PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

# Pr CIPROFLOXACIN INJECTION

**Ciprofloxacin 0.2 % Intravenous Infusion**

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

**Sterile**

**Antibacterial Agent**

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## PART I: HEALTH PROFESSIONAL INFORMATION

### SUMMARY PRODUCT INFORMATION

| Route of Administration | Dosage Form / Strength | All Nonmedicinal Ingredients |
|---|---|---|
| Intravenous | Intravenous Infusion Solution (2 mg / mL) | Lactic Acid<br>Dextrose Hydrochloric Acid<br>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 experience 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).**

To reduce the development of drug-resistant bacteria and maintain the effectiveness of CIPROFLOXACIN INJECTION and other antibacterial drugs, CIPROFLOXACIN INJECTION 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.

**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.

Ciprofloxacin should be limited in cases of uncomplicated acute bacterial cystitis to circumstances where no other treatment options are available. A urine culture should be obtained prior to treatment to ensure ciprofloxacin susceptibility.

Ciprofloxacin should not be prescribed to patients with acute bacterial exacerbations of simple / uncomplicated chronic obstructive pulmonary disease (i.e. patients who have chronic obstructive pulmonary diseases without underlying risk factors).[1]

Use of ciprofloxacin against uncomplicated gonorrhea should be limited where no other treatment options exist AND where ciprofloxacin susceptibility is demonstrated, OR ciprofloxacin susceptibility is highly likely, typically greater than or equal to 95% based on local susceptibility patterns.

## 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 agomelatine[a] is contraindicated since it may result in an undesirable increase in agomelatine exposure (see DRUG INTERACTIONS).

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).

[a] Currently not marketed in Canada

[1] Canadian Thoracic Society recommendations for management of chronic obstructive pulmonary disease - 2008 update - highlights for primary care. O'Donnell et al. Can Respir J 2008; 15(Suppl A):1A-8A.

## WARNINGS AND PRECAUTIONS

**Serious Warnings and Precautions**

- **Fluoroquinolones, including CIPROFLOXACIN INJECTION, 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.**
- **Ciprofloxacin has been shown to prolong the QT interval of the electrocardiogram in some patients (see WARNINGS AND PRECAUTIONS).**
- **Serious hypersensitivity and / or anaphylactic reactions have been reported in patients receiving quinolone therapy, including CIPROFLOXACIN INJECTION (see WARNINGS AND PRECAUTIONS).**
- **Fluoroquinolones including CIPROFLOXACIN INJECTION are associated with an increased risk of tendinitis and tendon rupture in all ages. The risk 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 (see WARNINGS AND PRECAUTIONS).**
- **Fluoroquinolones including CIPROFLOXACIN INJECTION may exacerbate muscle weakness in persons with myasthenia gravis. Avoid using CIPROFLOXACIN INJECTION in patients with a known history of myasthenia gravis (see WARNINGS AND PRECAUTIONS).**
- **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 INJECTION. CIPROFLOXACIN INJECTION should be used in caution in patients with known or suspected CNS disorders which may predispose them to seizures or lower the seizure threshold (see WARNINGS AND PRECAUTIONS).**
- **Cases of hepatic necrosis and life-threatening hepatic failure have been reported with ciprofloxacin (see WARNINGS AND PRECAUTIONS: Hepatic / Biliary / Pancreatic).**

The use of ciprofloxacin with other drugs may lead to drug-drug interactions. For established or potential drug interactions, see DRUG INTERACTIONS.

Prolonged use of CIPROFLOXACIN INJECTION 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.

**Cardiac Disorders**

**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 **DRUG INTERACTIONS** and **ADVERSE REACTIONS**).

**Central Nervous System Effects**
**Psychiatric Adverse Reactions**

Fluoroquinolones, including CIPROFLOXACIN INJECTION, 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 INJECTION, discontinue CIPROFLOXACIN INJECTION and institute appropriate measures.

**Central Nervous System Adverse Reactions**

Fluoroquinolones, including CIPROFLOXACIN INJECTION, 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 INJECTION 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 INJECTION, discontinue CIPROFLOXACIN INJECTION immediately and institute appropriate measures.

**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 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, 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**

Fluoroquinolones, including CIPROFLOXACIN INJECTION, 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 INJECTION immediately and initiate appropriate therapy.

**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*.

**Susceptibility / Resistance**

**Development of Drug Resistant bacteria**

Prescribing CIPROFLOXACIN INJECTION 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.

**Vision Disorders**

If vision disorder occurs in association with the use of CIPROFLOXACIN INJECTION, consult an eye specialist immediately.

## PRECAUTIONS

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.

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.

**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**
As CIPROFLOXACIN INJECTION infusion solution (bags) contain dextrose (glucose), it is unsuitable for patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrose-isomaltase insufficiency (see PHARMACEUTICAL INFORMATION). 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 **DOSAGE FORMS, COMPOSITION AND PACKAGING**).

**Psychiatric**
See NEUROLOGIC subsections of **ADVERSE REACTIONS**.

**Renal Impairment**
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.

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 AND PRECAUTIONS)**. Ciprofloxacin has been shown to be non-embryotoxic and non-teratogenic in animal studies.

**Nursing Women**
The safety of ciprofloxacin in nursing women has not been established. 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 AND PRECAUTIONS)**.

**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**). 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. CIPROFLOXACIN INJECTION is not recommended for use in pediatric patients and adolescents.

**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

### Adverse Drug Reaction Overview

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

*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.*

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 AND PRECAUTIONS**). 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 AND PRECAUTIONS**).

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 AND PRECAUTIONS**). 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 post-marketing 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).

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

## DRUG INTERACTIONS

### Overview

**SERIOUS AND FATAL REACTIONS HAVE BEEN REPORTED IN PATIENTS RECEIVING CONCURRENT ADMINISTRATION OF CIPROFLOXACIN AND THEOPHYLLINE.** These reactions include cardiac arrest, seizures, status epilepticus and respiratory failure. Similar serious adverse events have been reported in patients receiving theophylline alone; the possibility that

ciprofloxacin may potentiate these reactions cannot be eliminated. If concomitant use cannot be avoided, serum levels of theophylline should be monitored and dosage adjustments should be made as appropriate.

**Cytochrome P450:**
Ciprofloxacin is contraindicated in patients receiving concomitant treatment with agomelatine[a] or tizanidine as this may lead to an undesirable increase in exposure to these drugs.

Ciprofloxacin is known to be an 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, zolpidem). Increased plasma concentrations associated with drug specific side effects may be observed due to inhibition of their metabolic clearance by ciprofloxacin.

**Drug-Drug Interactions**

**Agomelatine[a]**
No clinical data are available for interaction with ciprofloxacin. Fluvoxamine, a CYP1A2 inhibitor, markedly inhibits the metabolism of agomelatine resulting in a 60-fold (range 12 to 412) increase of agomelatine exposure (AUC). Similar effects can be expected upon concurrent ciprofloxacin administration.

Agomelatine must not be administered concurrently with ciprofloxacin since it may result in an undesirable increase in agomelatine exposure and associated risk of hepatotoxicity (see CONTRAINDICATIONS).

[a] Currently not marketed in Canada

**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. 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.

Caution and careful monitoring of patients on concomitant therapy of ciprofloxacin and caffeine or pentoxifylline (oxpetifylline) containing products is recommended.

**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 AND PRECAUTIONS**).

**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 AND PRECAUTIONS**).

Clinical surveillance and appropriate adjustment of clozapine dosage during and shortly after co-administration with ciprofloxacin is advised.

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

It is necessary to monitor the serum creatinine concentrations in these patients (twice a week).

**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.

Caution and careful monitoring of patients on concomitant therapy is recommended.

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

Ciprofloxacin should be administered at least 2 hours before or 6 hours after this preparation.

**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 6 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.

Caution and careful monitoring of patients on concomitant therapy is recommended.

**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.

Caution and careful monitoring of patients on concomitant therapy is recommended.

**Omeprazole**
Concomitant administration of ciprofloxacin and omeprazole containing medicinal products results in a slight reduction of $C_{max}$ and AUC of ciprofloxacin.

No dosage adjustment is needed.

**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 co-administration 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.

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.

Caution and careful monitoring of patients on concomitant therapy is recommended.

**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.

Monitoring ropinirole-related undesirable effects, dose adjustment as appropriate is recommended during and shortly after co-administration with ciprofloxacin.

**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.

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.

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 AND PRECAUTIONS.)

**Zolpidem**
Zolpidem exposure (AUC) increased by 46% after a single 5 mg dose when administered together with a 500 mg oral ciprofloxacin dose to healthy volunteers pretreated with ciprofloxacin (300.2 ± 115.5 vs. 438.1 ± 142.6 ng h / ml).

Concurrent use with ciprofloxacin is not recommended.

**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.

**Drug-Food Interactions**
Although ciprofloxacin may be taken with meals that include milk, simultaneous administration with dairy products alone (calcium intake > 800 mg), with calcium-fortified products, or mineral-fortified drinks, should be avoided since decreased absorption is possible. It is recommended that ciprofloxacin be administered at least 2 hours before or 6 hours after these preparations (see DRUG INTERACTIONS).

**Drug-Herb Interactions**
The drug-herb interaction of ciprofloxacin has not been established.

**Drug-Laboratory Interactions**
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 INJECTION (See MONITORING AND LABORATORY TESTS Subsection under WARNINGS AND PRECAUTIONS or LABORATORY VALUES Subsection under ADVERSE REACTIONS).

**Drug-Lifestyle Interactions**
**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.

## 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 | q 12h | 400 mg to 800 mg |
| Respiratory Tract | Moderate / Severe | 400 mg | q 8h to q 12h | 800 mg to 1200 mg |
| Skin or Skin Structure<br>Blood<br>Bone | Moderate | 400 mg | q 12h | 800 mg |
| Intra-abdominal | Complicated | 400 mg | q 12h | 400 mg q 12h only when used in combination with metronidazole 500 mg IV q6h* |
| Empiric Therapy in Febrile Neutropenic Patients | Severe<br>Ciprofloxacin<br>+<br>Piperacillin | 400 mg<br><br>50 mg / kg | q 8h<br><br>q 4h | 1200 mg<br><br>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 |

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:** $\frac{\text{Weight (kg) x (140 – age)}}{\text{49 x serum creatinine (mcmol / L)}}$

**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 in individuals less than 18 years of age has not been established. Ciprofloxacin should not be used in pediatric patients and adolescents (**see WARNINGS AND PRECAUTIONS**).

**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 of a dilute solution 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 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, discolouration and leakage prior to administration, whenever solution and container permit.

## OVERDOSAGE

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

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.

## 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 mcg / mL at 30 minutes and 1.18 mcg / 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 mcg / mL at 30 minutes and 1.16 mcg / 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 were 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 | 4.6 |
| $t_{1/2}$ (hr) | 3.4 | 3.5 |
| $AUC_{0-\infty}$ (mg•h / L) | 5.24 | 11.69 |
| $T_{max}$ (hr) | 0.95 | 1 |

*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 |
| **(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 |
| Metronidazole | 153.0 ($AUC_{0-6}$) | 33.6 | 1 |

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 mcg / mL and 12 mcg / 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 15º C - 25º C.

## 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 mg of Ciprofloxacin | 508.8 mg eq. to 400 mg of Ciprofloxacin |
| Lactic acid | 10 mg | 20 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 3.5 to 4.6

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

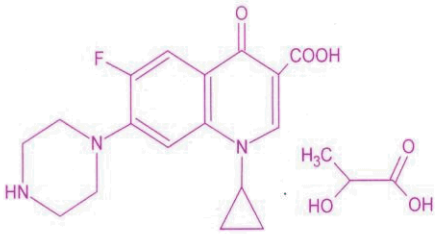
### Drug Substance

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 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

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 mcg / mL and 12 mcg / mL respectively.

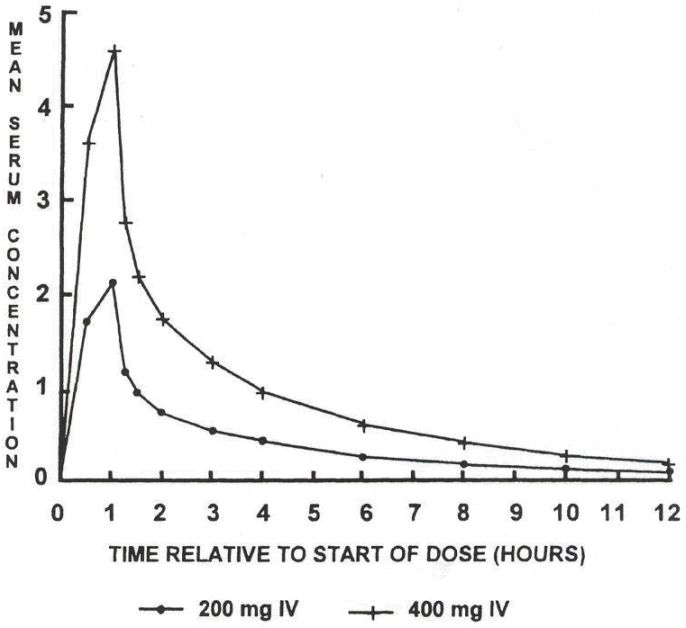



**Figure 1: Mean Serum Ciprofloxacin Concentration (mg / L) vs Time after A Single Intravenous Dose Administered over 60 Minutes**

**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 mcg / mL during the first two hours after dosing, and are generally greater than 10 mcg / 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 24 hours | 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 / 1.73m² | IV Ciprofloxacin Dose | Parameter | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Ciprofloxacin | | | M1 (desethylene ciprofloxacin) | | | M2 (sulfociprofloxacin) | | |
| | | | $AUC_{0-\infty}$ (mg·hr / L) | $Cl_r$ (L / hr) | $t_{1/2}$ (hr) | $AUC_{0-\infty}$ (mcg·h / mL) | $Cl_r$ (L / hr) | $t_{1/2}$ (hr) | $AUC_{0-\infty}$ (mcg·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 AND PRECAUTIONS).

**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 AND PRECAUTIONS).

**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 | 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 | 18 | 500 mg P.O. | 1.3 ± 0.66 to | 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 | 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 mcg / 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 mcg 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 mcg 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 (mcg / 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; mcg = 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 yielding MIC results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.

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 mcg ciprofloxacin disk should provide the zone diameters outlined in Table 14.

**Table 14: Quality Control for Susceptibility Testing**

| **Strains** | **MIC range (mcg / 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; mcg = 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* ATCC 49226 performed by disk diffusion using GC agar base and 1% defined growth supplement.

## TOXICOLOGY

### Acute Toxicity

**Table 15: LD50 (mg / kg) across species**

| 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 values.

**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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IMPORTANT: PLEASE READ

**READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICATION**

**PATIENT MEDICATION INFORMATION**

# [Pr]CIPROFLOXACIN INJECTION

**Ciprofloxacin 0.2% Intravenous Infusion**

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

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

**Serious Warnings and Precautions**

- Quinolone antibiotics, like CIPROFLOXACIN INJECTION, are related to disabling and possibly long lasting effects such as:
    - inflamed tendon (tendonitis), tendon rupture.
    - nerve damage (peripheral neuropathy).
    - problems in the brain such as:
        - convulsions
        - nervous breakdown
        - confusion
        - and other symptoms
- Quinolone antibiotics, like CIPROFLOXACIN INJECTION:
    - have lengthened the heartbeat (QT prolongation)
    - have led to serious allergic reactions, including death
    - may be related to increased tendonitis (inflamed tendon)
    - may worsen myasthenia gravis (a muscle disease)
    - may lead to seizures and nervous breakdowns. Tell your doctor if you have brain or spinal cord problems (such as epilepsy)
    - may cause liver injury which may lead to death
- For further information and symptoms see:
    - the "To help avoid side effects and ensure proper use…" section
    - the "What are possible side effects from using CIPROFLOXACIN INJECTION?" section

Talk to your doctor to see if CIPROFLOXACIN INJECTION is right for you.

**What is CIPROFLOXACIN INJECTION used for?**
CIPROFLOXACIN INJECTION is used to treat certain types of bacterial infections.

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

**How does CIPROFLOXACIN INJECTION work?**
CIPROFLOXACIN INJECTION is an antibiotic that kills the bacteria causing the infection.

**What are the ingredients in CIPROFLOXACIN INJECTION?**
Medicinal ingredients: ciprofloxacin lactate.

Non-medicinal ingredients: Each mL contains 2 mg of ciprofloxacin in bags of 100 mL and 200 mL.

| | **100 mL** | **200 mL** |
|---|---|---|
| Ciprofloxacin Lactate | 254.4 mg eq. to 200 mg of Ciprofloxacin | 508.8 mg eq. to 400 mg of Ciprofloxacin |
| Lactic acid | 10- mg | 20 mg |
| Dextrose | 5 g | 10 g |
| Hydrochloric Acid | q.s. to adjust pH to 3.5-4.6 | q.s. to adjust pH to 3.5-4.6 |
| Water for Injections | q.s. to 100 mL | q.s. to 200 mL |

**CIPROFLOXACIN INJECTION comes in the following dosage forms:**

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).

**Do not use CIPROFLOXACIN INJECTION if:**

- you are allergic to ciprofloxacin or other quinolone antibiotics
- you are allergic to any other ingredient in these products (see "What are the ingredients in CIPROFLOXACIN INJECTION?").
- you are taking tizanidine (ZANAFLEX®). Side effects such as drowsiness, sleepiness and low blood pressure may occur.
- you are currently taking agomelatine[a]. Agomelatine concentrations may increase and may cause further side effects such as liver toxicity.

[a]Currently not marketed in Canada

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

- have a family history of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase

deficiency as CIPROFLOXACIN INJECTION contains dextrose.
- have a history of seizures.
- have an irregular heart rhythm (such as QT prolongation).
- have low potassium blood levels.
- have a disease of the brain arteries in which the blood vessel walls are thickened.
- have epilepsy.
- have liver or kidney disease or damage.
- are taking theophylline (bronchodilator drug).
- already had diarrhea after taking antibacterial drugs.
- are pregnant, planning to become pregnant, breast feeding or planning to breast feed.
- are less than 18 years of age.
- have a history of tendon problems (such as pain, swelling or rupture of a tendon) related to the use of a quinolone antibiotic.
- have myasthenia gravis (a muscle disease).

**Other warnings you should know about:**

While taking CIPROFLOXACIN INJECTION:
- Avoid too much sunlight or artificial ultraviolet light (such as sunlamps).
    - Contact your doctor if a sunburn or rash occurs.
- Do not drive or use machinery if you feel dizzy or lightheaded.
- Blood Sugar Changes:

  Medicines like CIPROFLOXACIN INJECTION 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 INJECTION. If you have diabetes, check your blood sugar levels often while taking CIPROFLOXACIN INJECTION.

**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 INJECTION:**
- Theophylline or didanosine chewable / buffered tablets or pediatric powder. **Serious and fatal reactions have been reported in patients receiving ciprofloxacin, including CIPROFLOXACIN INJECTION, and theophylline.**
- Antacids, multivitamins, and other dietary supplements containing magnesium, calcium, aluminum, iron or zinc (see "How to take CIPROFLOXACIN INJECTION:").
- Antidiabetic agents (such as glyburide, glibenclamide, glimepiride, insulin); the combination of any of these agents with ciprofloxacin may cause lower blood sugar.
- Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) (such as fenbufen)
- Caffeine (such as coffee) and other xanthine derivatives (such as pentoxifylline).
- Certain heart medications known as antiarrhythmics (such as quinidine, procainamide, amiodarone, sotalol).
- Other medications including:
    - oral anticoagulants (like warfarin and acenocoumarol),
    - phenytoin, duloxetine, methylxanthines, sevelamer,
    - sucralfate, clozapine, ropinirole, lidocaine, sildenafil, probenecid,
    - methotrexate, metoclopramide, cyclosporine, lanthanum carbonate, zolpidem.

**How to take CIPROFLOXACIN INJECTION:**

- CIPROFLOXACIN INJECTION should be taken as prescribed at almost the same times each day with food or on an empty stomach.
- CIPROFLOXACIN INJECTION should not be taken with dairy products (like milk or yogurt) or calcium-fortified juices alone; however, CIPROFLOXACIN INJECTION may be taken with a meal that contains

these products (see "The following may interact with CIPROFLOXACIN INJECTION").
- You should avoid excessive caffeine consumption while taking CIPROFLOXACIN INJECTION.
- You should drink lots of water while taking CIPROFLOXACIN INJECTION.
- If you are taking the following medicines, take them at least 2 hours before or 6 hours after CIPROFLOXACIN INJECTION;
    - antiacids or mineral supplements containing magnesium or aluminium
    - sucralfate
    - supplements containing iron or zinc
    - any product (supplement or food) with more than 800 mg calcium
- Do not use CIPROFLOXACIN INJECTION for another condition or give it to others.

You should take CIPROFLOXACIN INJECTION for as long as your doctor prescribes it, even after you start to feel better. Stopping an antibiotic too early may result in failure to cure your infection.

**Usual dose:**

Your doctor (health care provider) will tell you how much of the medicine to take and for how long.

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

**Overdose:**

| |
|---|
| If you think you have taken too much CIPROFLOXACIN INJECTION, contact your health care professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms. |

**What are possible side effects from using CIPROFLOXACIN INJECTION?**
All medicines, including CIPROFLOXACIN INJECTION, can cause side effects, although not everyone gets them.

These are not all the possible side effects you may feel when taking CIPROFLOXACIN INJECTION. If you have any side effects not listed here or if conditions worsen or do not improve then:
- contact your health care professional.
- see the "To help avoid side effects and ensure proper use…" section.

Stop taking CIPROFLOXACIN INJECTION 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 face, lips, tongue or throat
    - difficulty breathing
    - irregular or rapid heartbeat, or fainting spells
b) you have sunburn-like skin reaction when exposed to sunlight or ultraviolet light
c) you have pain, swelling or rupture of a tendon. You should:
    - rest
    - avoid physical exercise
d) you have neuropathy (damage to the nerves) with symptoms such as:
    - pain, burning, tingling, numbness or weakness
e) 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.
f) you have mental problems such as:
    - confusion, headache, shaking

- hallucinations, depression, agitation
- difficulty sleeping, anxiety, nervousness, suicidal thoughts
  Contact your doctor if you have suicidal thoughts.

Other side effects include:

- your eyesight worsens or changes. See your doctor or eye specialist right away.
- nausea, dizziness, unsteady walk
- gas, cramping, feeling unwell, loss of hearing, problems of smell and taste, loss of appetite
- migraine, sweating
- worsening of myasthenia gravis (a muscle disease) with symptoms such as:
  - weakness
  - difficulty walking, swallowing, drooping eyelids

  Do not use CIPROFLOXACIN INJECTION if you have this condition.

Self-limiting side effects:

- feeling lightheaded.
- Insomnia (difficulty sleeping).
- nightmares.

**If any of these affect you severely, tell your doctor or pharmacist.**

| Serious Side Effects and What to do About Them | | | | |
|---|---|---|---|---|
| Symptom / Effect | | Talk to your health care professional | | Stop taking drug and get immediate medical help |
| | | Only if severe | In all cases | |
| **Rare** | **Allergic Reaction**:<br>• rash<br>• hives (skin eruptions),<br>• swelling of the face, lips, tongue or throat,<br>• difficulty swallowing or breathing,<br>• rapid heartbeat | | | ✓ |
| | **Central Nervous System Disorders:**<br>• Seizures / convulsions,<br>• confusion,<br>• tremors,<br>• hallucinations,<br>• depression,<br>• suicidal thoughts or psychotic reactions | | | ✓ |
| | **Photo-sensitivity Reaction:**<br>Sensitivity to light, blistering of skin | | | ✓ |
| | Tendon pain, inflammation, or rupture | | | ✓ |
| | **Increased Blood Sugar:**<br>• Frequent urination,<br>• thirst,<br>• hunger,<br>• tiredness,<br>• blurred vision,<br>• headache,<br>• trouble concentrating | ✓ | | |
| | **Low Blood Sugar:**<br>• change in mood,<br>• change in vision,<br>• confusion<br>• dizziness,<br>• fast heartbeat<br>• feeling faint<br>• weakness,<br>• headache,<br>• sweating,<br>• hunger<br>• shaking | | ✓ | |

| Serious Side Effects and What to do About Them | | | | |
|---|---|---|---|---|
| Symptom / Effect | | Talk to your health care professional | | Stop taking drug and get immediate medical help |
| | | Only if severe | In all cases | |
| **Unknown** | **Severe Bowel Disorder (Clostridium difficile colitis):**<br>• Persistent diarrhea,<br>• bloody or watery diarrhea,<br>• abdominal or stomach pain / cramping,<br>• blood / mucus in stool | | | ✓ |
| | **Nerve Disorder (Neuropathy):**<br>Pain, burning, tingling, numbness, weakness | | | ✓ |
| | **Liver Disorder:**<br>yellowing of the skin or eyes, dark urine, abdominal pain, nausea, vomiting, loss of appetite, pale stools | | ✓ | |
| | **Heart Disorder (QT Prolongation):**<br>Irregular heartbeat | | ✓ | |
| | **Mental Health Problems:**<br>• Anxiety,<br>• confusion,<br>• depression,<br>• feeling agitated,<br>• restless or nervous,<br>• suicidal thoughts or actions,<br>• hallucinations,<br>• inability to think clearly or pay attention,<br>• memory loss,<br>• paranoia or loss of touch with reality | | ✓ | |
| | **Neurological Problems:**<br>• seizures (convulsions)<br>• tremors | | | ✓ |
| | **Rise in the pressure within your skull:**<br>• blurred or double vision,<br>• headaches,<br>• nausea | | ✓ | |

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 (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) 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:**

Store between 15°C and 25°C. Protect from light, excessive heat and freezing. 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.

**Keep out of reach and sight of children.**

**If you want more information about CIPROFLOXACIN INJECTION:**

a. Talk to your healthcare professional.
b. Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://health-products.canada.ca/dpd-bdpp/index-eng.jsp); the manufacturer's website (https://www.baxter.ca) or by calling 1-888-719-9955

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