and dissection after intake of fluoroquinolones, particularly in the older population.

Therefore, fluoroquinolones should only be used after careful benefit-risk assessment and after consideration of other therapeutic options in patients with positive family history of aneurysm disease, or in patients diagnosed with pre-existing aortic aneurysm and/or aortic dissection, or in presence of other risk factors for aortic aneurysm and dissection (e.g., Marfan’s syndrome, vascular Ehlers-Danlos syndrome, Takayasu’s arteritis, giant cell arteritis, Behcet's disease, hypertension, atherosclerosis).

In case of sudden severe abdominal, chest or back pain, patients should be advised to immediately consult a physician in an emergency department.

Central Nervous System Effects

Psychiatric Adverse Reactions

Fluoroquinolones, including CIPROFLOXACIN INTRAVENOUS INFUSION, BP, have been associated with an increased risk of psychiatric adverse reactions, including: toxic psychoses, hallucinations, or paranoia; depression, or suicidal thoughts; anxiety, agitation, restlessness, or nervousness; confusion, delirium, disorientation, or disturbances in attention; insomnia or nightmares; and memory impairment. Cases of attempted or completed suicide have been reported, especially in patients with a medical history of depression, or an underlying risk factor for depression. These reactions may occur following the first dose. If these reactions occur in patients receiving CIPROFLOXACIN INTRAVENOUS INFUSION, BP, discontinue CIPROFLOXACIN INTRAVENOUS INFUSION, BP and institute appropriate measures.

Central Nervous System Adverse Reactions

Fluoroquinolones, including CIPROFLOXACIN INTRAVENOUS INFUSION, BP, have been associated with an increased risk of seizures (convulsions), increased intracranial pressure (including pseudotumor cerebri), tremors, and light-headedness. As with other fluoroquinolones, CIPROFLOXACIN INTRAVENOUS INFUSION, BP should be used with caution in patients with a known or suspected central nervous system (CNS) disorder that may predispose them to seizures or lower the seizure threshold (e.g., severe cerebral arteriosclerosis, epilepsy) or in the presence of other risk factors that may predispose them to seizures or lower the seizure threshold (e.g., certain drug therapy, renal dysfunction). If these reactions occur in patients receiving CIPROFLOXACIN INTRAVENOUS INFUSION, BP, discontinue CIPROFLOXACIN INTRAVENOUS INFUSION, BP immediately and institute appropriate measures.

Dextrose load for intravenous solution formulation
The 5.5% dextrose w/v intravenous solution is unsuitable for patients with rare glucose-galactose malabsorption. (See **PHARMACEUTICAL INFORMATION**).

Carcinogenesis and Mutagenesis
See animal data in Toxicology section.

Endocrine and Metabolism
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). Increased plasma concentrations associated with drug specific side effects may be observed due to inhibition of their metabolic clearance by ciprofloxacin.

Hepatic/Biliary/Pancreatic
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 **SCIENTIFIC INFORMATION - DETAILED PHARMACOLOGY**)

Pseudomembranous Colitis
Pseudomembranous colitis has been reported with virtually all antibacterial agents, including ciprofloxacin, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients with diarrhea subsequent to the administration of antibacterial agents. Subsequent to diagnosis of pseudomembranous colitis, therapeutic measures should be initiated. Mild cases will usually respond to discontinuation of drug alone. In moderate to severe cases, consideration should be given to the management with fluids, electrolytes, protein supplementation and treatment with an antibacterial drug effective against *C. difficile*.

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

Sensitivity/Resistance
Serious hypersensitivity and/or anaphylactic reactions have been reported in patients receiving

quinolone therapy, including ciprofloxacin. These reactions may occur within the first 30 minutes following the first dose and may require epinephrine and other emergency measures. Some reactions have been accompanied by cardiovascular collapse, hypotension/shock, seizure, loss of consciousness, tingling, angioedema (including tongue, laryngeal, throat or facial edema/swelling), airway obstruction (including bronchospasm, shortness of breath and acute respiratory distress), dyspnea, urticaria, itching and other serious skin reactions.

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

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

Skin

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.

Special Populations

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

Nursing 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, taking into account the importance of the drug to the mother and the possible risk to the infant.

Pediatrics (< 18 years of age): 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. Damage to juvenile weight-bearing joints and lameness were observed both in rat and dog studies but not in weaned piglets. Histopathological examination of the weight-bearing joints in immature dogs revealed permanent lesions of the cartilage. (See **SCIENTIFIC INFORMATION** - **TOXICOLOGY**)

Geriatrics: Ciprofloxacin is substantially excreted by the kidney and the risk of adverse reactions may be greater in patients with impaired renal function. (See **SCIENTIFIC INFORMATION** - **DETAILED PHARMACOLOGY**)

Susceptibility/Resistance
Prescribing Ciprofloxacin I.V. in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and risks the development of drug-resistant bacteria.

ADVERSE REACTIONS

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

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

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

Local IV 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 IV administration is not contraindicated unless the reactions recur or worsen.

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates*.

Less Common Clinical Trial Adverse Drug Reactions (<1%)
Events possibly, probably drug-related occurring at a frequency of less than 1% with ciprofloxacin oral and IV treatment during clinical trials and subsequent post-marketing surveillance are as follows:

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

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

Digestive: abdominal pain, anorexia, dry mouth, dyspepsia, dysphagia, enlarged abdomen, flatulence, gastrointestinal moniliasis, jaundice, stomatitis, vomiting, abnormal liver function test.

The following have been reported rarely: moniliasis (oral), cholestatic jaundice, and pseudomembranous colitis. The following have been reported very rarely: constipation, esophagitis, gastrointestinal hemorrhage, glossitis, hepatomegaly, ileus, increased appetite, intestinal perforation, life-threatening pseudomembranous colitis with possible fatal outcome, liver damage, melena, pancreatitis, tenesmus, tooth discoloration, toxic megacolon, ulcerative stomatitis.

Hemic and Lymphatic: agranulocytosis, anemia, eosinophilia, granulocytopenia, leukocytopenia, leukocytosis, pancytopenia. The following have been reported very rarely: altered prothrombin levels, haemolytic anemia, marrow depression (life threatening), pancytopenia (life threatening), thrombocytopenia, thrombocytosis.

Hypersensitivity: rash. The following have been reported rarely: allergic reaction, anaphylactic/anaphylactoid reactions including facial, vascular and laryngeal edema, drug fever, hemorrhagic 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. 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).

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

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

Musculoskeletal: The following have been reported rarely: achiness, arthralgia (joint pain), joint disorder (joint swelling), pain in the extremities, partial or complete tendon rupture (predominantly achilles tendon), tendonitis (predominantly achillotendonitis), myalgia (muscular pain). The following have been reported very rarely: myasthenia (exacerbation of symptoms of 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.

Nervous System: agitation, confusion, convulsion, dizziness, hallucinations, headache, hypesthesia, increased sweating, insomnia, somnolence, tremor (trembling). The following has been reported rarely: paresthesia (peripheral paralgesia). The following have been reported very rarely: abnormal dreams (nightmares), anxiety, apathy, ataxia, depersonalization, depression, diplopia, hemiplegia, hyperesthesia, hypertonia, increase of intracranial pressure, meningism, migraine, nervousness, neuritis, paresthesia, polyneuritis, sleep disorder, twitching, grand mal convulsions, abnormal (unsteady) gait, psychosis, intracranial hypertension. In some instances, these reactions occurred after the first administration of 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, rash, maculopapular rash. The following has been reported rarely: photosensitivity reaction. The following have been reported very rarely: alopecia, angioedema, fixed eruption, photosensitive dermatitis, petechia, urticaria.

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

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

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

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

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

Cardiovascular: peripheral edema

Digestive: colitis, gastritis, tongue discoloration

Hemic and Lymphatic: coagulation disorder, thrombocythemia

Skin: fungal dermatitis, pustular rash, sweating

Metabolic: healing abnormal, hypernatremia

Nervous: dementia

Urinary: kidney tumour necrosis, urinary incontinence

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

edema (conjunctivae, hands, lips, lower extremities, neck), epistaxis, exfoliative dermatitis, fever, gastrointestinal bleeding, gout (flare up), gynecomastia, hearing loss, hemoptysis, hemorrhagic cystitis, hyperpigmentation, joint stiffness, lightheadedness, lymphadenopathy, manic reaction, myoclonus, nystagmus, pain (arm, breast, epigastric, foot, jaw, neck, oral mucosa), paranoia, phobia, pleural effusion, polyuria, postural hypotension, pulmonary embolism, purpura, QT prolongation (frequency <1 per million), renal calculi, respiratory arrest, respiratory distress, restlessness, rhabdomyolysis, torsades de pointes (frequency <1 per million), toxic psychosis, unresponsiveness, urethral bleeding, urination (frequent), ventricular ectopy, ventricular fibrillation (frequency <1 per million), ventricular tachycardia (frequency <1 per million), vesicles, visual acuity (decreased) and visual disturbances (flashing lights, change in colour perception, overbrightness of lights).

Post-Market Adverse Drug Reactions

See section Less Common Clinical Trial Adverse Drug Reactions (<1%) above.

Serious Drug Interactions

Drug interaction with theophylline (see **Drug-Drug Interactions** below)

DRUG INTERACTIONS

Overview

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

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

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

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

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

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

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

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.

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 AND PRECAUTIONS**.)
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 Cmax of duloxetine. Although no clinical data are available on a possible interaction with ciprofloxacin, similar effects can be expected upon concomitant administration.

Drug-Drug Interactions

Table # 1- Established or Potential Drug-Drug Interactions

Ciprofloxacin	Ref	Effect	Clinical comment
Theophylline	CT	↑ theophylline conc.	Serum levels of theophylline should be monitored and dosage adjustment made as appropriate.
Caffeine	CT	Interferes with the metabolism and pharmacokinetic of ciprofloxacin	Excessive caffeine intake should be avoided
Cyclosporine	CS	Transient ↑ in serum creatine levels	
Warfarin	CS	↑ the effects of warfarin and its derivatives	Prothrombin time or other appropriate coagulant tests should be closely monitored
Probenecid	CT	↑ level of ciprofloxacin in the serum	
Fenbufen	CS	↑ risk of CNS stimulation and convulsive seizures	
Glyburide	CS	↑ the action of glyburide	
Methotrexate	T	might ↑ plasma levels of methotrexate	This might increase the risk of methotrexate associated toxic reactions

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

Drug-Herb Interactions
Interactions with herbal products have not been established.

Drug-Laboratory Interactions
Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

- Severity and nature of the infection
- Susceptibility of the causative organism
- Integrity of the patient's host-defense mechanisms
- Status of patients's renal function.

Recommended Dose and Dosage Adjustment

Ciprofloxacin should be administered by IV 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 Intravenous Infusion, BP are:

Table 2: Recommended Adult dosages of Ciprofloxacin Intravenous Infusion, BP

Location of Injection	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 Blood Bone	Moderate	400 mg	q12h	800 mg
Intra-abdominal	Complicated	400 mg	q12h	400 mg q12h only when used in combination with metronidazole 500 mg IV q6h*
Empiric Therapy in febrile Neutropenic Patients	Severe Ciprofloxacin + Piperacillin Sodium	400 mg 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 PO ql2h plus metronidazole 500 mg PO q6h) during day 3, 4 or 5 of therapy when able to take oral medication and having shown an initial clinical response to the intravenous therapy.

2) See Metronidazole Product Monograph for Prescribing Information including cautionary statements.

3) For information on ciprofloxacin plus metronidazole combination therapy, see **ACTION AND CLINICAL PHARMACOLOGY, SCIENTIFIC INFORMATION - DETAILED PHARMACOLOGY, and ADVERSE REACTION** sections of the Ciprofloxacin Product Monograph.

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

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

Sequential IV/PO 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 IV/PO 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 **SCIENTIFIC INFORMATION - DETAILED 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 3: 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
	IV	
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 3. On dialysis days, the dose should be administered after dialysis.

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

Creatinine Clearance mL/sec =

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

Females: 0.85 x the above value

In traditional units mL/min =

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

Females: 0.85 x the above value

Impaired Hepatic Function
No dosage adjustment is required.

Pediatric Use
The safety and efficacy of Ciprofloxacin Intravenous Infusion, BP in individuals less than 18 years of age has not been established. Ciprofloxacin Intravenous Infusion, BP should not be used in pediatric patients and adolescents. (See **WARNINGS AND PRECAUTIONS**)

Administration
Intermittent Intravenous Infusion
Ciprofloxacin Intravenous Infusion, BP should be administered only by intravenous infusion over a period of 60 minutes. The drug should not be given by rapid injection. Slow infusion of a dilute solution into a large vein will minimize patient discomfort and reduce the risk of venous irritation.

If Ciprofloxacin Intravenous Infusion, BP is to be given concomitantly with another drug, each drug should be given separately in accordance with the recommended dosage and route of administration for each drug. Only Ciprofloxacin Intravenous Infusion, BP contains ciprofloxacin at 2.0 mg/mL and should be administered "as is".

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

OVERDOSAGE

In the event of acute, excessive 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.

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

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 topoisomerases), which are required for bacterial DNA replication, transcription, repair, and recombination.

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

The mechanism of action of fluoroquinolones, including ciprofloxacin, is different from that of penicillins, cephalosporins, aminoglycosides, macrolides, and tetracyclines. Therefore, microorganisms resistant to these classes of drugs may be susceptible to ciprofloxacin. Conversely, microorganisms resistant to fluoroquinolones may be susceptible to these other classes of antimicrobial agents. (See **SCIENTIFIC INFORMATION - MICROBIOLOGY**.) There is no cross-resistance between ciprofloxacin and the mentioned classes of antibiotics.

Pharmacodynamics

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

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

Pharmacokinetics

Table #4 Summary of Ciprofloxacin's Pharmacokinetic Parameters in Healthy Volunteers

	$t_{½}$ (h)	Clearance	Volume of distribution
Single dose mean	**5-6 hours**	**35 L/h**	**2-3 L/kg**

General: Ciprofloxacin and metronidazole have been studied in combination and serum levels of ciprofloxacin are not significantly altered by metronidazole at the doses studied. Serum levels of metronidazole when administered orally at a dose of 500 mg q6h in combination with ciprofloxacin 500 mg PO ql2h 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 ql2h 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 **SCIENTIFIC INFORMATION - DETAILED 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.

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

Comparison of the pharmacokinetic parameters for a bid and tid i.v. dose regimen indicated no evidence of drug accumulation for ciprofloxacin and its metabolites.

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

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

The 400 mg i.v. dose administered over 60 minutes every 12 hours resulted in a Cmax 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: 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.

Excretion: Ciprofloxacin is largely excreted unchanged both renally and to a smaller extent non-renally. Renal clearance is between 0.18-0.3 L/h/kg and the total body clearance between 0.48-0.60 L/h/kg. Ciprofloxacin undergoes both glomerular filtration and tubular secretion.

Non-renal clearance of ciprofloxacin is mainly due to active transintestinal secretion as well as metabolization. 1% of the dose is excreted via the biliary route. Ciprofloxacin is present in the bile in high concentrations.

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.

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 IV 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.

STORAGE AND STABILITY

Minibags: Protect from light, excessive heat and freezing.
Store at controlled room temperature 15°-25°C (56°-77°F).
Use promptly when pouch is opened.

As with all parenteral drug products, injections/intravenous admixtures should be inspected visually for clarity, particulate matter, precipitate, discolouration and leakage prior to administration, whenever solution and container permits. Solutions showing haziness, particulate matter, precipitate or leakage should not be used. Discard unused portion.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Minibags: each mL contains 2 mg of ciprofloxacin in ready-to-use minibags of 100 mL and 200 mL.
The minibags are made of polyvinyl chloride (PVC) and an over pouch to protect from moisture.

Minibags:

Ciprofloxacin, USP	200 mg	400 mg
Dextrose Monohydrate, EP	5.5 g	11.0 g
Lactic Acid solution, EP	64 mg	128 mg
1 N Hydrochloric Acid	pH to 3.5-4.6	pH to 3.5-4.6
Water for Injection, EP	qs to 100 mL	qs to 200 mL

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

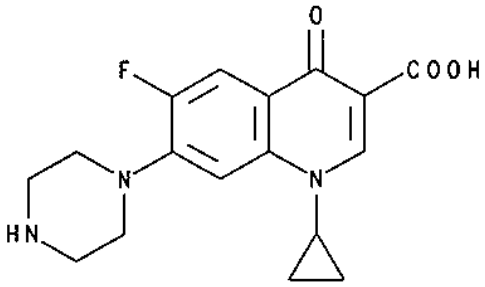
Drug Substance

Proper name: Ciprofloxacin

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

Molecular formula and molecular mass: $C_{17}H_{18}FN_3O_3$ 331.4 g/mol

Structural formula:



Physicochemical properties: Ciprofloxacin is a pale yellow to white crystalline powder which is soluble in dilute (0.1 N) hydrochloric acid and is practically insoluble in water and ethanol. Ciprofloxacin melts at about 255°C, with decomposition. pH of ciprofloxacin is 7.6 at 0.1 g/L water at 20°C. It has a pK_{a1} of 6.5 and pK_{a2} of 8.9 determined using a 3 x 10^{-4} M solution at 25°C.

DETAILED PHARMACOLOGY

Animal Pharmacology

Effects on histamine release

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

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

Bronchodilatory Effects

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

CNS Effects

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

Gastrointestinal Effects

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

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

Effect on Blood Glucose and Serum Triglycerides

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

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

Human Pharmacology

Pharmacokinetics

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 5). At steady-state, the serum elimination half-life was approximately 5-6 hours and the total clearance around 35 L/hr was observed. Comparison of the pharmacokinetic parameters following the 1st and 5th IV dose on a 12h regimen indicated no evidence of drug accumulation.

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

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

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

Table 5: Pharmacokinetic parameters of Ciprofloxacin Following Single Doses in Health Volunteers Oral/IV

Dose	250 mg	500 mg	750 mg	200 mg IV*	400 mg IV*
C_{max} (mg/L)	1.42	2.6	3.41	2.14	4.6
$t_{½}$ (hr)	4.19	4.87	5.34	3.4	3.5
$AUC_{0-\infty}$ (mg•h/mL)	5.43	10.6	15.03	5.24	11.69
t_{max} (hr)	1.11	1.11	1.56	0.95	1

*IV parameters following a 60-minute infusion period

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

Table 6: Mean Pharmacokinetic Parameters of Ciprofloxacin and Metronidazole at Stady State in Healthy Volunteers

Regimen	AUC (mg•h/mL)	C_{max} (mg/L)	t_{max} (h)
(i) When administered alone			
Ciprofloxacin 400 mg IV q12h	12.7 (AUC_{0-12})	4.56	1
(ii) When administered as Ciprofloxacin 400 mg IV q12h in combination with Metronidazole 500 mg IV q6h			
Ciprofloxacin	15.9 (AUC_{0-12})	5.21	1
Metronidazole	153.0 (AUC_{0-6})	33.6	1

Note: Following the repeated dosing of metronidazole 500 mg IV tid, the peak and minimum

mean plasma metronidazole concentrations, at steady-state, were 26 μ g/mL and 12 μ g/mL respectively.

Figure 1
Mean Serum Ciprofloxacin Serum Concentration (mg/L) vs Time after A Single Intravenous Dose Administered over 60 Minutes

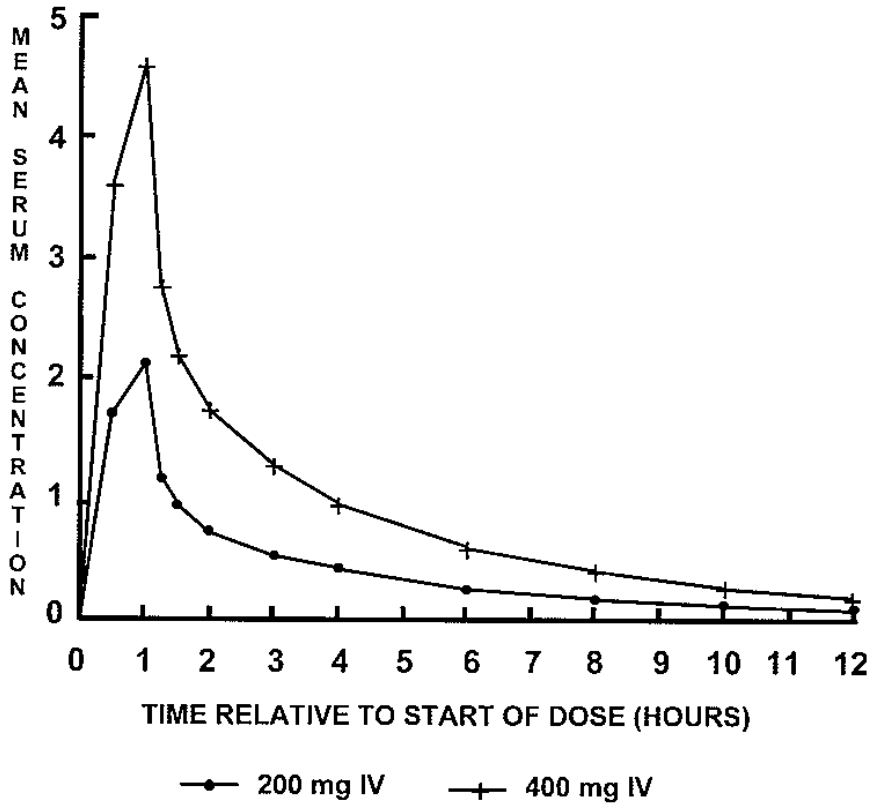


Table 7: Mean Urinary Excretion of Ciprofloxacin

Hours After Administration of a Single Dose				
	0 - 2	**2 - 4**	**4 - 8**	**8 - 12**
Urine Concentration mg/L (± S.D.)				
200 mg iv	335.2 (±61.5)	99.9 (±16.0)	71.7 (±10.9)	31.24 (±4.06)
400 mg iv	706.0 (±99.0)	181.3 (±25.9)	127.1 (±18.9)	63.5 (±7.4)
Amount Excreted mg (± S.D.)				
200 mg iv	58.8 (±9.3)	13.6 (±3.2)	14.1 (±9.0)	7.5 (±2.5)

400 mg iv	125.0 (±7.2)	24.1 (± 4.7)	35.1 (±12.7)	15.7 (±3.9)

Note: IV dose administered over 30 minutes.

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

Following the 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 yrs, 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 IV dose, urine concentrations of ciprofloxacin usually exceed 200 µg/mL during the first two hours after dosing, and are generally greater than 10 µ g/mL at 8 to 12 hours after dosing. The urinary excretion of ciprofloxacin is virtually complete by 24 hours after dosing. Approximately 15% of an IV dose is recovered from the feces within 5 days after dosing, which may arise from either biliary clearance or transintestinal elimination. Following intravenous administration, approximately 10% of the dose is recovered in the urine in the form of metabolites.

Factors Influencing the Pharmacokinetics

Impaired Renal Function

Ciprofloxacin is eliminated primarily by renal excretion. Some modification of dosage is recommended, particularly for patients with severe renal dysfunction.

The pharmacokinetics of ciprofloxacin following multiple IV doses were compared in subjects with normal renal function and in subjects with various degrees of renal impairment (see Table 8, Groups 1-4). Patients with renal insufficiency had significantly increased concentrations of ciprofloxacin, M1 and M2 metabolites and decreased renal clearances.

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

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

In an open-label crossover study, seven hemodialysis patients received a single dose of i.v. ciprofloxacin on two separate occasions, once immediately after hemodialysis, and once two hours before hemodialysis. The results demonstrated that the pharmacokinetic parameters were not significantly different between the two treatments for ciprofloxacin, M1 and M2 metabolites. Group 6 in Table 8 shows the pharmacokinetic results for the group dosed two hours before hemodialysis.

Table 8: Mean Pharmacokinetic Parameters for Ciprofloxacin and Metabolites M1 and M2 Following IV Dosing in Healthy Volunteers, Patients with Renal Insufficiency, Peritoneal Dialysis Patients, and Hemodialysis Patients

Group	Creatinine Clearance mL/min/1.73m^2	IV Ciprofloxacin Dose	Parameter								
			Ciprofloxacin			M1 (desethylene ciprofloxacin)			M2 (sulfociprofloxacin)		
			AUC_{0-12} (mg.hr/L)	$C1_r$ (L/hr)	$t_{½}$ (hr)	AUC_{0-12} (mg.hr/L)	$C1_r$ (L/hr)	$t_{½}$ (hr)	AUC_{0-12} (mg.hr/L)	$C1_r$ (L/hr)	$t_{½}$ (hr)
1	> 90	400 mg q8h x 11	10.2	20.3	4.59	0.19	19.9	5.04	0.98	19.5	2.3
2	61 - 90	400 mg q8h x 11	15.4	10.9	5.23	0.34	10.8	8.14	1.5	10.7	3.1
3	31 - 60	400 mg q12h x 8	21.5	6.91	5.72	0.57	7.1	9.1	4.21	6.52	5.3
4	≤ 30	300 mg q12h x 8	30.1	1.36	8.33	1.09	1.7	15.2	13	1.09	14
5	chronic renal failure patients on peritoneal dialysis	400 mg single dose	38.7	0.98	8.39	4.49	0.074	28.6	54.8	0.08	23
6	chronic renal failure patients on hemodialysis	400 mg single dose	38.4	0.11	11.40	2.05	0.087	11.6	29.9	0.073	13

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 IV 200 mg, there was no difference in pharmacokinetics between patients with stable chronic cirrhosis (with mild to moderate hepatic impairment) and healthy volunteers.

Drug Interactions

Theophylline

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

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

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 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 pharmacokinetic parameters.

Analysis with a three-compartmental pharmacokinetic model quantified approximate sizes and kinetics of distribution into two peripheral compartments. A rapidly equilibrating compartment (V_2) with a high intercompartmental clearance rate, accounting for the rapid decline in ciprofloxacin concentrations in serum immediately following drug infusion, and a third, slowly equilibrating tissue compartment with relatively slow intercompartmental clearance. This would contribute to the prolonged terminal half-life (4 to 5 h) of ciprofloxacin IV.

The results of this study were as follows:

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

Table 9 summarizes the results of tissue and fluid penetration of ciprofloxacin in man.

Table 9: 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)
Bronchial Tissues	10	200 mg iv	3.94 ± 2.5	1.62 ± 0.7	0.97
Vagina	18	100 mg iv	1.13 ±0.2	0.61 ± 0.12	0.5
Ovary	18	100 mg iv	1.00 ± 0.23	0.61 ± 0.12	0.5

MICROBIOLOGY

The *in vitro* activity of ciprofloxacin against clinical isolates of gram-positive and gram-negative aerobic and anaerobic bacteria is shown in Table 10. Its bactericidal action is achieved through inhibition of topoisomerase II (DNA gyrase) and topoisomerase IV (both Type II topoisomerases), which are required for bacterial DNA replication, transcription, repair, and recombination. Susceptibility was determined by both agar and broth dilution tests, pH 7.1-7.4, using inoculum sizes ranging from 10^4 to 10^5 colony forming units per mL.

The mechanism of action of fluoroquinolones, including ciprofloxacin, is different from that of penicillins, cephalosporins, aminoglycosides, macrolides, and tetracyclines. Therefore, microorganisms resistant to these classes of drugs may be susceptible to ciprofloxacin. Conversely, microorganisms resistant to fluoroquinolones may be susceptible to these other classes of antimicrobial agents. There is no cross-resistance between ciprofloxacin and the mentioned classes of antibiotics.

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

Table 10: Cumulative Percent of Strains Inhibited at the Indicated Concentration of Ciprofloxacin

		mg/L												
Genera or Species	**(Number of Strains)**	**0.02**	**0**	**0.1**	**0.12**	**0.25**	**0.5**	**1**	**2**	**4**	**8**	**16**	**32**	**64**
Acinetobacter antiratus	-42		2	12	19	52	86	95		98	100			
Actinomyces spp.	-3						33.3				100			
Branhamella catarrhalis	-28	4	43	100										
Campylobacter jejuni	-100			64	95	97	100							
Chlamydia trachomatis	-10							70	100					
Clostridium spp.	-8				10	55	75		95	100				
Clostridium perfringens	-12				8.3	83	100							
Citrobacter freundii	-19	88	94				100							
Citrobacter diversus	-3	66	100											
Citrobacter spp.	-4	100												
Enterobacter aerogenes	-5	50	83		100									
Enterobacter agglomerans	-2	100												

		mg/L												
Genera or Species	**(Number of Strains)**	**0.02**	**0**	**0.1**	**0.12**	**0.25**	**0.5**	**1**	**2**	**4**	**8**	**16**	**32**	**64**
Enterobacter cloaceae	-49	61	86	96	100									
Escherichio coli	-203	84	92	93	96	98	99	100						
Flavobacterium brevie	-3						66	100						
Fusobacterium spp.	-8					25	50		75	87.5	100			
Haemophilus ducreyi	-72	100												
Haemophilus influenzea beta-lactamase positive	-50		90	100										
Klebsiella oxytoca	-32	78	97		100									
Klebsiella pneumonia	-40	21	72	85	90	97	100							
Klebsiella species	-24	33	88	92		96	100							
Morganella morganii	-12	92	100											
Moraxella spp.	-5		20		40	60	80	100						
Neisseria gonorrhoeae beta-lactamase negative	-15		13	73	87	100								
Propionibacterium spp.	-42				2.4	28.6	88.1	92.9	100					
Proteus mirabilis	-57	28	88	93	98	100								
Proteus vulgaris	-3	100												
Providencia alcalifaciens	-6	33					66		100					
Providencia rettgeri	-5		80		100									
Providencia stuartii	-16	6	25	38	50	56	75		100					
Pseudomonas aeruginosa	-187	1	2	7	41	65	83	89	96		98	100		
Pseudomonas aeruginosa (Fibrocystic mucoid strain)	-(30)		3	20	43	63	80	100						
Pseudomas aeruginosa (Fibrocystic non-mucoid strain)				13	50	93	100							

		mg/L												
Genera or Species	**(Number of Strains)**	**0.02**	**0**	**0.1**	**0.12**	**0.25**	**0.5**	**1**	**2**	**4**	**8**	**16**	**32**	**64**
Pseudomonas aeruginosa (Bacteremic non-cyctic strain)			3	57	88	100								
Pseudomonas cepacia	-10							50	100					
Pseudomonas fluorescens	-8				50	75	100							
Pseudomonas maltophilia	-11			9			36	55	64	82	91	100		
Salmonella spp.	-81		33	68	96	100								
Serratia marcescens	-12		50	100										
Shigella spp.	-59		97	98	98	100								
Shigella sonnei	-45	100												
Staphylococcus aureus	-101		2	5	15	52	95	100						
Staphylococcus epidermidis	-64	5		6	28	84	95	100						
Streptococcus faecalis	-39						31	87	100					
Streptococcus pneumoniae	-51					9	27	100						
Ureaplasma urealyticum	-10						20	50	100					

The minimum inhibitory concentrations (MICs) of ciprofloxacin against aerobic bacteria are not significantly affected by changes in inoculum size in the range of 5 X 10^3 to 5 X 10^6 cfu/spot. Five bacterial species, *Staphylococcus aureus K734*, *Staphylococcus epidermidis H846*, *Streptococcus faecalis 7149*, *Escherichia coli 2345*, and *Proteus mirabilis 2349* were tested for MICs with inoculum size of 5 X 10^3 to 5 X 10^6. *Streptococcus faecalis* showed a four-fold increase while the remainder showed only a two to three-fold increase (Table 11). There were no differences between MICs determined in Mueller Hinton and Isosensitest broth.

MIC values 8 to 16 fold higher were seen when these organisms were tested in Mueller Hinton broth at pH 4.8 compared to values obtained at pH 7.3 (Table 11). This reduction in antibacterial activity suggests a significant pH effect.
Some studies have demonstrated that increasing the concentration of magnesium in the medium used for *in vitro* testing reduces the antibacterial activity of ciprofloxacin. Neither zinc nor calcium supplementation had the same effect. The mechanism by which magnesium antagonizes the activity of ciprofloxacin is unclear.

Table 11: Effect of Culture Medium Composition, pH and Inoculum Size On Antibacterial Activity of ciprofloxacin

Organism/Strain		MIC (mg/L)				
		pH[a]			Inoculum Size (cfu)[b]	
		4.8	7.3	8.8	5×10^3	5×10^6
Staphylococcus aureus	K 734	4	0.5	0.5	0.25	0.5
Staphylococcus epidermidis	H 846	2	0.25	0.25	0.125	0.25
Streptococcus faecalis	7 149	8	1	1	0.5	2
Escherichia coli	2345	0.5	0.016	0.016	0.008	0.016
Proteus mirabilis	2349	1	0.03	0.016	0.008	0.03

[a] Mueller Hinton broth (BBL) 5×10^5 cfu/mL.
[b] No difference between the MIC's determined in Mueller Hinton (BBL) and Isosensitest broth (Oxiod).

Development of Resistance

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

Susceptibility Testing

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

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

	Interpretation
≤1	Susceptible (S)
2	Intermediate (I)
≥4	Resistant (R)

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

causing major discrepancies in interpretation.

A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected. Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard ciprofloxacin powder should provide the following MIC values:

Microorganism		Zone Diameter (mm)
Enterococcus faecalis	ATCC 29212	0.25-2.0
Escherichia coli	ATCC 25922	0.004 - 0.015
Staphylococcus aureus	ATCC 25923	0.12-0.5

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

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

Zone Diameter (mm)	Interpretation
≥21	(S) Susceptible
16-20	(1) Intermediate
≤15	(R) Resistant

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

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

Table 12: Daily Ranges for Ciprofloxacin for Quality Control Strains

QC Strains	Disk Zone Diameter (mm)	MIC (mg/L)
S. aureus (ATCC 25923)	22 - 30	-
S. aureus (ATCC 29213)	-	0.25 - 1.0
E. coli (ATCC 25922)	30 - 40	0.008 - 0.03
P. aeruginosa (ATCC 27853)	25 - 33	0.25 - 1.0

N. gonorrhoeae (ATCC 49226)	48 - 58	≤ 0.008

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

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

Subchronic Tolerability Studies over 3 Months
Oral administration: All doses up to and including 500 mg/kg were tolerated without damage by rats. In monkeys, crystalluria and changes in the renal tubules were observed in the highest-dose group (135 mg/kg).

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

Chronic Tolerability Studies over 6 Months
Oral administration: Doses up to and including 500 mg/kg and 30 mg/kg were tolerated without damage by rats and monkeys, respectively. Changes in the distal renal tubules were again observed in some monkeys in the highest-dose group (90 mg/kg).

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

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

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

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

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

Mutagenicity
Eight *in vitro* mutagenicity tests have been conducted with ciprofloxacin. Test results are listed below:
Salmonella: Microsome Test (Negative)
E. coli: DNA Repair Assay (Negative)
Mouse Lymphoma Cell Forward Mutation Assay (Positive)
Chinese Hamster V79 Cell HGPRT Test (Negative)
Syrian Hamster Embryo Cell Transformation Assay (Negative)
Saccharomyces 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 occured 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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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

CIPROFLOXACIN INTRAVENOUS INFUSION, BP

Ciprofloxacin 2 mg/mL in 5.5 % Dextrose

Sterile

Read this carefully before you start taking **CIPROFLOXACIN INTRAVENOUS INFUSION** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **CIPROFLOXACIN INTRAVENOUS INFUSION**.

Serious Warnings and Precautions

Fluoroquinolones, including CIPROFLOXACIN INTRAVENOUS INFUSION, are associated with disabling and long lasting effects such as:

- **tendonitis (inflamed tendon), tendon rupture.**
- **peripheral neuropathy (problems in the nerves).**
- **problems in the brain such as seizures, psychoses, confusion and other symptoms.**

See SIDE EFFECTS AND WHAT TO DO ABOUT THEM in the Patient Medication Information section for further information and symptoms.

Talk to your doctor to see if this medication is suitable for you.

What is CIPROFLOXACIN INTRAVENOUS INFUSION used for?
Ciprofloxacin Intravenous Infusion is used to treat certain bacterial infections.

Antibacterial drugs like Ciprofloxacin I.V. treat only bacterial infections. They do not treat viral infections such as the common cold. Although you may feel better early in treatment, Ciprofloxacin I.V. should be used exactly as directed. Misuse or overuse of Ciprofloxacin I.V. could lead to the growth of bacteria that will not be killed by Ciprofloxacin I.V. (resistance). This means that Ciprofloxacin I.V. may not work for you in the future. Do not share your medicine.

How does CIPROFLOXACIN INTRAVENOUS INFUSION work?
Ciprofloxacin helps prevent the action of bacterial substances needed for growth. This kills the bacteria and reduces the infection.

What are the ingredients in CIPROFLOXACIN INTRAVENOUS INFUSION?
Medicinal ingredients: Ciprofloxacin, USP

Non-medicinal ingredients: dextrose monohydrate EP, lactic acid solution EP, and hydrochloric acid to adjust the pH.

CIPROFLOXACIN INTRAVENOUS INFUSION comes in the following dosage forms:
Solution for Injection
2 mg/mL in 5.5% dextrose (available in 200 mg/100 mL and 400 mg/200 mL).

Do not use CIPROFLOXACIN INTRAVENOUS INFUSION if you are:

- allergic to ciprofloxacin.
- allergic to quinolone medications.
- allergic to any of the non-medicinal ingredients in this medication.
- taking tizanidine. This may increase the effect of tizanidine and increase your chances of having the following side effects:
    - low blood pressure.
    - sleepiness.
    - drowsiness.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take CIPROFLOXACIN INTRAVENOUS INFUSION. Talk about any health conditions or problems you may have, including if you:

- have a history of seizures.
- have a history of tendon problems when using quinolone antibiotics.
- have a disease of the brain arteries in which the blood vessel walls are thickened.
- have epilepsy or kidney disease.
- are taking theophylline (bronchodilator drug).
- already had diarrhea after taking antibacterial drugs.
- are pregnant or planning to become pregnant.
- are breast feeding or planning to breastfeed. Ciprofloxacin is passed to human breast milk. Discuss with your doctor how to feed your baby.
- are a child under the age of 18.
- Have an aortic aneurysm which is an abnormal bulge in a large blood vessel called the aorta.
- Have or if anyone in your family has a condition called aneurysm disease which is an abnormal bulge in any large blood vessel in the body.
- Have an aortic dissection which is a tear in the wall of the aorta.
- Have any of the following conditions: Marfan syndrome, vascular Ehlers-Danlos syndrome, Takayasu arteritis, giant cell arteritis or Behcet's disease.
- Have high blood pressure.
- Have atherosclerosis, which is a hardening of your blood vessels.

Other Warnings:

- Ciprofloxacin may cause:
    - dizziness.
    - sleepiness.
    - light-headedness.

If this occurs, do not drive or operate machinery.

- Ciprofloxacin may cause a reaction to light (e.g. sunburn), so:

- avoid too much time in the sun, sunlamps and tanning beds.
- Stop taking this product and talk to your doctor if you get:
    - sunburn, blisters, rash or swelling of the skin.

Other warnings that you should know about:

- Blood Sugar Changes:

Medicines like CIPROFLOXACIN INTRAVENOUS INFUSION can cause blood sugar levels to rise and drop in patients with diabetes. Serious cases of hypoglycemia (low blood sugar levels) that caused coma or death have been seen with medicines like CIPROFLOXACIN INTRAVENOUS INFUSION. If you have diabetes, check your blood sugar levels often while taking CIPROFLOXACIN INTRAVENOUS INFUSION.

- Quinolones, including CIPROFLOXACIN INTRAVENOUS INFUSION, BP have been associated with an enlargement or "bulge" of a large blood vessel (aortic aneurysm or large vessel peripheral aneurysm) and aortic dissection (a tear in the aorta wall)

    - The risk of these problems is higher if you:
        - are elderly
        - have or anyone in your family has had aneurysm disease
        - have an aortic aneurysm or an aortic dissection
        - have any of the following conditions: Marfan syndrome, vascular Ehlers-Danlos syndrome, Takayasu arteritis or giant cell arteritis or Behcet's disease
        - have high blood pressure or atherosclerosis

    - If you experience sudden, severe pain in your abdomen, chest or back, a pulsating sensation in your abdomen, dizziness or loss of consciousness, get immediate medical help.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with CIPROFLOXACIN INTRAVENOUS INFUSION:

- Theophylline (serious reactions reported).
- Caffeine.
- Cyclosporine.
- Warfarin.
- Probenecid.
- Fenbufen.
- Glyburide and methotrexate.

How to take CIPROFLOXACIN INTRAVENOUS INFUSION:

Usual dose:

Your doctor will tell you how much medicine to take. This depends on what type of infection you have and how serious it is.

Overdose:

As CIPROFLOXACIN INTRAVENOUS INFUSION is given to you under the supervision of your doctor, it is very unlikely that you will receive too much. You may need urgent medical attention.

If you think you have taken too much CIPROFLOXACIN INTRAVENOUS INFUSION, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

What are the possible side effects from using CIPROFLOXACIN INTRAVENOUS INFUSION?

These are not all the possible side effects you may feel when taking CIPROFLOXACIN INTRAVENOUS INFUSION. If you have any side effects not listed here or if your condition gets worse or does not improve then:

- contact your healthcare professional.
- see the section "**To help avoid side effects and ensure proper use, talk to your healthcare professional before you take CIPROFLOXACIN INTRAVENOUS INFUSION. Talk about any health conditions or problems you may have, including if you:**"

Stop taking CIPROFLOXACIN INTRAVENOUS INFUSION and contact your doctor if:

a) you have symptoms of an allergic reaction such as:
   - rash, hives, blistering or other skin reaction.
   - swelling of the mouth, throat, limbs.
   - difficulty breathing.
   - irregular or rapid heartbeat, or fainting spells.

b) you have pain, swelling or rupture of a tendon. You should:
   - rest.
   - avoid physical exercise.

c) you have neuropathy (damage to the nerves) with symptoms such as:
   - pain, burning, tingling, numbness or weakness.

d) you have severe diarrhea (bloody or watery) with or without:
   - fever.
   - stomach pain or tenderness.

   You may have Clostridium difficile colitis (bowel inflammation). See your doctor right away.

Other side effects include:

- your eyesight worsens or changes. See your doctor or eye specialist right away.
- nausea, dizziness.
- worsening of myasthenia gravis (a muscle disease) with symptoms such as:
  - weakness.
  - difficulty walking, swallowing, drooping eyelids.

Do not use CIPROFLOXACIN INTRAVENOUS INFUSION if you have this condition.

- mental problems such as:
  - confusion, headache, shaking.
  - hallucinations, depression, agitation.
  - difficulty sleeping, anxiety, nervousness and suicidal thoughts.

  Contact your doctor if you have suicidal thoughts.

- injection site pain.
- diarrhea, gas, stomach pain, cramping, feeling unwell.
- loss of hearing, problems of smell and taste, loss of appetite.
- difficulty sleeping, migraine, rash, sweating.

Common side effects include:

- injection site reaction.
- rash.
- diarrhea.

Self-Limiting Side Effects:

- Feeling lightheaded
- Insomnia (difficulty sleeping)
- Nightmares

Neuropathy (problems in the nerves) has been reported in patients receiving quinolones, including CIPROFLOXACIN INTRAVENOUS INFUSION.

If neuropathy symptoms occur such as pain, burning, tingling, numbness, or weakness, you should:

- stop taking CIPROFLOXACIN INTRAVENOUS INFUSION.
- contact your doctor immediately.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
RARE			
Allergic Reaction: Rash, hives (skin eruption), swelling of the face, lips, tongue or throat, difficulty swallowing or breathing, rapid heartbeat			√
Photo-sensitivity Reaction: Sensitivity to light, blistering of			√

skin			
Tendon pain, inflammation, or rupture			√
Increased Blood Sugar: Frequent urination, thirst, hunger, tiredness, blurred vision, headache, trouble concentrating	√		
Hypoglycemia (Low Blood Sugar): Change in mood, change in vision, confusion, dizziness, fast heartbeat, feeling faint, headache, hunger, shaking, sweating, weakness		√	
UNKNOWN			
Severe Bowel Disorder: Persistent diarrhea, bloody or watery diarrhea, abdominal or stomach pain/cramping, blood/mucus in stool			√
Nerve Disorder (Neuropathy): Pain, burning, tingling, numbness, weakness			√
Liver Disorder: Yellowing of the skin or eyes, dark urine, abdominal pain, nausea, vomiting, loss of appetite, pale stools		√	
Heart Disorder (QT Prolongation): Irregular heartbeat		√	
Mental Health Problems: Anxiety, confusion, depression, feeling agitated, restless or nervous, suicidal thoughts or actions, hallucinations, inability to think clearly or pay attention, memory loss, paranoia or loss of touch with reality		√	
Neurological Problems: Seizures (convulsions), tremors			√
Rise in the pressure within your skull: Blurred or double vision, headaches, nausea		√	
Aortic aneurysm (abnormal bulge in a large blood vessel called the aorta) / Aortic dissection (tear in the wall of the aorta): dizziness, loss of consciousness, pulsating sensation in the			√

abdomen, sudden, severe pain in abdomen, chest or back.			

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
CIPROFLOXACIN INTRAVENOUS INFUSION will be stored in the pharmacy or in the ward. The product is kept at controlled room temperature 15°C to 25°C, protected from light and excessive heat and freezing.

Keep out of reach and sight of children.

If you want more information about CIPROFLOXACIN INTRAVENOUS INFUSION:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (http://hc-sc.gc.ca/index-eng.php); the manufacturer's website http://www.apotex.ca/products, or by calling 1-800-667-4708.

This leaflet was prepared by Apotex Inc. Toronto, Ontario, M9L 1T9

Last Revised: July 8, 2019