PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr CIPROFLOXACIN

Ciprofloxacin Tablets

Tablets, 250 mg, 500 mg and 750 mg ciprofloxacin (as ciprofloxacin hydrochloride), Oral

Manufacturer's Standard

Antibacterial Agent

Sivem Pharmaceuticals ULC
4705 Dobrin Street
Saint-Laurent, Quebec
Canada H4R 2P7

www.sivem.ca

Date of Initial Authorization:
JUN 08, 2012

Date of Revision:
NOV 08, 2022

Submission Control Number: 268314

RECENT MAJOR LABEL CHANGES

N/A

TABLE OF CONTENTS

Sections or subsections that are not applicable at the time of authorization are not listed.

RECENT MAJOR LABEL CHANGES 2
TABLE OF CONTENTS 2
PART I: HEALTH PROFESSIONAL INFORMATION 4
1 INDICATIONS 4
1.1 Pediatrics 6
1.2 Geriatrics 7
2 CONTRAINDICATIONS 7
3 SERIOUS WARNINGS AND PRECAUTIONS BOX 7
4 DOSAGE AND ADMINISTRATION 8
4.1 Dosing Considerations 8
4.2 Recommended Dose and Dosage Adjustment 8
4.4 Administration 10
4.5 Missed Dose 10
5 OVERDOSAGE 11
6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING 11
7 WARNINGS AND PRECAUTIONS 12
7.1 Special Populations 16
7.1.1 Pregnant Women 16
7.1.2 Breast-feeding 16
7.1.3 Pediatrics 16
7.1.4 Geriatrics 17
8 ADVERSE REACTIONS 17
8.1 Adverse Reaction Overview 17
8.2 Clinical Trial Adverse Reactions 17
8.3 Less Common Clinical Trial Adverse Reactions 17
8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data 19
8.5 Post-Market Adverse Reactions 20

9 DRUG INTERACTIONS 20
9.2 Drug Interactions Overview 20
9.3 Drug-Behavioural Interactions 21
9.4 Drug-Drug Interactions 21
9.5 Drug-Food Interactions 26
9.6 Drug-Herb Interactions 26
9.7 Drug-Laboratory Test Interactions 26
10 CLINICAL PHARMACOLOGY 27
10.1 Mechanism of Action 27
10.3 Pharmacokinetics 27
11 STORAGE, STABILITY AND DISPOSAL 37
12 SPECIAL HANDLING INSTRUCTIONS 37
PART II: SCIENTIFIC INFORMATION 38
13 PHARMACEUTICAL INFORMATION 38
14 CLINICAL TRIALS 40
14.3 Comparative Bioavailability Studies 40
15 MICROBIOLOGY 40
16 NON-CLINICAL TOXICOLOGY 43
17 SUPPORTING PRODUCT MONOGRAPHS 47
PATIENT MEDICATION INFORMATION 48

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

A) Oral Administration

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

Respiratory Tract Infections

Acute exacerbation of chronic bronchitis caused by:
Haemophilus influenzae
Moraxella catarrhalis

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

Acute sinusitis caused by:
Haemophilus influenzae
Moraxella catarrhalis

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

CIPROFLOXACIN is not indicated for acute bronchitis.

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

Urinary Tract Infections

Upper and lower urinary tract infections, such as complicated and uncomplicated cystitis,

[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.

pyelonephritis, and pyelitis caused by:
Citrobacter diversus
Citrobacter freundii
Enterobacter cloacae
Escherichia coli
Klebsiella pneumoniae
Klebsiella oxytoca
Morganella morganii
Proteus mirabilis
Pseudomonas aeruginosa
Serratia marcescens
Staphylococcus aureus
Staphylococcus epidermidis
Staphylococcus saprophyticus
Streptococcus faecalis

Acute uncomplicated cystitis:
in females caused by *Eschericia coli*

In cases of uncomplicated acute bacterial cystitis, limit the use of CIPROFLOXACIN to circumstances where no other treatment options are available. A urine culture should be obtained prior to treatment to ensure ciprofloxacin susceptibility.

Chronic Bacterial Prostatitis

Caused by:
Escherichia coli

Skin and Soft Tissue Infections

Caused by:
Enterobacter cloacae
Escherichia coli
Klebsiella pneumoniae
Proteus mirabilis
Proteus vulgaris
Pseudomonas aeruginosa
Staphylococcus aureus
Staphylococcus epidermidis
Streptococcus pyogenes

Bone and Joint Infections

Caused by:
Enterobacter cloacae
Pseudomonas aeruginosa
Serratia marcescens
Staphylococcus aureus

Infectious Diarrhea (**when antibacterial therapy is indicated**)

Caused by:
Campylobacter jejuni
Escherichia coli (enterotoxigenic strains)
Shigella dysenteriae
Shigella flexneri
Shigella sonnei

Meningococcal Carriers

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

Typhoid Fever (enteric fever)

Caused by:
Salmonella paratyphi
Salmonella typhi

Uncomplicated Gonorrhea

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

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

Limit the use of CIPROFLOXACIN to patients 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.

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

1.1 Pediatrics

The safety and efficacy of CIPROFLOXACIN in individuals less than 18 years of age has not been established. CIPROFLOXACIN is not recommended for children under the age of 18 years

(see 7 WARNINGS AND PRECAUTIONS: 7.1 Special Populations, 7.1.3 Pediatrics).

1.2 Geriatrics

Elderly patients should receive a dose dependent on the severity of their illness and their creatinine clearance (see 4 DOSAGE AND ADMINISTRATION : Special Populations : Impaired Renal Function for dose modification based on creatinine clearance or serum creatinine).

2 CONTRAINDICATIONS

- Ciprofloxacin (ciprofloxacin hydrochloride tablets) is contraindicated in patients who have shown hypersensitivity to ciprofloxacin, or other quinolone antibacterial agents or any of the excipients. For a complete listing, see the 4 DOSAGE AND ADMINISTRATION section.

- Concurrent administration of ciprofloxacin and agomelatinea is contraindicated since it may result in an undesirable increase in agomelatine exposure (see 9 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) (see 9 DRUG INTERACTIONS)

[a]Currently not marketed in Canada

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- Fluoroquinolones, including CIPROFLOXACIN 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 7 WARNINGS AND PRECAUTIONS: Cardiovascular).
- Serious hypersensitivity and/or anaphylactic reactions have been reported in patients receiving fluoroquinolone therapy, including CIPROFLOXACIN (see 7 WARNINGS AND PRECAUTIONS: Immune).
- Fluoroquinolones including CIPROFLOXACIN 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 7 WARNINGS AND PRECAUTIONS: Musculoskeletal).
- Fluroquinolones including CIPROFLOXACIN may exacerbate muscle weakness in persons with myasthenia gravis. Avoid CIPROFLOXACIN in patients with a known history of myasthenia gravis (see 7 WARNINGS AND PRECAUTIONS: Musculoskeletal).

- Seizures and toxic psychoses may occur with fluoroquinolone therapy. Convulsions, increased intracranial pressure (including pseudotumor cerebri) and toxic psychoses have been reported in patients receiving fluoroquinolones, including CIPROFLOXACIN CIPROFLOXACIN should be used with caution in patients with known or suspected CNS disorders which may predispose them to seizures or lower the seizure threshold (see 7 WARNINGS AND PRECAUTIONS: Neurologic).
- Cases of hepatic necrosis and life-threatening hepatic failure have been reported with ciprofloxacin (see 7 WARNINGS AND PRECAUTIONS: Hepatic/Biliary/Pancreatic).

4 DOSAGE AND ADMINISTRATION

4.1 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.

Oral Administration
CIPROFLOXACIN (ciprofloxacin hydrochloride tablets) may be taken before or after meals. Absorption is faster on an empty stomach.

Patients should be advised to drink fluids liberally and avoid taking dairy products or antacids containing magnesium or aluminum.

4.2 Recommended Dose and Dosage Adjustment

Adults
The recommended dosages of Ciprofloxacin are:

Table 1: Recommended Dosages for Sandoz Ciprofloxacin

Location of Infection	Type/Severity	Unit Dose	Frequency	Daily Dose
Urinary Tract	Mild/Moderate	250 mg	q12h	500 mg
	Severe/Complicated	500 mg	q12h	1000 mg
Chronic Bacterial Prostatitis	Asymptomatic/Mild/Moderate	500 mg	q12h	1000 mg
Respiratory Tract Bone & Joint Skin & Soft Tissue	Mild/Moderate	500 mg	q12h	1000 mg
	Severe*/Complicated	750 mg	q12h	1500 mg
Infectious Diarrhea	Mild/Moderate/Severe	500 mg	q12h	1000 mg
Urogenital and Extragenital Gonorrhea	Uncomplicated	500 mg	once	500 mg
Typhoid Fever	Mild/Moderate	500 mg	q12h	1000 mg
Neisseria meningitidis Nasopharyngeal Colonization	Carrier State	750 mg	once	750 mg

Location of Infection	Type/Severity	Unit Dose	Frequency	Daily Dose
Acute Sinusitis	Moderate	500 mg	q12h	1000 mg

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

Depending on the severity of the infections, as well as the clinical and bacteriological responses, the average treatment period should be approximately 7 to 14 days. Generally, treatment should last 3 days beyond the disappearance of clinical symptoms or until cultures are sterile. Patients with osteomyelitis may require treatment for a minimum of 6 to 8 weeks and up to 3 months. With acute cystitis in females a 3- to 5-day treatment may be sufficient. With infectious diarrhea a five-day treatment may be sufficient. Typhoid fever should be treated for 14 days. Acute sinusitis should be treated for 10 days with 500 mg q12h. Chronic bacterial prostatitis should be treated for 28 days with 500 mg q12h.

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

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

Sequential IV/PO Therapy

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

Special Populations

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 10 CLINICAL PHARMACOLOGY, Detailed 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 of CIPROFLOXACIN. 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/1.73m^2	Maximum Daily Dose		Serum Creatinine Concentration mg/100 mL
	Oral	IV	
31-60	1000 mg	800 mg	1.4-1.9
≤30	500 mg	400 mg	≥2.0

Maximum daily doses are 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 (ciprofloxacin hydrochloride tablets) should not be used in pediatric patients and adolescents (see 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.3 Pediatrics.)

4.4 Administration

Ciprofloxacin should be administered at least 2 hours before or 6 hours after antacids and mineral supplements containing magnesium or aluminum, as well as sucralfate, didanosine chewable/buffered tablets or pediatric powder, metal cations such as iron, and multivitamin preparations with zinc (see 9 DRUG INTERACTIONS).

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 9 DRUG INTERACTIONS).

4.5 Missed Dose

If a dose is missed, it should be taken anytime but not later than 6 hours prior to the next scheduled dose. If less than 6 hours remain before the next dose, the missed dose should not

be taken and treatment should be continued as prescribed with the next scheduled dose. Double doses should not be taken to compensate for a missed dose.

5 OVERDOSAGE

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

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

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 3: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength / Composition	Non-medicinal Ingredients
Oral	Tablet: 250 mg, 500 mg, 750 mg	For a complete listing see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING - Composition.

CIPROFLOXACIN 250 mg tablet: White round film-coated tablet with breaking notch on one side. Embossed "cip" on top and "250" on the bottom of the breaking notch. Bottles of 100.

CIPROFLOXACIN 500 mg tablet: White oblong film-coated tablet with breaking notch on both sides. Embossed "cip" on one side of breaking notch and "500" on the other side, on one side of the tablet only. Bottles of 100.

CIPROFLOXACIN 750 mg tablet: White oblong film-coated tablet with breaking notch on both sides. Embossed "cip" on one side of breaking notch and "750" on the other side, on one side of the tablet only. Bottles of 50.

Composition

Medicinal Ingredient: 250 mg, 500 mg, or 750 mg ciprofloxacin as ciprofloxacin hydrochloride. Nonmedicinal ingredients: microcrystalline cellulose, sodium starch glycolate, povidone, silica colloidal anhydrous, stearic acid, magnesium stearate, croscarmellose sodium, hypromellose, polyethyelene glycol, titanium oxide and talc.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX

General

The use of ciprofloxacin with other drugs may lead to drug-drug interactions. For established or potential drug interactions, see 9 DRUG INTERACTIONS.

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

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

Cardiovascular

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 (e.g., class IA or III antiarrhythmics) or in patients with risk factors for torsade de pointes (e.g., known QT prolongation, uncorrected hypokalemia) (see 9 DRUG INTERACTIONS and 8 ADVERSE REACTIONS).

Aortic Aneurysm and Aortic Dissection

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

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

Endocrine and Metabolism

Blood Glucose Disturbances

Fluoroquinolones, including CIPROFLOXACIN has 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 immediately and initiate appropriate therapy (see 8 ADVERSE REACTIONS and 9 DRUG INTERACTIONS, 9.4 Drug-Drug Interactions).

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 *C. 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 *C. difficile*. Drugs that inhibit peristalsis may delay clearance of *C. 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 8 ADVERSE REACTIONS).

Hepatic/Biliary/Pancreatic

Cases of hepatic necrosis and life-threatening hepatic failure have been reported with ciprofloxacin. In the event of any signs and symptoms of hepatic disease (such as anorexia, jaundice, dark urine, pruritus, or tender abdomen), treatment should be discontinued (see 8 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 8 ADVERSE REACTIONS).

Immune

Serious hypersensitivity and/or anaphylactic reactions have been reported in patients receiving fluoroquinolone therapy, including CIPROFLOXACIN (see 8 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 (ciprofloxacin hydrochloride tablets) should be discontinued at the first appearance of a skin rash or any other sign of hypersensitivity. Serious acute hypersensitivity reactions may require treatment with epinephrine and other resuscitative measures, including oxygen, intravenous fluids, antihistamines, corticosteroids, pressor amines and airway

management, as clinically indicated.

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

Monitoring and Laboratory 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

Fluoroquinolones, including CIPROFLOXACIN, have neuromuscular blocking activity and may exacerbate muscle weakness in persons with myasthenia gravis. Postmarketing serious adverse events, including deaths and requirement for ventilatory support, have been associated with fluoroquinolone use in persons with myasthenia gravis. Avoid CIPROFLOXACIN (ciprofloxacin hydrochloride tablets) in patients with a known history of myasthenia gravis (see 8 ADVERSE REACTIONS).

Tendinitis and Tendon Rupture

Tendinitis and tendon rupture (predominantly Achilles tendon), sometimes bilateral, may occur with CIPROFLOXACIN, even within the first 48 hours of treatment. Rupture of the shoulder, hand and Achilles tendons that required surgical repair or resulted in prolonged disability have been reported in patients receiving fluoroquinolones, including CIPROFLOXACIN (see 8 ADVERSE REACTIONS). CIPROFLOXACIN (ciprofloxacin hydrochloride tablets) 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 (ciprofloxacin hydrochloride tablets) 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-fluoroquinolone antimicrobial drug.

CIPROFLOXACIN (ciprofloxacin hydrochloride tablets) should not be used in patients with a history of tendon disease/disorder related to previous fluoroquinolone treatment.

Neurologic

Psychiatric Adverse Reactions

Fluoroquinolones, including CIPROFLOXACIN, 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, discontinue CIPROFLOXACIN and institute appropriate measures (see 8 ADVERSE REACTIONS).

Central Nervous System Adverse Reactions

Fluoroquinolones, including CIPROFLOXACIN, has been associated with an increased risk of seizures (convulsions), increased intracranial pressure (including pseudotumor cerebri), tremors, and light-headedness. Cases of status epilepticus have also been reported. As with other fluoroquinolones, CIPROFLOXACIN 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, discontinue CIPROFLOXACIN immediately and institute appropriate measures (see 8 ADVERSE REACTIONS).

Ophthalmologic

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

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 fluoroquinolones, 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 8 ADVERSE REACTIONS).

Renal

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 should be used with caution and at a reduced dosage in patients with impaired renal function (see 4 DOSAGE AND ADMINISTRATION and 10 CLINICAL PHARMACOLOGY, Detailed Human Pharmacology).

Sensitivity/Resistance

Development of Drug-Resistant bacteria

Prescribing CIPROFLOXACIN (ciprofloxacin tablet) 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.

Skin

Phototoxicity

Ciprofloxacin has been shown to produce photosensitivity reactions. 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 (e.g., sunburn-like skin reactions).

7.1 Special Populations

7.1.1 Pregnant Women

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

7.1.2 Breast-feeding

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 (ciprofloxacin hydrochloride tablets), taking into account the importance of the drug to the mother and the possible risk to the infant.

7.1.3 Pediatrics

The safety and efficacy of ciprofloxacin in the pediatric population less than 18 years of age have not been established. Fluoroquinolones, including ciprofloxacin, cause arthropathy and osteochondrosis in juvenile animals of several species. Damage to juvenile weight-bearing joints and lameness were observed both in rat and dog studies but not in weaned piglets (see 16 NON-CLINICAL TOXICOLOGY). Histopathological examination of the weight-bearing joints in immature dogs revealed permanent lesions of the cartilage. CIPROFLOXACIN is not recommended for use in pediatric patients and adolescents.

7.1.4 Geriatrics

Ciprofloxacin is substantially excreted by the kidney, and the risk of adverse reactions may be greater in elderly patients with impaired renal function (see 10 CLINICAL PHARMACOLOGY, Detailed Human Pharmacology).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The following sections summarize the safety information derived from clinical trials and postmarket use of ciprofloxacin.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Ciprofloxacin hydrochloride tablets are generally well tolerated. During worldwide clinical investigation (1991), 16,580 courses of ciprofloxacin treatment were evaluated for drug safety.

The incidence of adverse reactions was 8.0%. In orally treated patients enrolled in clinical trials, the most frequently reported events, possibly, probably drug-related were: nausea (1.3%), and diarrhea (1.0%).

The incidence of adverse reactions was 17% for the group treated with ciprofloxacin injection and 15.3% for the group treated sequentially. The difference between the oral and IV group relates to adverse vascular reactions which are known to be associated with IV administration.

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

8.3 Less Common Clinical Trial Adverse Reactions

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

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

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

Digestive: abdominal pain, 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 7 WARNINGS AND PRECAUTIONS, Immune). 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), toxic epidermal necrolysis (Lyell Syndrome, potentially life-threatening).

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 completed tendon rupture (shoulder, hand or Achilles tendon), tendinitis (predominantly achillotendinitis), myalgia (muscular pain). The following have been reported very rarely: myasthenia (exacerbation of symptoms of myasthenia gravis) (see 7 WARNINGS AND PRECAUTIONS, Musculoskeletal).

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 7 WARNINGS AND PRECAUTIONS, Neurologic). 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 has 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, leukorrhea, nephritis interstitial, urinary retention, vaginitis, vaginal moniliasis.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

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.

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 discolouration.

Hemic and Lymphatic: coagulation disorder, thrombocythemia.

Skin: fungal dermatitis, pustular rash, sweating.

Metabolic: healing abnormal, hypernatremia.

Nervous: dementia.

Urinary: kidney tumour necrosis, urinary incontinence.

8.5 Post-Market Adverse Reactions

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).

In isolated instances, some serious adverse drug reactions may be long-lasting (> 30 days) and disabling; such as tendinitis, tendon rupture, musculoskeletal disorders, and other reactions affecting the nervous system including psychiatric disorders and disturbance of senses.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

SERIOUS AND FATAL REACTIONS HAVE BEEN REPORTED IN PATIENTS RECEIVING CONCURRENT ADMINISTRATION OF CIPROFLOXACIN AND THEOPHYLLINE. These reactions include cardiac arrest, seizure, status epilepticus and respiratory failure. Similar serious adverse events have been 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 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.

[a]Currently not marketed in Canada

9.3 Drug-Behavioural 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 (see 8 ADVERSE REACTIONS.)

9.4 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 4 - Established or Potential Drug-Drug Interactions

Proper Name	Source of Evidence	Effect	Clinical Comment
Agomelatine[a]	T	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 2 CONTRAINDICATIONS).
Antidiabetic Agents	C	Disturbances of blood glucose, including symptomatic hyperglycemia and hypoglycemia, have been reported with fluoroquinolones, 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 8 ADVERSE REACTIONS).
Caffeine and Other Xanthine Derivatives	CT	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	Caution and careful monitoring of patients on concomitant therapy of ciprofloxacin and caffeine or pentoxifylline (oxpentifylline) containing products is recommended.

Proper Name	Source of Evidence	Effect	Clinical Comment
		(oxpentifylline)-containing products, raised serum concentrations of this xanthine derivative were reported.	
Class IA or III Antiarrhythmics	C	Ciprofloxacin may have an additive effect on the QT interval (see 7 WARNINGS AND PRECAUTIONS).	Like other fluoroquinolones, precaution should be taken when using ciprofloxacin together with class IA (e.g., quinidine, procainamide) or III (e.g., amiodarone, sotalol) antiarrhythmics.
Clozapine	C	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 7 WARNINGS AND PRECAUTIONS).	Clinical surveillance and appropriate adjustment of clozapine dosage during and shortly after co-administration with ciprofloxacin is advised.
Cyclosporine	CT	Some fluoroquinolones, 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	C	In clinical studies it was demonstrated that concomitant use of duloxetine with 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	CT	Oral ferrous sulfate at therapeutic doses decreases the bioavailability of oral ciprofloxacin.	Ciprofloxacin should be administered at least 2 hours before or 6 hours after this preparation.
Calcium-Fortified Products (including Food and Dairy	CT	Although, ciprofloxacin may be taken with meals that include milk, simultaneous administration with dairy products alone, or with	It is recommended that ciprofloxacin be administered at least 2 hours before or 6 hours

Proper Name	Source of Evidence	Effect	Clinical Comment
Products		calcium-fortified products, should be avoided, since decreased absorption is possible.	after substantial calcium intake (>800 mg) (see 4 DOSAGE AND ADMINISTRATION).
Histamine H_2-receptor Antagonists	CT	Histamine H_2-receptor antagonists appear to have no significant effect on the bioavailability of ciprofloxacin.	No dosage adjustment is required.
Lidocaine	CT	It was demonstrated in healthy subjects that concomitant use of lidocaine with ciprofloxacin, an 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	C	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.	Patients under methotrexate therapy should be carefully monitored when concomitant ciprofloxacin therapy is indicated.
Metoclopramide	CT	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.	No dosage adjustment is required.
Multivalent Cations	CT	Concurrent administration of a fluoroquinolone, including ciprofloxacin, with multivalent cation-containing products such as magnesium/aluminum antacids, polymeric phosphate binders such as sevelamer, lanthanum carbonate, sucralfate, didanosine chewable/buffered tablets or pediatric powder, mineral supplements or products containing calcium, iron, or zinc may substantially interfere with the absorption of the fluoroquinolone, resulting in serum and urine levels considerably lower than desired. Absorption of ciprofloxacin is	Ciprofloxacin should be administered at least 2 hours before or 6 hours after these preparations.

Proper Name	Source of Evidence	Effect	Clinical Comment
		significantly reduced by concomitant administration of multivalent cation-containing products.	
Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)	CT	Concomitant administration of a nonsteroidal anti-inflammatory drug (fenbufen) with a fluoroquinolone (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	CT	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	CT	Simultaneous administration of ciprofloxacin with an oral anticoagulant (e.g., 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 fluoroquinolones. 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 co-administration of ciprofloxacin with an oral anticoagulant (e.g., warfarin, acenocoumarol).
Phenytoin	CT	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.

Proper Name	Source of Evidence	Effect	Clinical Comment
Probenecid	CT	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.
Ropinirole	CT	In a clinical study it was shown that concomitant use of ropinirole with ciprofloxacin, an 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	CT	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.	Caution should be used when prescribing ciprofloxacin concomitantly with sildenafil, taking into consideration the risks and the benefits.
Theophylline	CT	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	CT	In a clinical study in healthy	Tizanidine must not be

Proper Name	Source of Evidence	Effect	Clinical Comment
		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.	administered together with ciprofloxacin (see 2 CONTRAINDICATIONS).
Zolpidem	CT	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.

Legend: C=Case Study; CT=Clinical Trial; T=Theoretical
[a]Currently not marketed in Canada

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.

9.5 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 9 DRUG INTERACTIONS, 9.4 Drug-Drug Interactions, and 4 DOSAGE AND ADMINISTRATION, 4.1 Dosing Considerations).

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test 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.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

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

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

The mechanism of action of fluoroquinolones, including ciprofloxacin, is different from that of penicillins, cephalosporins, aminoglycosides, macrolides, and tetracyclines. Therefore, microorganisms resistant to these classes of drugs may be susceptible to ciprofloxacin. Conversely, microorganisms resistant to fluoroquinolones may be susceptible to these other classes of antimicrobial agents (see **Part II**: 13 PHARMACEUTICAL INFORMATION, 15 MICROBIOLOGY). There is no cross-resistance between ciprofloxacin and the mentioned classes of antibiotics.

10.3 Pharmacokinetics

(See 10 CLINICAL PHARMACOLOGY, Detailed Human Pharmacology)

General
Ciprofloxacin and metronidazole have been studied in combination and serum levels of ciprofloxacin are not significantly altered by metronidazole at the doses studied. Serum levels of metronidazole when administered orally at a dose of 500 mg q6h in combination with ciprofloxacin 500 mg PO q12h are: $AUC_{0\rightarrow6}$ 156.3 mg.h/L, C_{max} 31.3 mg/L and t_{max} 1.71 hours.

Absorption: Following oral administration of single doses of 250 mg, 500 mg, and 750 mg of ciprofloxacin tablets, ciprofloxacin is absorbed rapidly and extensively mainly from the small intestine, reaching maximum serum concentrations 1-2 hours later.

The absolute bioavailability is approximately 70% to 80%. Maximum serum concentrations (C_{max}) and total areas under serum concentration vs. time curves (AUC) increased in proportion to dose.

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

Distribution: The protein binding of ciprofloxacin is low (20% to 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 to 0.3 L/h/kg and the total body clearance between 0.48 to 0.60 L/h/kg. Ciprofloxacin undergoes both glomerular filtration and tubular secretion.

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

Special Populations and Conditions

- **Geriatrics (≥ 65 years of age):** No dosage adjustment based on age alone is necessary for elderly patients. Compromised renal function may lead to increased drug exposure in this population group as ciprofloxacin is substantially excreted by the kidney (see 10 CLINICAL PHARMACOLOGY, Detailed 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 10 CLINICAL PHARMACOLOGY, Detailed Human Pharmacology).

- **Renal Impairment:** Ciprofloxacin is eliminated primarily by renal excretion. Patients with renal insufficiency had significantly increased AUCs, prolonged (about 2-fold) elimination half-lives, and decreased renal clearances (see 10 CLINICAL PHARMACOLOGY, Detailed Human Pharmacology).

Some modification of dosage is recommended, particularly for patients with severe renal dysfunction. Only a small amount of ciprofloxacin (< 10%) is removed from the body after hemodialysis or peritoneal dialysis (see 4 DOSAGE AND ADMINISTRATION, Special Populations: Impaired Renal Function).

Detailed Human Pharmacology

Pharmacokinetics

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

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

Maximum serum concentrations (C_{max}) increased dose-proportionally and were attained 1 to 2 hours after oral dosing. The total areas under the serum concentration-time curves (AUC) were also increased in proportion to dose. Mean concentrations 12 hours after dosing with 250 mg, 500 mg, or 750 mg were 0.1, 0.2, and 0.4 mg/L, respectively. The serum elimination half-lives ($t_{½}$) were between 4 and 6 hours (see Table 5 and Figure 1).

Table 5: Pharmacokinetic Parameters of Ciprofloxacin Following Single Doses In Healthy Volunteers Oral/IV

Dose	250 mg	500 mg	750 mg	200 mg IV*	400 mg IV*
Cmax (mg/L)	1.42	2.60	3.41	2.14	4.60
t½ (h)	4.19	4.87	5.34	3.4	3.5
AUC 0-∞ (mg•h/L)	5.43	10.60	15.03	5.24	11.69
tmax (h)	1.11	1.11	1.56	0.95	1.00

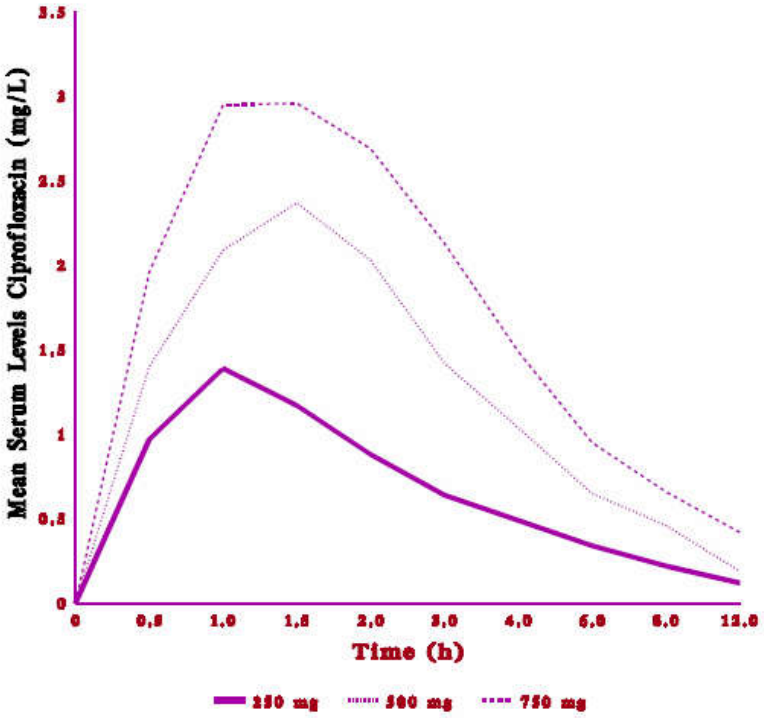
* IV parameters following a 60-minute infusion period

Similar values were obtained following the oral administration of multiple doses every 12 hours for 7 days (see Table 6).

Table 6: Mean Pharmacokinetic Parameters of Ciprofloxacin at Steady State in Healthy Volunteers

Regimen	AUC_{0-12h} (mg•h/L)	C_{max} (mg/L)	t_{max} (h)
(i) When administered alone			
Ciprofloxacin 500 mg PO q12h	13.7	2.97	1.23
Ciprofloxacin 400 mg IV q12h	12.7	4.56	1.0

Figure 1: Mean Ciprofloxacin Serum Concentration After Single Oral Doses


Mean Serum Levels Ciprofloxacin (mg/L)
3,5
3
2,5
2
1,5
1
0,5
0
0
0,5
1,0
1,5
2,0
3,0
4,0
6,0
8,0
12,0
Time (h)
250 mg
500 mg
750 mg

Metabolism and Excretion

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

Following the oral administration of a single 259 mg dose of ^{14}C-labelled ciprofloxacin to six healthy male volunteers (age: 25.0 ± 1.46 years, weight: 70.0 ± 3.39 kg), approximately 94% of the dose was recovered in the urine and feces over five days. Most of the radioactivity was recovered in the urine (55.4%). Unchanged ciprofloxacin was the major radioactive moiety identified in both urine and feces, accounting for 45% and 25% of the dose, respectively. Total (urine and feces) excretion of all metabolites was 18.8%.

Table 7 shows urinary recovery data from another trial where healthy subjects were administered a single dose of ciprofloxacin in tablet form (see Table 7).

Table 7: Mean Urinary Excretion of Ciprofloxacin

Hours After Administration of a Single Dose				
	0 - 2	**2 - 4**	**4 - 8**	**8 - 12**
Urine Concentration mg/L (± S.D.)				
250 mg PO	205 (±89)	163 (±145)	101 (±65)	32 (±28)
500 mg PO	255 (±204)	358 (±206)	117 (±86)	26 (±10)
750 mg PO	243 (±143)	593 (±526)	169 (±131)	55 (±36)
200 mg IV	335.2 (±61.5)	99.9 (±16.0)	71.7 (±10.9)	31.24 (±4.06)
400 mg IV	706.0 (±99.0)	181.3 (±25.9)	127.1 (±18.9)	63.5 (±7.4)
Amount Excreted mg (± S.D.)				
250 mg dose	54.38 (±36.22)	26.79 (±11.78)	22.84 (±6.79)	8.90 (±4.25)
500 mg dose	64.51 (±25.06)	47.37 (±15.65)	39.54 (±11.17)	15.52 (±5.39)
750 mg dose	68.90 (±41.85)	72.43 (±33.13)	61.07 (±21.68)	28.11 (±7.64)
200 mg IV	58.8 (±9.3)	13.6 (±3.2)	14.1 (±9.0)	7.5 (±2.5)
400 mg IV	125.0 (±7.2)	24.1 (±4.7)	35.1 (±12.7)	15.7 3 (±.9)

Note: IV dose administered over 30 minutes.

Following the intravenous administration of a single 107 mg dose of ^{14}C-labelled ciprofloxacin to six healthy male volunteers (age: 23.7 ± 1.89 years, weight: 80.2 ± 3.45 kg), 15% of unchanged ciprofloxacin was recovered in the feces, suggesting that hepatic extraction and biliary excretion is an extra-renal clearance pathway for ciprofloxacin. Direct evidence of biliary excretion of ciprofloxacin was obtained in 12 patients (age 28-58) with T-tube drainage. A peak biliary concentration of 16 mg/L was seen 4 hours after a single oral dose of ciprofloxacin 500 mg.

After intravenous administration to a group of 9 healthy male volunteers (age: 26.8 ± 9.7 yrs, weight: 63.9 ± 6.4 kg), approximately 50% to 70% of the dose is excreted in the urine as unchanged drug. After a 200 mg IV dose, urine concentrations of ciprofloxacin usually exceed 200 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 IV dose is recovered from the feces within 5 days after dosing, which may arise from either biliary clearance or transintestinal elimination. Following intravenous administration, approximately 10% of the dose is recovered in the urine in the form of metabolites.

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

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

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

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

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

Table 8 summarizes the results of tissue and fluid penetration of ciprofloxacin in man.

Table 8: 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 (h)
Skin Blister Fluid	6	500 mg PO	1.4 ± 0.36	2.3 ± 0.7	1 - 6
Bone	4	750 mg PO	1.4 ± 1.0	2.9 ± 2.2	2 - 4
Gynecological Tissue	18	500 mg PO	1.3 ± 0.66 to 1.6 ± 0.97	1.4 ± 0.87	2 - 4
Prostatic Tissue	1	500 mg PO	3.76	1.84	2.5
Muscle	4	250 mg PO	2.4 ± 1.0	2.9 ± 2.2	2 - 4
Nasal Secretions	20	500 mg PO	1.4 ± 0.81	1.8 ± 0.48	1 - 3
Bronchial Tissues	10	200 mg IV	3.94 ± 2.5	1.62 ± 0.7	0.97
Vagina	18	100 mg IV	1.13 ± 0.2	0.61 ± 0.12	0.5
Ovary	18	100 mg IV	1.00 ± 0.23	0.61 ±0.12	0.5

Special Populations

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.

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.)
Cmax (mg/L)	1.8 ± 0.5	1.3 ± 0.4
tmax (hr)	1.2 ± 0.3	1.2 ± 0.1
t½ (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

Renal Impairment
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 I, Table 10) were compared to 6 patients (3 male, 3 female, age: 63 ± 6 years) with renal impairment (see Group II, Table 10) and to 5 patients (2 male, 3 female, age: 63 ± 6 years) with end-stage renal failure, treated by haemodialysis (see Group III, Table 10). Patients with renal insufficiency had significantly increased AUCs, prolonged (about 2-fold) elimination half-lives, and decreased renal clearances.

Haemodialysis resulted in a minimal decrease in plasma levels. From the dialysate concentrations, it can be estimated that no more than 2% of the dose was removed by dialysis over 4 hours, which was less than the amount lost in the urine over 24 hours in patients of Group II (see Table 10).

Table 10: Mean Pharmacokinetic Parameters for Ciprofloxacin Following Oral Administration of a Single 250 mg Tablet in Healthy Volunteers and in Patients with Renal Insufficiency

Group	Creatinine Clearance (mL/s/1.73 m²) (mL/min/1.73 m²)	Parameter					
		Cmax (mg/L)	tmax (h)	Half-Life (h)	Total AUC (mg•h/mL)	Renal Clearance (mL/min)	% Dose Urinary Recovery 0-24 h
I	> 1.0 (> 60)	1.52 (± 0.21)	1.0 (± 0.0)	4.4 (±0.2)	6.94 (± 0.97)	232.9 (± 44.8)	37.0 (± 3.7)
II	< 0.33 (< 20)	1.70 (± 0.41)	1.7 (± 0.5)	8.7 (±0.9)	14.36 (± 3.5)	18.3 (± 3.5)	5.3 (± 1.7)
III	End-Stage Renal Failure Treated by Hemodialysis	2.07 (± 0.23)	1.6 (± 0.2)	5.8 (± 0.9)	15.87 (± 2.0)		

The pharmacokinetics of ciprofloxacin following multiple IV doses were compared in subjects with normal renal function and in subjects with various degrees of renal impairment (see Table 11, Groups 1-4). Patients with renal insufficiency had significantly increased concentrations of ciprofloxacin, M_1 and M_2 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 IV 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, M_1 and M_2 metabolites were not significantly different for frequent versus delayed dialysis, except that dialysate clearances for ciprofloxacin and M_2 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 IV ciprofloxacin on two separate occasions, once immediately after hemodialysis, and once two hours before hemodialysis. The results demonstrated that the pharmacokinetic parameters were not significantly different between the two treatments for ciprofloxacin, M_1 and M_2 metabolites. Group 6 in Table 11 shows the pharmacokinetic results for the group dosed two hours before hemodialysis.

Table 11: Mean Pharmacokinetic Parameters for Ciprofloxacin and Metabolites M_1 and M_2 Following IV Dosing in Healthy Volunteers, Patients with Renal Insufficiency, Peritoneal Dialysis Patients, and Hemodialysis Patients

Group	Creatinine Clearance mL/min/1.73m^2	IV Ciprofloxacin Dose	Parameter								
			Ciprofloxacin			M1 (desethyleneciprofloxacin)			M2 (sulfociprofloxacin)		
			$AUC_{0-\infty}$ (mg•hr/L)	$C1_r$ (L/hr)	$t_{½}$ (hr)	$AUC_{0-\infty}$ (mg.hr/L)	$C1_r$ (L/hr)	$t_{½}$ (hr)	$AUC_{0-\infty}$ (mg•hr/L)	$C1_r$ (L/hr)	$t_{½}$ (hr)
1	>90	400 mg q8h x 11	10.2	20.3	4.59	0.19	19.9	5.04	0.98	19.5	2.33
2	61-90	400 mg q8h x 11	15.4	10.9	5.23	0.34	10.8	8.14	1.50	10.7	3.12
3	31-60	400 mg q12h x 8	21.5	6.91	5.72	0.57	7.1	9.10	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 injection 200 mg, there was no difference in pharmacokinetics between patients with stable chronic cirrhosis (with mild to moderate hepatic impairment) and healthy volunteers.

11 STORAGE, STABILITY AND DISPOSAL

Store between 15°C and 30°C.

12 SPECIAL HANDLING INSTRUCTIONS

There are no special handling requirements for this product.

PART II: SCIENTIFIC INFORMATION

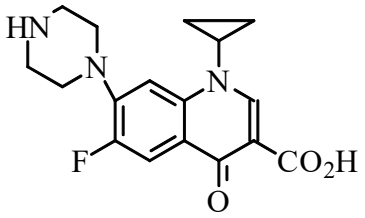
13 PHARMACEUTICAL INFORMATION

Drug substance

Proper Name: Ciprofloxacin hydrochloride

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

Structural Formula:



, HCl, H_2O

Molecular Formula: $C_{17}H_{18}FN_3O_3 \cdot HCl \cdot H_2O$

Molecular Mass: 385.8 g/mol

Physicochemical properties: Ciprofloxacin hydrochloride is a pale yellow crystalline powder. It is soluble in water. Its solubility in aqueous buffer of pH 7.4 at 21°C is 0.19 g/L, while the solubility is considerably higher at slightly acidic or slightly alkaline pH. At 140°C, water of crystallization is lost. At 307°C, decomposition takes place. The pH of ciprofloxacin hydrochloride is between 3 and 4.5 in a solution (1 in 40). The pK_{a1} is 6.5 and pK_{a2} is 8.9 determined using a $3x10^{-4}$M solution of 25°C.

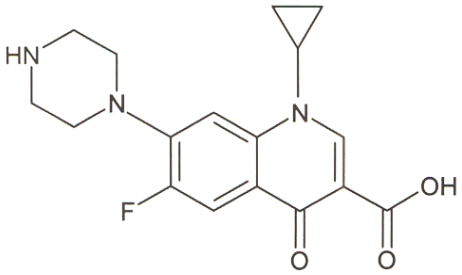
Drug substance

Proper Name: Ciprofloxacin

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

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

Structural Formula:



Molecular Formula: $C_{17}H_{18}FN_30_3$

Molecular Mass: 331.34 g/mol

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

14 CLINICAL TRIALS

14.3 Comparative Bioavailability Studies

A single-centre, open, randomised, three period crossover study was performed to assess the bioequivalence of ciprofloxacin 1 x 500 mg tablets in healthy male subjects. The table below does not include data derived from the Swiss reference product Ciproxin®. The summary of the comparative bioavailability study is presented in the following table:

Summary Table of the Comparative Bioavailability Data
From measured data (fasting conditions)

Parameter	Test** (A)	Reference† (B)	% Ratio of Geometric Means (A/B)	90% Confidence Interval
AUC_{0-t} (ng·h/mL)	7105 7398 (24.2)*	7471 7662 (21.7)*	95%	85-107
AUC_I (ng·h/mL)	7871 8154 (22.9)*	8237 8423 (20.5)*	96%	86-107
C_{max} (ng/mL)	2037 2114 (24.9)*	1999 2052 (21.1)*	102%	89-116
T_{max}^* (h)	1.23 (42.8)	1.10 (40.2)	---	---
$T_{½}^*$ (h)	3.69 (9.0)	3.90 (14.6)	---	---
K_{el}* (h)	0.189 (9.6)	0.182 (14.7)	---	---

* expressed as arithmetic mean (CV %) only
†Ciprobay ® 500 mg tablet (Bayer German reference product).
** CIPROFLOXACIN 500 mg tablet (Sivem Pharmaceuticals ULC)

15 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 $1x\ 10^{-6}$.

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
Citrobacter diversus
Citrobacter freundii
Enterobacter cloaceæ
Escherichia coli
Haemophilus influenzæ
Haemophilus parainfluenzæ
Klebsiella pneumoniæ
Moraxella catarrhalis
Morganella morganii
Neisseria gonorrhoeæ
Proteus mirabilis
Proteus vulgaris
Providencia rettgeri
Providencia stuartii
Pseudomonas aeruginosa
Salmonella typhi
Serratia marcescens
Shigella boydii
Shigella disenteriæ
Shigella flexneri
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 iwoffi
Aeromonas hydrophila
Edwardsiella tarda
Enterobacter ærogenes
Legionella pneumophila
Pasteurella multocida
Salmonella enteritidis
Vibrio cholerae
Vibrio parahaemolyticus
Vibrio vulnificus
Yersinia enterocolitica

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 (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 12.

Diffusion Techniques: Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 5 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 12. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for ciprofloxacin.

Table 12: Susceptibility Interpretative Criteria for Ciprofloxacin

	MIC (mcg/L)			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 æruginosa	≤1	2	≥4	≥21	16-20	≤15
Hæmophilus influenzæ	≤1[a]	[g]	[g]	≥21[b]	[g]	[g]
Hæmophilus parainfluenzæ	≤1[a]	[g]	[g]	≥21[b]	[g]	[g]
Streptococcus pyogenes	≤1[c]	2[c]	≥4[c]	≥21[d]	16-20[d]	≤15[d]
Neisseria gonorrhoeæ	≤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).

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

[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 13. For diffusion technique, the 5 mcg ciprofloxacin disk should provide the zone diameters outlined in Table 13.

Table 13: Quality Control for Susceptibility Testing

Strains	MIC range (mcg/L)	Zone Diameter (mm)
Enterococcus faecalis ATCC 29212	0.25- 2	-
Escherichia coli ATCC 25922	0.004- 0.015	30- 40
Hæmophilus influenzæ ATCC 49247	0.004- 0.03 [a]	34- 42 [d]
Pseudomonas æruginosa ATCC 27853	0.25 -1	25- 33
Staphylococcus aureus ATCC 29213	0.12- 0.5	-
Staphylococcus aureus ATCC 25923	-	22- 30
Neisseria gonorrhoeæ 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).
[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.
[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).
[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.

16 NON-CLINICAL TOXICOLOGY

Acute Toxicity

Table 14: LD_{50} (mg/kg) across species

Species	Mode of Administration	LD_{50} mg/kg
Mouse	PO	Approx. 5000
Rat	PO	Approx. 5000

Rabbit	PO	Approx. 2500
Mouse	IV	Approx. 290
Rat	IV	Approx. 145
Rabbit	IV	Approx. 125
Dog	IV	Approx. 250

Chronic Toxicity

Subacute Tolerability Studies Over 4 Weeks

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

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

Subchronic Tolerability Studies Over 3 Months

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

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

Chronic Tolerability Studies Over 6 Months

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

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

Carcinogenicity

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

Reproductive 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.

Mutagenesis

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

Salmonella: Microsome Test (Negative)
E. coli: DNA Repair Assay (Negative)
Mouse Lymphoma Cell Forward Mutation Assay (Positive)
Chinese Hamster V79 Cell HGPRT Test (Negative)
Syrian Hamster Embryo Cell Transformation Assay (Negative)
Saccharomyces cerevisiæ: 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 studies

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.

Detailed Animal Pharmacology

Effects on Histamine Release

Ciprofloxacin was administered intravenously to 9 anaesthetized dogs (initially with thiopental sodium at 25 mg/kg IV, followed by continuous infusion of a mixture of fentanyl 0.04 mg/kg/h and dehydrobenzperidol 0.25 mg/kg/h) 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.

Central Nervous System (CNS) Effects

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

Gastrointestinal Effects

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

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

Effect on Blood Glucose and Serum Triglycerides

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

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

17 SUPPORTING PRODUCT MONOGRAPHS

1. CIPRO®, CIPRO® ORAL SUSPENSION, submission control 248370, Product Monograph, Bayer Inc., Date of Revision: June 21, 2021.

PATIENT MEDICATION INFORMATION
READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICATION

PrCIPROFLOXACIN
Ciprofloxacin Tablets

Read this carefully before you start taking **CIPROFLOXACIN** 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.**

Serious Warnings and Precautions

- Fluoroquinolone antibiotics, like CIPROFLOXACIN, 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
- Fluoroquinolone antibiotics, like CIPROFLOXACIN:
    - 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?” section

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

What is CIPROFLOXACIN used for?
CIPROFLOXACIN is used to treat certain types of bacterial infections. They do not treat viral infections such as the common cold.

CIPROFLOXACIN is used to treat infections caused by bacteria. These include infections of the:
- Respiratory tract
- Urinary tract
- Prostate

- Skin and soft tissues
- Bone and joint
  It is also used to remove meningococci (a type of bacteria) from the nasopharynx (upper throat area) in patients not infected with meningitis.

It is also used to treat the following conditions:
- Diarrhea caused by bacterial infections
- Typhoid fever
- Uncomplicated gonorrhea

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

What are the ingredients in CIPROFLOXACIN?
Medicinal ingredients: ciprofloxacin as ciprofloxacin hydrochloride.

Non-medicinal ingredients: croscarmellose sodium, hypromellose, magnesium stearate, microcrystalline cellulose, polyethyelene glycol, povidone, silica colloidal anhydrous, sodium starch glycolate, stearic acid, talc, titanium oxide.

CIPROFLOXACIN comes in the following dosage forms:

CIPROFLOXACIN 250 mg tablet: White round film-coated tablet with breaking notch on one side. Embossed "cip" on top and "250" on the bottom of the breaking notch. Bottles of 100.

CIPROFLOXACIN 500 mg tablet: White oblong film-coated tablet with breaking notch on both sides. Embossed "cip" on one side of breaking notch and "500" on the other side, on one side of the tablet only. Bottles of 100.

CIPROFLOXACIN 750 mg tablet: White oblong film-coated tablet with breaking notch on both sides. Embossed "cip" on one side of breaking notch and "750" on the other side, on one side of the tablet only. Bottles of 50.

Do not use CIPROFLOXACIN 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?”
- you are taking tizanidine (ZANAFLEX®), a medication that relaxes muscles. Side effects such as drowsiness, sleepiness and low blood pressure may occur.
- you are currently taking agomelatine[a], a type of medication used to treat depression. 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.

Talk about any health conditions or problems you may have, including if you:

- have a history of seizures or have any other medical conditions or are taking medicines that could cause seizures.
- have an irregular heart rhythm (such as QT prolongation).
- you are taking medications that can affect your heart rhythm such as class IA or III antiarrhythmics that can cause QT prolongation
- have hypokalemia (low potassium blood levels).
- have liver or kidney disease or damage.
- 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 fluoroquinolone antibiotics.
- have myasthenia gravis (a muscle disease).
- have an aortic aneurysm (an abnormal bulge in a large blood vessel called the aorta.)
- have or if anyone in your family has a condition called aneurysm disease which is an abnormal bulge in any large blood vessel in the body.
- have an aortic dissection (a tear in the wall of the aorta.)
- have any of the following conditions: Marfan syndrome, vascular Ehlers-Danlos syndrome, Takayasu arteritis, giant cell arteritis or Behcet's disease.
- have high blood pressure.
- have atherosclerosis, which is a hardening of your blood vessels.

Other warnings you should know about:

Using CIPROFLOXACIN for too long or not long enough may cause the bacteria to become resistant, and your infection may not be resolved. Your doctor will tell you exactly how long you should be taking CIPROFLOXACIN for.

Blood Sugar Changes

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

CIPROFLOXACIN can make your skin more sensitive to the sun.

While taking CIPROFLOXACIN:

- Avoid too much sunlight or artificial ultraviolet light (such as sunlamps).
    - Stop taking CIPROFLOXACIN and contact your doctor if a sunburn or rash occurs.
- Do not drive or use machinery if you feel dizzy or lightheaded.

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

- The risk of these problems is higher if you:
    - are elderly
    - have or anyone in your family has had an aneurysm
    - have an aortic aneurysm or an aortic dissection

- have any of the following conditions: Marfan syndrome, vascular Ehlers-Danlos syndrome, Takayasu arteritis or giant cell arteritis or Behcet's disease
- have high blood pressure or atherosclerosis

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

Tendon problems can happen within the first 48 hours of treatment.

Clostridium difficile-associated disease (CDAD)
CIPROFLOXACIN can cause infections of the colon caused by a bacteria called clostridium difficile. These infections can vary in severity from mild diarrhea to fatal colitis (inflammation of the colon). If you experience diarrhea or other symptoms of colitis, talk to your doctor. Symptoms of colitis can include stomach pain or cramping, rectal bleeding, urgency or inability to pass stool, fatigue, weight loss and fever.

Allergic Reactions
Serious allergic reactions can happen from taking CIPROFLOXACIN. Stop taking CIPROFLOXACIN and talk to your doctor if you experience any of the following allergic reactions;

- severe hypotension (low blood pressure)
- seizure
- loss of consciousness
- tingling
- angioedema (swelling of the deeper layers of the skin including swelling of the tongue, throat or face)
- shortness of breath
- hives, itching, rashes and other skin reactions.

Psychiatric (Mental) Adverse Reactions
Psychiatric (mental) adverse reactions can happen from taking CIPROFLOXACIN. Stop taking CIPROFLOXACIN and talk to your doctor if you experience any of the following adverse reactions:

- psychosis, hallucinations, paranoia (see, hear, or believe things that are not real)
- depression or suicidal thoughts
- anxiety, agitation, restlessness, or nervousness
- confusion, disorientation, or disturbances in attention
- insomnia or nightmares
- problems with your memory

Ophthalmic (Eye) Problems
If you experience any problems with your vision while taking CIPROFLOXACIN, contact an eye doctor immediately.

Peripheral Neuropathy (damaged nerves outside of the brain and spinal cord)
Nerve damage can happen from taking CIPROFLOXACIN. Stop taking CIPROFLOXACIN and talk to your doctor if you experience any of the following symptoms:

- pain, burning, tingling, numbness, weakness in your hands or feet

- decreased sensation of light touch, pain, temperature, position sense, vibration, and/or motor strength

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:

- Theophylline or didanosine chewable/buffered tablets or pediatric powder. Serious and fatal reactions have been reported in patients receiving ciprofloxacin, including CIPROFLOXACIN, and theophylline**.**
- Antacids, multivitamins, and other dietary supplements containing magnesium, calcium, aluminum, iron or zinc (see "How to take CIPROFLOXACIN:").
- 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)
- 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, tizanidine, duloxetine, methylxanthines, sevelamer,
    - sucralfate, omeprazole, clozapine, ropinirole, lidocaine, sildenafil, probenecid,
    - ferrous sulfate, calcium-fortified products (including food and dairy products),
    - histamine H2-receptor antagonists
    - methotrexate, metoclopramide, cyclosporine, lanthanum carbonate, zolpidem.

How to take CIPROFLOXACIN:

- Take CIPROFLOXACIN as prescribed by your doctor at almost the same times each day. Take CIPROFLOXACIN with food or on an empty stomach.
- Do not take CIPROFLOXACIN with dairy products (like milk or yogurt) or calcium-fortified juices alone. However, you may take CIPROFLOXACIN with a meal that contains these products (see "The following may interact with CIPROFLOXACIN").
- Do not take CIPROFLOXACIN with antacids that contain magnesium or aluminum.
- You should avoid excessive caffeine consumption while taking CIPROFLOXACIN.
- You should drink lots of water while taking CIPROFLOXACIN.
- Swallow the CIPROFLOXACIN tablets whole, with water as needed. **DO NOT SPLIT, CRUSH, OR CHEW THE TABLET.**
- After treatment has been completed, any remaining CIPROFLOXACIN should not be reused.
- If you are taking the following medicines, take them at least 2 hours before or 6 hours after CIPROFLOXACIN;
    - antacids or mineral supplements containing magnesium or aluminum
    - sucralfate
    - didanosine chewable/buffered tablets or pediatric powder
    - supplements containing iron or zinc
    - any product (supplement or food) with more than 800 mg calcium
- Do not use CIPROFLOXACIN for another condition or give it to others.

Although you may feel better early in treatment, CIPROFLOXACIN should be taken exactly as directed. Misuse or overuse of CIPROFLOXACIN could lead to the growth of bacteria that will not be killed by CIPROFLOXACIN (resistance). This means that CIPROFLOXACIN may not work for you in the future. Do not share your medicine.

You should take CIPROFLOXACIN 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, or a person you are caring for, have taken too much CIPROFLOXACIN, contact a health care professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:
If you forget to take CIPROFLOXACIN and it is:

- 6 hours or more until your next scheduled dose, take your missed dose right away. Then take the next dose at your regular time.
- Less than 6 hours until your next scheduled dose, do not take the missed dose. Take the next dose at your regular time.

Do not take a double dose to make up for a forgotten dose. If you are unsure about what to do, consult your healthcare professional.

What are possible side effects from using CIPROFLOXACIN?

All medicines, including CIPROFLOXACIN, can cause side effects, although not everyone gets them.

These are not all the possible side effects you may feel when taking CIPROFLOXACIN. If you have any side effects not listed here, tell your healthcare professional.

Stop taking CIPROFLOXACIN and contact your doctor if:

- you have sunburn-like skin reaction when exposed to sunlight or ultraviolet light

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 healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
UNCOMMON			
Digestive: • vomiting • gastro-intestinal and abdominal pain (stomach-ache) • flatulence (gas) • dyspepsia(indigestion/heartburn) • decreased appetite and food intake		✓	
Hemic and Lymphatic: • eosinophilia (a high concentration of eosinophils, a type of white blood cell)		✓	
Musculoskeletal: • arthralgia (joint pain)			✓
Skin: • pruritis (itching), • urticaria (hives and/or skin eruptions)			✓
Urogenital: • renal impairment (abnormal/poor kidney function)		✓	
RARE			
Allergic Reaction: • rash, • bleeding diathesis (easy to bleed or bruise), • Alopecia (hair loss patches), • hyperpigmentation, • exfoliative dermatitis (peeling skin), • purpura (blood or purple spots on skin) • Allergic edema or angioedema (swelling of the face, lips, tongue, throat or mucous membranes) • difficulty swallowing or breathing, bronchospasm (wheezing), tachycardia (irregular or rapid heartbeat), or fainting spells			✓
Cardiovascular: • angina pectoris (chest pain), cardiac arrest (sudden loss of heart function), cerebrovascular disorder (disorders that affect blood supply to the brain), myocardial infarct (heart attack), cardiac murmur (heart murmur), cardiopulmonary arrest (loss of heart function and			✓

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
respiration), cardiovascular collapse (loss of consciousness due to loss of blood flow to the brain) • pulmonary embolism (blockage of artery in lung) • phlebitis (inflammation of the veins), thrombophlebitis (inflammation in vein due to blood clot), cerebral thrombosis (blood clot of a cerebral vein in the brain), pericarditis (inflammation of the sac surrounding heart) • vasodilation (expansion of blood vessels, hot flashes), hypotension (low blood pressure), postural hypotension (low blood pressure/light-headedness when standing)			
Digestive: • dry mouth, dysphagia (difficulty swallowing), moniliasis (yeast infection of the mouth and throat), gastrointestinal moniliasis (yeast infection in the gut), cholestatic jaundice, hepatomegaly (enlarged liver) enlarged abdomen, stomatitis (swelling of the mouth or lips), stomatitis and ulcerative stomatitis (ulcers in the mouth), tooth discoloration • esophagitis (irritation or inflammation of the esophagus), glossitis (swelling of the tongue), ileus (intestinal obstruction), increased appetite, intestinal perforation (hole in wall of stomach), constipation • melena(black or tarry stools), tenesmus (cramping rectal pain), toxic megacolon (unable to pass gas or feces from colon), gastrointestinal bleeding or hemorrhage • pseudomembranous colitis or antibiotic associated colitis (inflammation of the bowel linked to antibiotic use), can be fatal in very rare cases • lipase increased (higher level of lipase in blood		✓	
Hemic and Lymphatic: • leukopenia, anemia, leukocytosis (changes to white blood cell count) thrombocytopenia or thrombocytemia		✓	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
(changes in platelet levels) • abnormal prothrombin (a clotting factor) level or increased amylase (increased levels of the enzyme amylase), acidosis (increased acidity in blood and body tissues) • kidney vasculitis (inflammation of the walls of blood vessels in kidneys), haemorrhagic bullae and small nodules (papular rash) with crust formation showing vascular involvement			
Hepatic: • liver disorder: jaundice (yellowing of the skin or eyes), dark urine, abdominal pain, nausea, vomiting, loss of appetite, pale stools • liver damage, • abnormal liver function tests, • hepatic impairment (liver disorders), jaundice, non-infective hepatitis			✓
Hyperglycemia (Increased Blood Sugar): • frequent urination, • thirst, • hunger, • tiredness, • blurred vision, • headache, • trouble concentrating	✓		
Hypoglycemia (low blood sugar): • change in mood • change in vision • confusion • dizziness, • fast heartbeat • feeling faint • headache, • hunger • shaking • sweating, • weakness		✓	
Mental Health: • anxiety • confusion, delirium			✓

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
• depression, • feeling agitated • restless or nervous, difficulty sleeping • suicidal thoughts or actions and self injurious behaviour, • hallucinations, manic reaction (mental disturbances) • inability to think clearly or pay attention • disorientation • memory loss • phobia • paranoia or loss of touch with reality • unresponsiveness (These side effects may last more than 30 days)			
Musculoskeletal: • pain in extremities, achiness, joint disorder (joint swelling or stiffness), arthritis (inflammation of the joints), gout (flare up of arthritis) • myalgia (muscular pain), increased muscle tone and cramping, myoclonus (muscle spasms), rhabdomyolysis (breakdown and leakage of muscle fibres)			✓
Neurological: • seizures (convulsions) • tremors • shaking • headache • dysphasia (language disorder)			✓
Photosensitivity Reaction: Sensitivity to light, blistering of skin			✓
Rise in the pressure within your skull: • blurred vision or diplopia (double vision) • headache • nausea		✓	
Special Senses: • Eyes: your eyesight worsens or changes (These side effects may last more than 30 days), visual disturbances (flashing lights, changes in colour perception, verbrightness of lights), chromatopsia (abnormal vision colour), colour blindness, conjunctivitis (pink eye), corneal opacity			✓

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
(scarring and clouding over cornea), eye pain, nystagmus (uncontrolled eye movements) • Ears: ear pain, hearing loss, tinnitus (loss of hearing), problems of smell and taste, loss of appetite (These side effects may last more than 30 days).			
Symptoms of an Infection: • fever, chills, drowsiness • drug fever		✓	
Tendon pain, inflammation, or rupture (these side effects may last more than 30 days)			✓
Urogenital: • blood creatinine increased, acute kidney failure, albuminuria (increased albumin in urine), dysuria (pain during urination), urinary retention, • leukorrhea (changes in vaginal discharge), vaginitis (inflammation of the vagina) or vaginal moniliasis, candiduria (yeast urinary infection), • urethral bleeding (blood in urine), frequent urination • renal failure (kidney failure), hematuria (blood in the urine), crystalluria (crystals in the urine) or tubulointerstitial nephritis (a type of urinary tract inflammation), electrolyte abnormality (loss of bodily fluids), hypercalcemia (increased calcium in blood), hypocalcemia (decreased calcium in blood), hemorrhagic cystitis (inflammation of the bladder), polyuria (frequent urination), renal calculi (kidney stones)		✓	
VERY RARE			
Digestive: • pancreatitis (inflammation of the pancreas)		✓	
Hemic and Lymphatic: • hemolytic anemia (a special type of reduced red blood cell count), • granulocytopenia, agranulocytosis (decrease in a type of white blood cells), or pancytopenia (an extreme drop in all blood cell counts) which may be life- threatening;		✓	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
or bone marrow depression, which may also be life- threatening vasculitis (inflammation of the walls of the blood vessels)			
Hepatic: • Liver necrosis very rarely progressing to life-threatening hepatic failure (death of liver cells very rarely leading to life-threatening liver failure)			✓
Hypersensitivity: • petechiae (small, pin-point bleeding rash under the skin), • erythema multiforme, erythema nodosum (various skin eruptions, blisters, peeling or rashes), • Stevens-Johnson syndrome, toxic epidermal necrolysis which may be life-threatening (severe allergic skin reactions) • serum sickness-like reaction (an allergic reaction)			✓
Mental Health: • toxic psychosis (substance-induced psychosis)			✓
Musculoskeletal: • worsening of myasthenia gravis (a muscle disease) with symptoms such as: weakness, difficulty walking, swallowing, drooping eyelids (Do not use CIPRO if you have this condition)			✓
Neurological: • migraine		✓	
UNKNOWN			
Acute generalized exanthematous pustulosis (AGEP) (pustular rash) **Aortic aneurysm** (abnormal bulge in a large blood vessel called the aorta) /**Aortic dissection** (tear in the wall of the aorta): • dizziness • loss of consciousness • pulsating sensation in the abdomen sudden, severe pain in abdomen, chest or back			✓
Clostridium difficile colitis (severe bowel disorder):			✓

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
• persistent diarrhea, • bloody or watery diarrhea with or without fever and stomach pain or tenderness, • abdominal or stomach pain/cramping, blood/mucus in stool			
Epistaxis (acute haemorrhage from nose or nosebleed)		✓	
Gynecomastia (swelling of breast tissue in males)		✓	
Lymphadenopathy (swollen lymph nodes)		✓	
Neuropathy (nerve disorder): peripheral neuropathy and polyneuropathy (troubles associated with the nervous system such as pain, burning, tingling, numbness, weakness in your hands and feet			✓
QT Prolongation (heart disorder) and other cardiovascular effects: Irregular heartbeat, ventricular arrhythmia or Torsades de Pointes (abnormal heart rhythm, life-threatening irregular heart rhythm, alteration of the heart rhythm)			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell 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 30°C.

Keep out of reach and sight of children.

If you want more information about CIPROFLOXACIN:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website www.sivem.ca,or by calling 1-800-788-3153.

This leaflet was prepared by

Sivem Pharmaceuticals ULC
4705 Dobrin Street
Saint-Laurent, Quebec
Canada H4R 2P7

Last revised: NOV 08, 2022