Product Monograph
Including Patient Medication Information

[Pr]CIPRO® ORAL SUSPENSION

Ciprofloxacin oral suspension

For oral use

10 g/ 100 mL of Ciprofloxacin

Antibacterial Agent

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Recent Major Label Changes

7 Warnings and Precautions, Cardiovascular	2025-10
7 Warnings and Precautions, Immune	2025-10

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Certain sections or subsections that are not applicable at the time of the preparation of the most recent authorized product monograph are not listed.

Part 1: Healthcare Professional Information

1 Indications

CIPRO ORAL SUSPENSION (ciprofloxacin oral suspension) 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

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

CIPRO ORAL SUSPENSION 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, CIPRO ORAL SUSPENSION 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.

[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.

Urinary Tract Infections

Upper and lower urinary tract infections, such as complicated and uncomplicated cystitis, pyelonephritis, and pyelitis caused by:

Citrobacter diversus

Citrobacter freundii

Enterobacter cloacae

Escherichia coli

Klebsiella pneumoniae

Klebsiella oxytoca

Morganella morganii

Proteus mirabilis

Pseudomonas aeruginosa

Serratia marcescens

Staphylococcus aureus

Staphylococcus epidermidis

Staphylococcus saprophyticus

Streptococcus faecalis

Acute uncomplicated cystitis:

in females caused by *Escherichia coli*

In cases of uncomplicated acute bacterial cystitis, limit the use of CIPRO ORAL SUSPENSION 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 gonorrhoeae*. 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 CIPRO ORAL SUSPENSION and other antibacterial drugs, CIPRO ORAL SUSPENSION 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 CIPRO ORAL SUSPENSION 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 CIPRO ORAL SUSPENSION 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 CIPRO ORAL SUSPENSION in individuals less than 18 years of age has not been established. CIPRO ORAL SUSPENSION is not recommended for children under the age of 18 years (see 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 4.2 Recommended Dose and Dosage Adjustment, Impaired Renal Function for dose modification based on creatinine clearance or serum creatinine).

2 Contraindications

- CIPRO ORAL SUSPENSION 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 6 Dosage Forms, Strengths, Composition, and Packaging.
- Concurrent administration of ciprofloxacin and agomelatine (currently not marketed in Canada) 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).

3 Serious Warnings and Precautions Box

- Fluoroquinolones, including CIPRO ORAL SUSPENSION, have been associated with disabling and potentially persistent adverse reactions which to date include, but are not limited to: tendinitis, tendon rupture, peripheral neuropathy and neuropsychiatric effects.
- CIPRO ORAL SUSPENSION 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 CIPRO ORAL SUSPENSION (see 7 Warnings and Precautions, Immune).
- Fluoroquinolones including CIPRO ORAL SUSPENSION 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 CIPRO ORAL SUSPENSION may exacerbate muscle weakness in persons with myasthenia gravis. Avoid using CIPRO ORAL SUSPENSION 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 CIPRO ORAL SUSPENSION. CIPRO ORAL SUSPENSION 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 CIPRO ORAL SUSPENSION (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.

CIPRO ORAL SUSPENSION[2] 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 oral dosages for CIPRO ORAL SUSPENSION are:

Table 1: Recommended Oral Dosages

Location of Infection	Type/Severity	Unit Dose[a]	Frequency	Daily Dose
Urinary Tract	Mild/Moderate	250 mg	q12h	500 mg
Urinary Tract	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
Respiratory Tract Bone & Joint Skin & Soft Tissue	Severe[b]/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
Acute Sinusitis	Moderate	500 mg	q12h	1000 mg

a One teaspoon (5 mL) of 10% oral ciprofloxacin suspension = 500 mg of ciprofloxacin
b E.g., hospital-acquired pneumonia, osteomyelitis

[2] One teaspoon (5 mL) of 10% oral ciprofloxacin suspension = 500 mg of ciprofloxacin

See instructions below for Use/Handling.

Table 2: Use/Handling of Ciprofloxacin Suspension

Dosage	Volume (mL) of 10% Oral Suspension
250 mg	2.5 mL
500 mg	5 mL
750 mg	7.5 mL

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.

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 10.3 Pharmacokinetics). 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 CIPRO ORAL SUSPENSION. However, monitoring of serum drug levels provides the most reliable basis for dosage adjustments.

Table 3: Maximum Daily Oral Dose With Stated Creatinine Clearance or Serum Creatinine

Creatinine Clearance mL/min/1.73m^2	Maximum Daily Oral Dose	Serum Creatinine Concentration mg/100 mL
31-60	1000 mg	1.4 -1.9
≤ 30	500 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 3. On dialysis days, the dose should be administered after dialysis.

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

Creatinine Clearance mL/sec =

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

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 CIPRO ORAL SUSPENSION in individuals less than 18 years of age has not been established. CIPRO ORAL SUSPENSION is not recommended for use in pediatric patients and adolescents (see 7.1.3 Pediatrics).

4.3 Reconstitution

Instructions to the Pharmacist for Use/Handling of CIPRO ORAL SUSPENSION:

Preparation of the suspension:

The small bottle contains the ciprofloxacin microcapsules; the large bottle contains the diluent.

Open both bottles. Child-proof cap: Press down according to the instructions on the cap while turning to the left.

Pour the microcapsules completely into the large bottle of diluent. **Do not add water to the suspension.**

Close the large bottle completely according to the instructions on the cap and shake vigorously for about 15 seconds. The suspension is ready for use.

Instructions to the Patient for Taking CIPRO ORAL SUSPENSION:

Shake vigorously each time before use for approximately 15 seconds.

Swallow the prescribed amount of suspension. Do not chew the microcapsules. Reclose the bottle completely after use according to instruction on the cap. The suspension is stable for 14 days when stored in a refrigerator or at room temperature (5°C-25°C). Store in an upright position. After treatment has been completed, any remaining suspension should not be reused. After use, clean the graduated measuring spoon under running water with detergent, then dry thoroughly (see 11 Storage, Stability, and Disposal).

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 9.4 Drug-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 9.4 Drug-Drug Interactions and 9.5 Drug-Food 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 Overdose

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

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

For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844-POISON-X (1-844-764-7669).

6 Dosage Forms, Strengths, Composition, and Packaging

Table 4: Dosage Forms, Strengths, and Composition

Route of Administration	Dosage Form / Strength/Composition	Non-Medicinal Ingredients
Oral	Oral suspension, 10 g/100 mL	For a complete listing see Composition

CIPRO ORAL SUSPENSION is supplied as a 10% (10 g ciprofloxacin in 100 mL) strength. The drug product is composed of two components (microcapsules and diluent) which are mixed prior to dispensing (see 4.3 Reconstitution).

Table 5: CIPRO ORAL SUSPENSION

Total Volume After Reconstitution	Ciprofloxacin Contents After Reconstitution	Ciprofloxacin Contents per Bottle
100 mL	500 mg/5 mL	10,000 mg

Store at room temperature (15°C-25°C) in an upright position. Protect from freezing.

Reconstituted product may be stored in a refrigerator or at room temperature (5°C -25°C) for 14 days. Store in an upright position. A teaspoon is provided for the patient.

Composition

A. Microcapsules

Ciprofloxacin "oral, new" micronized

Hypromellose 3 cP, Magnesium Stearate, Poly Acrylate Dispersion 30%, Polysorbate 20, Povidone 25

B. Diluent

Medium Chain Triglycerides, Purified Water, Soy-Lecithin, Strawberry flavour 52312, Strawberry flavour 54267, Sucrose micronized

7 Warnings and Precautions

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.

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

As the oral suspension contains sucrose, it is unsuitable for patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency (see 6 Dosage Forms, Strengths, Composition, and Packaging).

Cardiovascular

CIPRO ORAL SUSPENSION 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 9.4 Drug-Drug Interactions and 8.5 Post-Market Adverse Reactions).

Kounis syndrome (see Immune and 8.5 Post-Market 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 CIPRO ORAL SUSPENSION, have been associated with disturbances of blood glucose, including symptomatic hyperglycemia and hypoglycemia, usually in diabetic patients receiving concomitant treatment with an oral hypoglycemic agent (e.g., glyburide) or with insulin. In these patients, careful monitoring of blood glucose is recommended. Severe cases of hypoglycemia resulting in coma or death have been reported. If a hypoglycemic reaction occurs, discontinue CIPRO ORAL SUSPENSION immediately and initiate appropriate therapy (see 8.3 Less Common Clinical Trial Adverse Reactions and 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 CIPRO ORAL SUSPENSION (see 8.5 Post-Market Adverse Reactions). 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 may 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.

Hepatic/Biliary/Pancreatic

Cases of hepatic necrosis and life-threatening hepatic failure have been reported with CIPRO ORAL SUSPENSION. 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 8.3 Less Common Clinical Trial 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 CIPRO ORAL SUSPENSION (see 8.3 Less Common Clinical Trial Adverse Reactions and 8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry, and Other Quantitative Data).

Immune

Serious hypersensitivity and/or anaphylactic reactions have been reported in patients receiving fluoroquinolone therapy, including CIPRO ORAL SUSPENSION (see 8.3 Less Common Clinical Trial 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.

Cases of acute myocardial ischemia with or without myocardial infarction as part of a hypersensitivity reaction (Kounis syndrome) have also been reported (see 8.5 Post-Market Adverse Reactions). In the event of Kounis syndrome while on treatment with CIPRO ORAL SUSPENSION, discontinue CIPRO ORAL SUSPENSION immediately.

CIPRO ORAL SUSPENSION 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 CIPRO ORAL SUSPENSION, 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 CIPRO ORAL SUSPENSION in patients with a known history of myasthenia gravis (see 8.5 Post-Market Adverse Reactions).

Tendinitis and Tendon Rupture

Tendinitis and tendon rupture (predominantly Achilles tendon), sometimes bilateral, may occur with CIPRO ORAL SUSPENSION, 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 CIPRO ORAL SUSPENSION (see 8.3 Less Common Clinical Trial Adverse Reactions and 8.5 Post-Market Adverse Reactions). CIPRO ORAL SUSPENSION 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. CIPRO ORAL SUSPENSION 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.

CIPRO ORAL SUSPENSION should not be used in patients with a history of tendon disease/disorder related to previous fluoroquinolone treatment.

Neurologic

Central Nervous System Adverse Reactions

Fluoroquinolones, including CIPRO ORAL SUSPENSION, have 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, CIPRO ORAL SUSPENSION 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 CIPRO ORAL SUSPENSION, discontinue CIPRO ORAL SUSPENSION immediately and institute appropriate measures (see 8.3 Less Common Clinical Trial Adverse Reactions).

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 CIPRO ORAL SUSPENSION.

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 8.5 Post-Market Adverse Reactions).

Psychiatric Adverse Reactions

Fluoroquinolones, including CIPRO ORAL SUSPENSION, 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 CIPRO ORAL SUSPENSION, discontinue CIPRO ORAL SUSPENSION and institute appropriate measures (see 8.3 Less Common Clinical Trial Adverse Reactions and 8.5 Post-Market Adverse Reactions).

Ophthalmologic

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

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, CIPRO ORAL SUSPENSION should be used with caution and at a reduced dosage in patients with impaired renal function (see 4.2 Recommended Dose and Dosage Adjustment, Special Populations and 10.3 Pharmacokinetics).

Sensitivity/Resistance

Development of Drug-Resistant Bacteria

Prescribing CIPRO ORAL SUSPENSION 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.

Overgrowth of Non-Susceptible Organisms

Prolonged use of CIPRO ORAL SUSPENSION 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.

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 Pregnancy

The safety of CIPRO ORAL SUSPENSION in pregnancy has not yet been established. CIPRO ORAL SUSPENSION should not be used in pregnant women unless the likely benefits outweigh the possible risk to the fetus. CIPRO ORAL SUSPENSION has been shown to be non-embryotoxic and non-teratogenic in animal studies (see 16 Non-Clinical Toxicology, Reproductive and developmental toxicology).

7.1.2 Breastfeeding

The safety of CIPRO ORAL SUSPENSION 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 CIPRO ORAL SUSPENSION, 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. CIPRO ORAL SUSPENSION 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 10.3 Pharmacokinetics).

8 Adverse Reactions

8.1 Adverse Reaction Overview

The following sections summarize the safety information derived from clinical trials and post-market use of CIPRO ORAL SUSPENSION, as well as ciprofloxacin tablets provided as CIPRO which is no longer marketed.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. Therefore, the frequences of adverse reactions observed in the clinical trials may not reflect frequences observed in clinical practice and should not be compared to frequencies reported in clinical trials of another drug.

CIPRO ORAL SUSPENSION is 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%).

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 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. 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, taste perversion, vomiting, abnormal liver function test. The following have been reported rarely: taste loss (impaired taste), 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.

Ear and Labyrinth Disorders: tinnitus. The following have been reported rarely: transitory deafness (especially at higher frequencies). The following have been reported very rarely: ear pain.

Eye Disorders: abnormal vision (visual disturbances). The following have been reported very rarely: chromatopsia, colour blindness, conjunctivitis, corneal opacity, diplopia, eye pain.

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: anosmia (usually reversible on discontinuation), apathy, ataxia, depersonalization, diplopia, hemiplegia, hyperesthesia, hypertonia, increase of intracranial pressure, meningism, migraine, nervousness, neuritis, paresthesia, parosmia (impaired smell), 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.

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.

8.5 Post-Market Adverse Reactions

The additional adverse events summarized in Table 6, in alphabetical order, regardless of incidence or relationship to drug, have been reported during clinical trials and/or from worldwide postmarketing experience in patients given ciprofloxacin (includes all formulations, all dosages, all drug-therapy durations, and in all indications).

Table 6: Post-Market Adverse Reactions

System Organ Class	Adverse Events
Body as a Whole	Chills, fever, pain (arm, breast, epigastric, foot, jaw, neck, oral mucosa)
Cardiovascular	Arrhythmia, atrial flutter, cardiac murmur, cardiopulmonary arrest, cardiovascular collapse, cerebral thrombosis, Kounis syndrome (acute myocardial ischemia with or without myocardial infarction occurring as part of an allergic reaction), postural hypotension, QT prolongation, torsades de pointes, ventricular ectopy, ventricular fibrillation, ventricular tachycardia
Digestive	*C. difficile* associated diarrhea, gastrointestinal bleeding
Ear and Labyrinth Disorders	Hearing loss
Eye Disorders	Nystagmus, visual acuity (decreased) and visual disturbances (change in colour perception, flashing lights, overbrightness of lights)
Hemic and Lymphatic	Bleeding diathesis, epistaxis, lymphadenopathy, purpura
Hypersensitivity	Edema (conjunctivae, hands, lips, lower extremities, neck)
Metabolic and Nutritional Disorder	Gout (flare up)
Musculoskeletal	Joint stiffness, rhabdomyolysis, tendinitis, tendon rupture
Nervous System	Delirium, drowsiness, dysphasia, lightheadedness, myoclonus, peripheral neuropathy, polyneuropathy, unresponsiveness
Other	International normalized ratio (INR) increased (in patients treated with Vitamin K antagonists)
Psychiatric	Manic reaction, paranoia, phobia, restlessness, toxic psychosis
Respiratory System	Bronchospasm, hemoptysis, pleural effusion, pulmonary embolism, respiratory arrest, respiratory distress
Skin/Appendages	Acute generalized exanthematous pustulosis (AGEP), exfoliative dermatitis, hyperpigmentation, vesicles

System Organ Class	Adverse Events
Urogenital System	Candiduria, gynecomastia, hemorrhagic cystitis, polyuria, renal calculi, urethral bleeding, urination (frequent)

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

9.1 Serious Drug Interactions

- Concurrent administration of ciprofloxacin and agomelatine (currently not marketed in Canada) is contraindicated since it may result in an undesirable increase in agomelatine exposure (see 2 Contraindications and 9.4 Drug-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 2 Contraindications and 9.4 Drug-Drug Interactions).
- Serious and fatal reactions have been reported in patients receiving concurrent administration of ciprofloxacin and theophylline (see 9.2 Drug Interactions Overview and 9.4 Drug-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 (currently not marketed in Canada) or tizanidine as this may lead to an undesirable increase in exposure to these drugs.

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

9.3 Drug-Behaviour 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 8.3 Less Common Clinical Trial Adverse Reactions and 8.5 Post-Market 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 7: Established or Potential Drug-drug Interactions

Non-proprietary names of the drug products	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 8.3 Less Common Clinical Trial 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 (oxpentifylline)-containing products, raised serum concentrations of this xanthine derivative were reported.	Caution and careful monitoring of patients on concomitant therapy of ciprofloxacin and caffeine or pentoxifylline (oxpentifylline) containing products is recommended.
Class IA or III Antiarrhythmics	C	Ciprofloxacin may have an additive effect on the QT interval (see 7 Warnings and Precautions, Cardiovascular).	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.

Non-proprietary names of the drug products	Source of evidence	Effect	Clinical comment
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 9.2 Drug Interactions Overview).	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 Products)	CT	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 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.

Non-proprietary names of the drug products	Source of evidence	Effect	Clinical comment
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 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 significantly reduced by concomitant administration of multivalent cation-containing products.	Ciprofloxacin should be administered at least 2 hours before or 6 hours after these preparations.
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 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).

Non-proprietary names of the drug products	Source of evidence	Effect	Clinical comment
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.
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.

Non-proprietary names of the drug products	Source of evidence	Effect	Clinical comment
Tizanidine	CT	In a clinical study in healthy subjects there was an increase in tizanidine serum concentrations (C_{max} increase: 7-fold, range: 4- to 21-fold; AUC increase: 10-fold, range: 6- to 24-fold) when given concomitantly with ciprofloxacin. Associated with the increased serum concentrations was a potentiated hypotensive and sedative effect.	Tizanidine must not be administered together with ciprofloxacin (see 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 9.4 Drug-Drug Interactions, and 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 CIPRO ORAL SUSPENSION.

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 13 Pharmaceutical Information, 15 Microbiology). There is no cross-resistance between ciprofloxacin and the mentioned classes of antibiotics.

10.3 Pharmacokinetics

Absorption:

Following oral administration of a single dose of 500 mg of the ciprofloxacin tablet, 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.

The pharmacokinetics of ciprofloxacin oral suspension 10% are virtually identical to those of tablets.

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 (M1), sulphociprofloxacin (M2), oxociprofloxacin (M3) and formylciprofloxacin (M4). M1 to M3 display antibacterial activity comparable to or inferior to that of nalidixic acid. M4, 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.

- **Hepatic Insufficiency:**

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.

- **Renal Insufficiency:**

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.

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 4.2 Recommended Dose and Dosage Adjustment, Impaired Renal Function).

11 Storage, Stability, and Disposal

The trade pack supplied to the Pharmacist (microcapsules and diluent in separate bottles) is to be stored at room temperature (15°C-25°C) and protected from freezing. Store in an upright position.

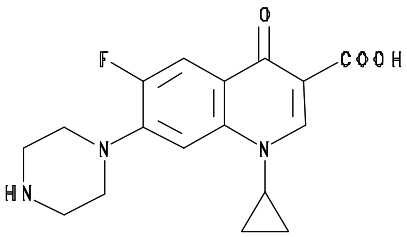
The freshly reconstituted suspension is stable for 14 days when stored in the refrigerator or at room temperature (5°C-25°C). Store in an upright position.

Shake vigorously for 15 seconds each time before use.

Part 2: Scientific Information

13 Pharmaceutical Information

Drug Substance

Non-proprietary name of the drug substance:	Ciprofloxacin
Chemical name:	1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(piperazinyl)-3-quinolinecarboxylic acid
Molecular formula and molecular mass:	$C_{17}H_{18}FN_3O_3$, 331.4
Structural formula:	
Physicochemical properties:	Ciprofloxacin is a pale yellow to white crystalline powder which is soluble in dilute (0.1 N) hydrochloric acid and is practically insoluble in water and ethanol. Decomposition occurs between 261°C - 265°C. pH of ciprofloxacin is 7.6 at 0.1 g/L water at 20°C. It has a pKa_1 of 6.5 and pKa_2 of 8.9 determined using a 3 x 10^{-4}M solution at 25°C.

14 Clinical Trials

The clinical trial data on which the original indication was authorized is not available.

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 $1x10^{-6}$.

Activity in vitro and in vivo

Ciprofloxacin has in vitro activity against a wide range of gram-positive and gram-negative microorganisms. Ciprofloxacin is slightly less active when tested at acidic pH. The inoculum size has little effect when tested in vitro. The minimal bactericidal concentration (MBC) generally does not exceed the minimal inhibitory concentration (MIC) by more than a factor of 2.

Ciprofloxacin has been shown to be active against most strains of the following microorganisms, both in vitro and in clinical infections:

Aerobic gram-positive microorganisms

Enterococcus faecalis (Many strains are only moderately susceptible.)

Staphylococcus aureus (methicillin-susceptible strains only)

Staphylococcus epidermidis (methicillin-susceptible strains only)

Staphylococcus saprophyticus

Streptococcus pyogenes

Aerobic gram-negative microorganisms

Campylobacter jejuni

Citrobacter diversus

Citrobacter freundii

Enterobacter cloacae

Escherichia coli

Haemophilus influenzae

Haemophilus parainfluenzae

Klebsiella pneumoniae

Moraxella catarrhalis

Morganella morganii

Neisseria gonorrhoeae

Proteus mirabilis

Proteus vulgaris

Providencia rettgeri

Providencia stuartii

Pseudomonas aeruginosa

Salmonella typhi

Serratia marcescens

Shigella boydii

Shigella dysenteriae

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 µg/mL or less against most (≥90%) strains of the following microorganisms; however, the safety and effectiveness of ciprofloxacin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Aerobic gram-positive microorganisms

Staphylococcus haemolyticus

Staphylococcus hominis

Aerobic gram-negative microorganisms

Acetinobacter iwoffii

Aeromonas hydrophila

Edwardsiella tarda

Enterobacter aerogenes

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 8.

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

Reports from the laboratory providing results of the standard single disk susceptibility test with a 5 µg ciprofloxacin disk should be interpreted according to the criteria outlined in Table 8. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for ciprofloxacin.

Table 8: Susceptibility Interpretative Criteria for Ciprofloxacin

	MIC (µg/mL)			Zone Diameter (mm)		
Species	**S**	**I**	**R**	**S**	**I**	**R**
Enterobacteriacae	≤1	2	≥4	≥21	16-20	≤15
Enterococcus faecalis	≤1	2	≥4	≥21	16-20	≤15
Methicillin susceptible *Staphylococcus* species	≤1	2	≥4	≥21	16-20	≤15
Pseudomonas aeruginosa	≤1	2	≥4	≥21	16-20	≤15
Haemophilus influenzae	≤1[a]	[g]	[g]	≥21[b]	[g]	[g]
Haemophilus parainfluenzae	≤1[a]	[g]	[g]	≥21[b]	[g]	[g]
Streptococcus pyogenes	≤1[c]	2[c]	≥4[c]	≥21[d]	16-20[d]	≤15[d]
Neisseria gonorrhoeae	≤0.06[e]	0.12 – 0.5[e]	≥1[e]	≥41[f]	28-40[f]	≤27[f]

Abbreviations: I = Intermediate; MIC = minimum inhibitory concentration; µg = microgram; mL = milliliter; mm = millimiter; 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 9. For diffusion technique, the 5 µg ciprofloxacin disk should provide the zone diameters outlined in Table 9.

Table 9: Quality Control for Susceptibility Testing

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

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

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

General toxicology

Acute toxicity:

Table 10: 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	I.V.	Approx. 290
Rat	I.V.	Approx. 145
Rabbit	I.V.	Approx. 125
Dog	I.V.	Approx. 250

Chronic toxicity:

Subacute Tolerability Studies Over 4 Weeks

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

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

Subchronic Tolerability Studies Over 3 Months

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

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

Chronic Tolerability Studies Over 6 Months

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

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

Genotoxicity

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

Salmonella: Microsome Test (Negative)

E. coli: DNA Repair Assay (Negative)

Mouse Lymphoma Cell Forward Mutation Assay (Positive)

Chinese Hamster V79 Cell HGPRT Test (Negative)

Syrian Hamster Embryo Cell Transformation Assay (Negative)

Saccharomyces cerevisiae: Point Mutation Assay (Negative)

Mitotic Crossover and Gene Conversion Assay (Negative)

Rat Hepatocyte Primary Culture DNA Repair Assay (LIDS) (Positive)

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

Rat Hepatocyte DNA Repair Assay

Micronucleus Test (Mice)

Dominant Lethal Test (Mice)

Chinese Hamster Bone Marrow

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 and developmental 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.

Special toxicology

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 I.V., 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.

Patient Medication Information

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]CIPRO® ORAL SUSPENSION

Ciprofloxacin oral suspension

This Patient Medication Information is written for the person who will be taking **CIPRO ORAL SUSPENSION**. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.

This Patient Medication Information is a summary. It will not tell you everything about this medication. If you have more questions about this medication or want more information about **CIPRO ORAL SUSPENSION** talk to a healthcare professional.

Serious warnings and precautions box

Fluoroquinolone antibiotics, like CIPRO ORAL SUSPENSION, are related to disabling and possibly long lasting serious side effects including but not limited to:

- **Tendinitis and tendon rupture:** CIPRO ORAL SUSPENSION has caused tendinitis (inflamed tendon) and tendon rupture (partial or complete tear), which may require surgery. If you experience pain, swelling or inflammation around your joints, stop taking CIPRO ORAL SUSPENSION and talk to your healthcare professional. This may happen while you are taking CIPRO ORAL SUSPENSION or for up to several months afterwards. The risk of tendon side effects is higher if you are taking corticosteroids. Tendon problems can happen within the first 48 hours of treatment.
- **Peripheral neuropathy:** problems in the nerves that can cause numbness and tingling in your hands and feet, decreased sensation of light touch, pain, temperature, position sense, vibration, and/or motor strength.
- **Neurological and mental health problems:** problems in the brain such as seizures, psychosis (loss of touch with reality), confusion and other mental health symptoms. Before you take CIPRO ORAL SUSPENSION, tell your healthcare professional if you have a condition that may increase your chance of having a seizure or if you have a history of seizures or epilepsy. Stop taking CIPRO ORAL SUSPENSION and get immediate medical help if you have any of these symptoms:
    - 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

Fluoroquinolone antibiotics can also cause serious side effects such as:

- **Heart rhythm problems:** QT interval prolongation (lengthened heartbeat on an electrocardiogram (ECG) test) and arrhythmia (irregular heartbeat) can happen in patients taking CIPRO ORAL SUSPENSION. In rare cases patients have reported a condition called torsades de pointes, which can cause sudden cardiac death. Talk to your healthcare professional before taking CIPRO ORAL SUSPENSION if you have QT interval prolongation, or any other heart condition that affects your heart rhythm, low levels of potassium in your blood, or are taking any other medications that can affect your heart rhythm.

- **Allergic reactions:** CIPRO ORAL SUSPENSION has caused serious allergic reactions that have been fatal. Stop taking CIPRO ORAL SUSPENSION and get immediate medical help if you develop a skin rash or any other symptoms of an allergic reaction.
- **Myasthenia gravis:** quinolone antibiotics, including CIPRO ORAL SUSPENSION, can make muscle weakness in people with myasthenia gravis worse. You should not take CIPRO ORAL SUSPENSION if you have myasthenia gravis.
- **Liver problems:** CIPRO ORAL SUSPENSION has caused serious liver injury that has resulted in death. Talk to your healthcare professional before taking CIPRO ORAL SUSPENSION if you have liver problems.

See the **Serious side effects and what to do about them** table, below for information on these and other serious side effects.

What CIPRO ORAL SUSPENSION is used for:

CIPRO ORAL SUSPENSION is an antibiotic used to treat infections caused by bacteria in adults. These include infections of the:

- respiratory tract
- urinary tract (bladder, kidneys)
- prostate
- skin and soft tissues
- bone and joint

It is also used in adults to treat the following conditions:

- carriers of the bacteria *Neisseria meningitidis* that causes meningitis. It is **not** used to treat meningitis infections.
- diarrhea caused by bacterial infections
- Typhoid fever
- gonorrhea (an infection caused by the bacteria *Neisseria gonorrhea*)

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

How CIPRO ORAL SUSPENSION works:

CIPRO ORAL SUSPENSION is an antibiotic that kills the bacteria causing the infection.

The ingredients in CIPRO ORAL SUSPENSION are:

Medicinal ingredient: ciprofloxacin

Non-medicinal ingredients: hypromellose, magnesium stearate, medium chain triglycerides, poly acrylate dispersion, polysorbate 20, polyvidone 25, soy-lecithin, strawberry flavouring, sucrose and water.

CIPRO ORAL SUSPENSION comes in the following dosage form:

Oral suspension: 10 g / 100 mL

Do not use CIPRO ORAL SUSPENSION if:

- you are allergic to ciprofloxacin, other quinolone antibiotics or any of the non-medicinal ingredients in CIPRO ORAL SUSPENSION (see **The ingredients in CIPRO ORAL SUSPENSION are:**)
- you are taking tizanidine, a medication that relaxes muscles
- you are currently taking agomelatine (currently not marketed in Canada), used to treat depression

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

- have, or have had a family history of, fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase deficiency as CIPRO ORAL SUSPENSION contains sucrose
- have a history of seizures or epilepsy or are taking medicines that could cause seizures
- have kidney problems
- have risk factors for an aortic aneurysm (an abnormal bulge in a large blood vessel called the aorta), or aortic dissection (a tear in the wall of the aorta):
    - have had an aortic aneurysm or aortic dissection
    - 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 any of the following conditions: Marfan syndrome, vascular Ehlers-Danlos syndrome, Takayasu arteritis, giant cell arteritis or Behcet's disease
    - are 65 years of age or older
    - have high blood pressure
    - have atherosclerosis, which is a hardening of your blood vessels
    - are taking corticosteroids, medicines used to treat inflammation and suppress the immune system
- have a history of depression
- have vision problems
- have diabetes or are taking antidiabetic medication
- are pregnant or are planning to become pregnant
- are breastfeeding or planning to breastfeed. CIPRO ORAL SUSPENSION passes into breast milk. Talk to your healthcare professional about ways to feed your baby while you are taking CIPRO ORAL SUSPENSION.

Other warnings you should know about:

Aortic aneurysm and aortic dissection: Quinolone antibiotics, including CIPRO ORAL SUSPENSION, have been associated with aneurysms (an enlargement or "bulge" of the aorta or other large blood vessel) and aortic dissection (a tear in the wall of the aorta). Stop taking CIPRO ORAL SUSPENSION and get immediate medical help if you experience sudden, severe pain in your abdomen, chest or back, a pulsating sensation in your abdomen, dizziness or loss of consciousness.

Blood sugar changes: Medicines like CIPRO ORAL SUSPENSION 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 CIPRO ORAL SUSPENSION. If you have diabetes, check your blood sugar levels often while taking CIPRO ORAL SUSPENSION. Blood sugar changes have also been seen in patients without diabetes.

Sensitivity to light: Sun sensitivity (photosensitivity) can happen when taking CIPRO ORAL SUSPENSION after exposure to sunlight or artificial ultraviolet (UV) light (e.g. tanning beds). You should avoid too much sunlight or artificial UV light while you are taking CIPRO ORAL SUSPENSION. Stop taking CIPRO ORAL SUSPENSION and talk to your healthcare professional if you have sunburn-like skin reactions when exposed to sunlight or UV light.

***Clostridium difficile* colitis** (bowel inflammation): CIPRO ORAL SUSPENSION 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 healthcare professional. Symptoms of colitis can include stomach pain or cramping, rectal bleeding, urgency or inability to pass stool, fatigue, weight loss and fever.

Driving and using machines: Do not drive or use machinery if you feel dizzy or lightheaded. This is more likely to happen if you drink alcohol while taking CIPRO ORAL SUSPENSION.

Blood tests and monitoring: CIPRO ORAL SUSPENSION can cause abnormal blood test results. Your healthcare professional will decide when to perform blood tests and will interpret the results.

Drug resistance: Using CIPRO ORAL SUSPENSION for too long or not long enough may cause the bacteria to become resistant, and your infection may not be resolved. Your healthcare professional will tell you exactly how long you should be taking CIPRO ORAL SUSPENSION for.

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

Serious drug interactions:

Do not take CIPRO ORAL SUSPENSION if are you taking the drugs listed below. Serious drug interactions with CIPRO ORAL SUSPENSION include:

- agomelatine, used to treat depression
- tizanidine, a medication that relaxes muscles
- theophylline, used to treat lung and breathing problems. Serious and fatal reactions have been reported in patients taking CIPRO ORAL SUSPENSION and theophylline

The following may also interact with CIPRO ORAL SUSPENSION:

- antidiabetic medicines, such as glyburide, glibenclamide, glimepiride, insulin
- Nonsteroidal Anti-Inflammatory Drugs (NSAIDS), used to treat pain and inflammation
- caffeine
- xanthine derivatives, used to treat lung and breathing problems, such as pentoxifylline
- certain heart medications known as antiarrhythmics, used to treat irregular heartbeat, such as quinidine, procainamide, amiodarone, sotalol
- oral anticoagulants, used to prevent blood clots, such as warfarin, acenocoumarol
- phenytoin, used to prevent seizures
- duloxetine, used to treat depression
- clozapine, used to treat mental health problems such as schizophrenia
- ropinirole, used to treat Parkinson's disease
- lidocaine, a topical pain reliever
- sildenafil, used to treat erectile dysfunction
- probenecid, used to treat gout

- methotrexate, used to treat cancer and inflammatory conditions such as arthritis and psoriasis
- cyclosporine, used to suppress the immune system in patients who have had organ transplants
- zolpidem, used to treat insomnia
- CIPRO ORAL SUSPENSION should be taken at least 2 hours before or 6 hours after the following:
    - antacids, used to treat heartburn and indigestion
    - multivitamins, and other dietary supplements containing magnesium, calcium, aluminum, iron or zinc
    - calcium-fortified products including food and dairy products
    - medicines used to treat patients with kidney disease on dialysis, such as sevelamer, lanthanum carbonate
    - sucralfate, used to treat and prevent ulcers
    - didanosine chewable/buffered tablets and powder, used to treat HIV infection and AIDS

How to take CIPRO ORAL SUSPENSION:

- Take CIPRO ORAL SUSPENSION exactly as prescribed by your healthcare professional. Do not stop taking it or change your dose even if you feel better. Stopping too soon may cause your symptoms to return.
- Take CIPRO ORAL SUSPENSION at about the same times each day. CIPRO ORAL SUSPENSION can be taken with food or on an empty stomach.
- Do not take CIPRO ORAL SUSPENSION with dairy products (like milk or yogurt) or calcium-fortified juices alone. However, you may take CIPRO ORAL SUSPENSION with a meal that contains these products.
- Do not take CIPRO ORAL SUSPENSION with antacids that contain magnesium or aluminum.
- You should avoid excessive caffeine consumption while taking CIPRO ORAL SUSPENSION.
- You should drink lots of water while taking CIPRO ORAL SUSPENSION.
- **Shake** CIPRO ORAL SUSPENSION vigorously each time before use for approximately 15 seconds. Swallow the prescribed amount of suspension. Do not chew the microcapsules. Close the bottle completely after use and store it in an upright position.
- After use, the graduated measuring spoon should be cleaned under running water with detergent and dried completely afterwards.

Usual dose:

Your healthcare professional will decide on the dose that is right for you, and the length of time you should take CIPRO ORAL SUSPENSION, based on your age, weight and the condition being treated.

Overdose:

If you think you, or a person you are caring for, have taken too much CIPRO ORAL SUSPENSION, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844-POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Missed dose:

If you forget to take CIPRO ORAL SUSPENSION 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, talk to your healthcare professional.

Possible side effects from using CIPRO ORAL SUSPENSION:

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

Side effects may include:

- nausea, vomiting, diarrhea
- constipation, gas
- abdominal pain, indigestion, heartburn
- loss of appetite
- dry mouth, trouble swallowing
- feeling lightheaded
- insomnia (difficulty sleeping)
- nightmares
- joint pain, swelling and stiffness
- muscle pain, cramps and spasms
- skin rash, itching
- hot flashes

Serious side effects and what to do about them

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
Uncommon			
Kidney disorder/problems: nausea, vomiting, fever, swelling of extremities, fatigue, thirst, dry skin, irritability, dark urine, increased or decreased urine output, blood in the urine, rash, weight gain (from retaining fluid), loss of appetite, abnormal blood test results, mental status changes (drowsiness, confusion, coma)		✓	

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
Rare			
Allergic reaction: difficulty swallowing or breathing, wheezing, feeling sick to your stomach and throwing up, hives or rash, swelling of the face, lips, tongue or throat			✓
Ear problems: hearing loss, ringing in the ears (These side effects may last more than 30 days)		✓	
Edema: unusual swelling of the face, arms, hands, legs, feet and ankles	✓		
Eye problems: repetitive, uncontrolled movements of the eyes, redness and swelling, eye pain, irritation, vision problems, double vision (These side effects may last more than 30 days)		✓	
Heart problems (including heart attack): fast heartbeat, palpitations, chest pain, difficulty breathing, fainting			✓
Hyperglycemia (high blood sugar): increased thirst, frequent urination, dry skin, headache, hunger, blurred vision, fatigue	✓		
Hypoglycemia (low blood sugar): thirst, frequent urination, hunger, nausea and dizziness, headache, blurred vision, fast heartbeat, tingling, shaking, nervousness, sweating, low energy		✓	
Increased intracranial pressure (swelling in the brain): headache, blurred or double vision, confusion, shallow breathing, high blood pressure, nausea			✓
Infection: fever, chills, drowsiness, nausea, vomiting, diarrhea, generally feeling unwell		✓	
Liver damage: jaundice (yellowing of the skin or eyes), dark urine and pale stools, abdominal pain, nausea, vomiting, loss of appetite, tiredness, fever, skin rash, joint pain and inflammation, pain in the upper right abdomen			✓

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
Mental health problems: hallucinations, paranoia (see, hear, or believe things that are not real), psychosis (loss touch with reality), confusion, disorientation, anxiety, depression, suicidal thoughts or actions, feeling agitated, restless or nervous, inability to think clearly or pay attention, memory loss (These side effects may last more than 30 days)			✓
Neurological problems: abnormally high level of muscle tone, clumsy involuntary movements, facial paralysis, tongue or throat muscle weakness, trouble speaking, confusion, seizures (convulsions or fits)			✓
Photosensitivity (sensitivity to sunlight): itchy, red or blistering of skin when exposed to sunlight			✓
Rhabdomyolysis (breakdown of damaged muscle): muscle tenderness, weakness, red-brown (tea-coloured) urine			✓
Tendinitis (inflamed tendon) **or Tendon rupture** (partial or complete tear): swelling and tenderness of one or more joints, pain, inflammation, muscle aches (These side effects may last more than 30 days)			✓
Vaginal yeast infection (inflammation of the vagina): itching, burning or discharge from the vagina		✓	
Very rare			
Migraine: severe headache, often accompanied by nausea, vomiting and sensitivity to light		✓	
Myasthenia gravis: muscle weakness, drooping eyelids, vision changes, difficulty chewing or swallowing, trouble breathing			✓
Pancreatitis (inflammation of the pancreas): upper abdominal pain, tenderness when touching the abdomen, fever, rapid heartbeat, nausea, vomiting		✓	

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) (severe skin reactions): redness, blistering and/or peeling of the skin and/or inside of the lips, mouth, nose, eyes and genitals, accompanied by fever, chills, headache, cough, body aches or swollen glands			✓
Unknown			
Acute generalized exanthematous pustulosis (AGEP): rash with small pustules, red and swollen skin, fever, itching, burning			✓
Aortic aneurysm (abnormal bulge in the aorta) or **Aortic dissection** (tear in the wall of the aorta): sudden, severe pain in abdomen, chest or back, pulsating sensation in the abdomen, dizziness, loss of consciousness			✓
Clostridium difficile colitis (bowel inflammation): severe or persistent diarrhea, abdominal or stomach pain, nausea and vomiting, fever			✓
Kounis syndrome: a mixture of symptoms and signs of an allergic reaction and heart attack or unstable angina, with chest pain, shortness of breath, faintness, nausea, vomiting, fainting, itching, hives, sudden, heavy sweating, unusual paleness, palpitations, hypotension, slow heartbeat			✓
Peripheral neuropathy (problems with nerves): pain, burning, tingling, numbness, weakness in your hands and feet			✓
Prolongation of QT interval (a heart rhythm condition): irregular heartbeat, fainting, loss of consciousness, seizures			✓

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 (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

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

Storage:

Store CIPRO ORAL SUSPENSION for 14 days in the refrigerator or at room temperature (5°C-25°C). Store in an upright position.

Any unused suspension should be brought back to your pharmacist for safe disposal.

Keep out of reach and sight of children.

If you want more information about CIPRO ORAL SUSPENSION:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes the Patient Medication Information by visiting the Health Canada Drug Product Database website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website http://www.bayer.ca, or by contacting Bayer Medical Information at 1-800-265-7382 or canada.medinfo@bayer.com.

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