PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

[Pr]TEVA-CIPROFLOXACIN

(Ciprofloxacin Hydrochloride Tablets)
USP

250 mg, 500 mg, 750 mg

Antibacterial Agent

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form, Strength	All Nonmedicinal Ingredients
Oral	Tablet, 250 mg, 500 mg and 750 mg	Colloidal silicon dioxide, crospovidone, hydroxypropyl cellulose, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, sodium lauryl sulfate, sodium starch glycolate and titanium dioxide

INDICATIONS AND CLINICAL USE

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

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

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

Acute sinusitis caused by:
Haemophilus influenzae
Moraxella catarrhalis

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, TEVA-CIPROFLOXACIN (ciprofloxacin hydrochloride) tablets should be used alternately with other antipseudomonal agents. Some strains of *Pseudomonas aeruginosa* may develop resistance during treatment. Therefore, susceptibility testing should be performed periodically during therapy to detect the emergence of bacterial resistance.

Urinary Tract Infections
Upper and lower urinary tract infections, such as complicated and uncomplicated cystitis, 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*

Chronic Bacterial Prostatitis
Caused by:
Escherichia coli

Skin and Soft Tissue Infections
Caused by:
Enterobacter cloacae
Escherichia coli
Klebsiella pneumoniae
Proteus mirabilis
Proteus vulgaris
Pseudomonas aeruginosa
Staphylococcus aureus
Staphylococcus epidermidis
Streptococcus pyogenes

Bone and Joint Infections
Caused by:
Enterobacter cloacae
Pseudomonas aeruginosa
Serratia marcescens

Staphylococcus aureus

Infectious Diarrhea (when antibacterial therapy is indicated)
Caused by:
Campylobacter jejuni
Escherichia coli (enterotoxigenic strains)
Shigella dysenteriae
Shigella flexneri
Shigella sonnei

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

Typhoid Fever (enteric fever)
Caused by:
Salmonella paratyphi
Salmonella typhi

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

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

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 TEVA-CIPROFLOXACIN tablets may be initiated before results of these tests are known. However, modification of this treatment may be required once results become available or if there is no clinical improvement. Culture and susceptibility testing performed periodically during therapy will provide information on the possible emergence of bacterial resistance. If anaerobic organisms are suspected to be contributing to the infection, appropriate therapy should be administered.

Geriatrics (≥ 65 years of age)
Elderly patients should receive a dose dependent on the severity of their illness and their creatinine clearance (see **DOSAGE AND ADMINISTRATION: Special Populations – Impaired Renal Function** for dose modification based on creatinine clearance or serum creatinine).

Pediatrics (< 18 years of age)

The safety and efficacy of TEVA-CIPROFLOXACIN in individuals less than 18 years of age have not been established. TEVA-CIPROFLOXACIN is not recommended for children under the age of 18 years (see **WARNINGS AND PRECAUTIONS: Special Populations – Pediatrics (< 18 years of age)).**

CONTRAINDICATIONS

- TEVA-CIPROFLOXACIN (ciprofloxacin hydrochloride) tablets are contraindicated in patients who have shown hypersensitivity to ciprofloxacin, or other quinolone antibacterial agents or any of the excipients. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section.

- Concurrent administration of ciprofloxacin and agomelatine[a] is contraindicated since it may result in an undesirable increase in agomelatine exposure (see **DRUG INTERACTIONS**).

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

[a] Currently not marketed in Canada

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- Fluoroquinolones, including TEVA-CIPROFLOXACIN (ciprofloxacin hydrochloride) tablets, have been associated with disabling and potentially persistent adverse reactions which to date include, but are not limited to tendonitis, tendon rupture, peripheral neuropathy and neuropsychiatric effects.

- Ciprofloxacin has been shown to prolong the QT interval of the electrocardiogram in some patients (see **WARNINGS AND PRECAUTIONS**: **Cardiovascular**).

- Serious hypersensitivity and/or anaphylactic reactions have been reported in patients receiving quinolone therapy, including TEVA-CIPROFLOXACIN (see **WARNINGS AND PRECAUTIONS**: **Immune**).

- Fluoroquinolones including TEVA-CIPROFLOXACIN are associated with an increased risk of tendinitis and tendon rupture in all ages. The risk is further increased in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants (see **WARNINGS AND PRECAUTIONS**: **Musculoskeletal**).

- Fluoroquinolones including TEVA-CIPROFLOXACIN may exacerbate muscle weakness in persons with myasthenia gravis. Avoid using TEVA-CIPROFLOXACIN in patients with a known history of myasthenia gravis (see **WARNINGS AND PRECAUTIONS**: **Musculoskeletal**).

- Seizures and toxic psychoses may occur with quinolone therapy. Convulsions, increased intracranial pressure (including pseudotumor cerebri) and toxic psychoses have been reported in patients receiving quinolones, including TEVA-CIPROFLOXACIN. TEVA-CIPROFLOXACIN should be used with caution in patients with known or suspected CNS disorders which may predispose them to seizures or lower the seizure threshold (see **WARNINGS AND PRECAUTIONS**: **Neurologic**).

- Cases of hepatic necrosis and life-threatening hepatic failure have been reported with TEVA-CIPROFLOXACIN (see **WARNINGS AND PRECAUTIONS**: **Hepatic/Biliary/Pancreatic**).

General

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

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

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

Cardiovascular

Ciprofloxacin has been shown to prolong the QT interval of the electrocardiogram in some patients. In general, elderly patients may be more susceptible to drug-associated effects on the QT interval. Precaution should be taken when using TEVA-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 **DRUG INTERACTIONS** and **ADVERSE REACTIONS**).

Endocrine and Metabolism

Disturbances of Blood Glucose

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

Gastrointestinal

Clostridium difficile-associated disease

Clostridium difficile-associated disease (CDAD) has been reported with the use of many antibacterial agents, including TEVA-CIPROFLOXACIN. CDAD may range in severity from mild diarrhea to fatal colitis. It is important to consider this diagnosis in patients who present with diarrhea or

symptoms of colitis, pseudomembranous colitis, toxic megacolon, or perforation of the colon subsequent to the administration of any antibacterial agent. CDAD has been reported to occur over 2 months after the administration of antibacterial agents.

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

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

Hepatic/Biliary/Pancreatic

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

There can be an increase in transaminases, alkaline phosphatase, or cholestatic jaundice, especially in patients with previous liver damage, who are treated with TEVA-CIPROFLOXACIN (see **ADVERSE REACTIONS**).

Immune

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

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

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

aplastic, thrombocytopenia including thrombotic thrombocytopenic purpura, leukopenia, agranulocytosis, pancytopenia, and/or other hematologic abnormalities.

Musculoskeletal

Myasthenia Gravis
Fluoroquinolones, including TEVA-CIPROFLOXACIN, have neuromuscular blocking activity and may exacerbate muscle weakness in persons with myasthenia gravis. Post-marketing serious adverse events, including deaths and requirement for ventilatory support, have been associated with fluoroquinolone use in persons with myasthenia gravis. Avoid TEVA-CIPROFLOXACIN in patients with a known history of myasthenia gravis (see **ADVERSE REACTIONS**).

Tendinitis
Rupture of the shoulder, hand and Achilles tendons that required surgical repair or resulted in prolonged disability have been reported in patients receiving quinolones, including TEVA-CIPROFLOXACIN (see **ADVERSE REACTIONS**). TEVA-CIPROFLOXACIN 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. TEVA-CIPROFLOXACIN should be discontinued if the patient experiences pain, swelling, inflammation**,** or rupture of a tendon. Patients should be advised to rest at the first sign of tendinitis or tendon rupture, and to contact their healthcare provider regarding changing to a non-quinolone antimicrobial drug.

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

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

may predispose to seizures or lower the seizure threshold (e.g. certain drug therapy, renal dysfunction) (see **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 quinolones, including TEVA-CIPROFLOXACIN.

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

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, TEVA-CIPROFLOXACIN should be used with caution and at a reduced dosage in patients with impaired renal function (see **DOSAGE AND ADMINISTRATION** and **DETAILED PHARMACOLOGY: Human Pharmacology**).

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).

Susceptibility/Resistance

Development of Drug-resistant Bacteria

Prescribing TEVA-CIPROFLOXACIN (ciprofloxacin tablets) in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and risks the development of drug-resistant bacteria.

Vision Disorders

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

Special Populations

Pregnant Women

The safety of TEVA-CIPROFLOXACIN tablets in pregnancy has not yet been established. TEVA-CIPROFLOXACIN tablets should not be used in pregnant women unless the likely benefits outweigh

the possible risk to the fetus. TEVA-CIPROFLOXACIN tablets have been shown to be non-embryotoxic and non-teratogenic in animal studies.

Nursing Women
The safety of TEVA-CIPROFLOXACIN in nursing women has not been established. Ciprofloxacin is excreted in human milk. Because of the potential for serious adverse reactions in infants nursing from women taking ciprofloxacin, a decision should be made to discontinue nursing or to discontinue the administration of TEVA-CIPROFLOXACIN, taking into account the importance of the drug to the mother and the possible risk to the infant.

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

Geriatrics (≥ 65 years of age)
Ciprofloxacin is substantially excreted by the kidney, and the risk of adverse reactions may be greater in elderly patients with impaired renal function (see **DETAILED PHARMACOLOGY: Human Pharmacology**).

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.

ADVERSE REACTIONS

Adverse Drug Reaction Overview
The following sections summarize the safety information derived from clinical trials and post-market use of ciprofloxacin.

Clinical Trial Adverse Drug Reactions

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

Ciprofloxacin hydrochloride 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.

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

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

Hypersensitivity: rash. The following have been reported rarely: allergic reaction, anaphylactic/anaphylactoid reactions including facial, vascular and laryngeal edema, drug fever, haemorrhagic bullae and small nodules (papules) with crust formation showing vascular involvement (vasculitis), hepatitis, interstitial nephritis, petechiae (punctuate skin hemorrhages), pruritus, serum sickness-like reaction, Stevens-Johnson syndrome (potentially life-threatening) (see **WARNINGS AND PRECAUTIONS: 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 and 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), tendonitis (predominantly achillotendonitis), myalgia (muscular

pain). The following have been reported very rarely: myasthenia (exacerbation of symptoms of myasthenia gravis) (see **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 behaviour, such as suicidal ideations/thoughts and attempted or completed suicide) (see **WARNINGS AND PRECAUTIONS: Neurologic**). The following have been reported very rarely, apathy, ataxia, depersonalization, diplopia, hemiplegia, hyperesthesia, hypertonia, increase of intracranial pressure, meningism, migraine, nervousness, neuritis, paresthesia, polyneuritis, sleep disorder, twitching, grand mal convulsions, abnormal (unsteady) gait, psychotic reactions (potentially culminating in self-injurious behaviour, such as suicidal ideations / thoughts and attempted or completed suicide), intracranial hypertension (including pseudotumor cerebri). In some instances these reactions occurred after the first administration of ciprofloxacin. In these instances, ciprofloxacin has to be discontinued and the doctor should be informed immediately.

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

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

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

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

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

Abnormal Hematologic and Clinical Chemistry Findings

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.

Post-Market Adverse Drug Reactions

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

The following has been reported at an unknown frequency: international normalized ratio (INR) increased (in patients treated with Vitamin K antagonists).

DRUG INTERACTIONS

Overview

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

Cytochrome P450

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

Ciprofloxacin is known to be an inhibitor of the CYP450 1A2 enzymes. Care should be taken when other drugs are administered 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**.**

[a] Currently not marketed in Canada.

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 1 – Established or Potential Drug-drug Interactions

Proper Name	Ref	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 **CONTRAINDICATIONS**).
Antidiabetic Agents	C	Disturbances of blood glucose, including symptomatic hyperglycemia and hypoglycemia, have been reported with quinolones, including ciprofloxacin, usually in diabetic patients receiving concomitant treatment with an oral antidiabetic agent (mainly sulfonylureas such as glyburide/glibenclamide, glimepiride) or with insulin.	In diabetic patients, careful monitoring of blood glucose is recommended. If a hypoglycemic reaction occurs in a patient receiving ciprofloxacin, discontinue the drug immediately and an appropriate therapy should be instituted (see **ADVERSE REACTIONS**).
Caffeine and Other Xanthine Derivatives	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 **WARNINGS AND PRECAUTIONS**).	Like other fluoroquinolones, precaution should be taken when using ciprofloxacin together with class IA (e.g. quinidine, procainamide) or III (e.g. amiodarone, sotalol) antiarrhythmics.
Clozapine	C	Following concomitant administration of 250 mg ciprofloxacin for 7 days, serum concentrations of clozapine and N-desmethylclozapine were increased by 29% and 31%, respectively (see **WARNINGS AND PRECAUTIONS**).	Clinical surveillance and appropriate adjustment of clozapine dosage during and shortly after co-administration with ciprofloxacin is advised.

Proper Name	Ref	Effect	Clinical Comment
Cyclosporine	CT	Some quinolones, including ciprofloxacin, have been associated with transient increases in serum creatinine levels in patients who are concomitantly receiving cyclosporine.	It is necessary to monitor the serum creatinine concentrations in these patients (twice a week).
Duloxetine	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 **DOSAGE AND ADMINISTRATION**).
Histamine H_2-receptor Antagonists	CT	Histamine H_2-receptor antagonists appear to have no significant effect on the bioavailability of ciprofloxacin.	No dosage adjustment is required.
Lidocaine	CT	It was demonstrated in healthy subjects that concomitant use of lidocaine with ciprofloxacin, an inhibitor of CYP450 1A2 isozyme, reduces clearance of intravenous lidocaine by 22%. Ciprofloxacin may increase the systemic toxicity of lidocaine.	Caution and careful monitoring of patients on concomitant therapy is recommended.
Methotrexate	C	Renal tubular transport of methotrexate may be inhibited by concomitant administration of ciprofloxacin, potentially leading to increased plasma levels of methotrexate. This might increase the risk of methotrexate associated toxic reactions.	Patients under methotrexate therapy should be carefully monitored when concomitant ciprofloxacin therapy is indicated.
Metoclopramide	CT	Metoclopramide accelerates the absorption of ciprofloxacin (oral), resulting in a shorter time to reach maximum plasma concentrations. No effect was seen on the bioavailability of ciprofloxacin.	No dosage adjustment required.
Multivalent Cations	CT	Concurrent administration of a quinolone, including ciprofloxacin, with multivalent cation-containing products such as magnesium/aluminum antacids, polymeric phosphate binders such as sevelamer, lanthanum carbonate,	Ciprofloxacin should be administered at least 2 hours before or 6 hours after these preparations.

Proper Name	Ref	Effect	Clinical Comment
		sucralfate, VIDEX® (didanosine) chewable/buffered tablets or pediatric powder, mineral supplements or products containing calcium, iron, or zinc may substantially interfere with the absorption of the quinolone, resulting in serum and urine levels considerably lower than desired. Absorption of ciprofloxacin is significantly reduced by concomitant administration of multivalent cation-containing products.	
Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)	CT	Concomitant administration of a nonsteroidal anti-inflammatory drug (fenbufen) with a quinolone (enoxacin) has been reported to increase the risk of CNS stimulation and convulsive seizures.	Caution and careful monitoring of patients on concomitant therapy is recommended.
Omeprazole	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 quinolones. The risk may vary with the underlying infection, age, and general status of the patient so that the contribution of ciprofloxacin to the increase in INR (international normalized ratio) is difficult to assess.	INR and/or prothrombin time should be monitored frequently during and shortly after co-administration of ciprofloxacin with an oral anticoagulant (e.g. warfarin, acenocoumarol).
Phenytoin	CT	Altered (decreased or increased) serum levels of phenytoin were observed in patients receiving ciprofloxacin and phenytoin simultaneously.	Monitoring of phenytoin therapy is recommended, including phenytoin serum concentration measurements, during and shortly after co-administration of ciprofloxacin with phenytoin to avoid the loss of seizure control associated with decreased phenytoin levels and to prevent phenytoin overdose-related undesirable effects.
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	Caution and careful monitoring of patients on concomitant therapy is recommended.

Proper Name	Ref	Effect	Clinical Comment
		resulted in about 50% reduction in the ciprofloxacin renal clearance and a 50% increase in its concentration in the systemic circulation.	
Ropinirole	CT	In a clinical study it was shown that concomitant use of ropinirole with ciprofloxacin, an inhibitor of the CYP450 1A2 isozyme, resulted in increases in the C_{max} and AUC of ropinirole of 60% and 84%, respectively. Ciprofloxacin may increase the systemic toxicity of ropinirole.	Monitoring ropinirole-related undesirable effects, dose adjustment as appropriate is recommended during and shortly after co-administration with ciprofloxacin.
Sildenafil	CT	C_{max} and AUC of sildenafil were increased approximately two-fold in healthy subjects after an oral dose of 50 mg was given concomitantly with 500 mg ciprofloxacin.	Caution should be used when prescribing ciprofloxacin concomitantly with sildenafil, taking into consideration the risks and the benefits.
Theophylline	CT	Concurrent administration of ciprofloxacin with theophylline may lead to elevated serum concentrations of theophylline and prolongation of its elimination half-life. This may result in increased risk of theophylline-related adverse reactions. Studies with immediate-release ciprofloxacin have shown that concomitant administration of ciprofloxacin with theophylline decreases the clearance of theophylline, resulting in elevated serum theophylline levels and increased risk of a patient developing CNS or other adverse reactions.	If concomitant use cannot be avoided, serum levels of theophylline should be monitored and dosage adjustments made as appropriate.
Tizanidine	CT	In a clinical study in healthy subjects there was an increase in tizanidine serum concentrations (C_{max} increase: 7-fold, range: 4- to 21-fold; AUC increase: 10-fold, range: 6- to 24-fold) when given concomitantly with ciprofloxacin. Associated with the increased serum concentrations was a potentiated hypotensive and sedative effect.	Tizanidine must not be administered together with ciprofloxacin (see **CONTRAINDICATIONS**).
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.

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

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

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

Drug-Lifestyle Interactions

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

DOSAGE AND ADMINISTRATION

Dosing Considerations
The determination of dosage for any particular patient must take into consideration the severity and nature of the infection, the susceptibility of the causative organism, the integrity of the patient's host-defence mechanisms, and the status of renal function.

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

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

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, VIDEX® (didanosine) chewable/buffered tablets or pediatric powder, metal cations such as iron and multivitamin preparations with zinc (see **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 **DRUG INTERACTIONS**).

Recommended Dose and Dosage Adjustment

Adults

The recommended dosages of TEVA-CIPROFLOXACIN tablets are:

Table 2: Recommended Dosages for Oral TEVA-CIPROFLOXACIN Tablets

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

* e.g. hospital acquired pneumonia, osteomyelitis

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

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 **DETAILED PHARMACOLOGY: Human Pharmacology**). This alternate pathway of drug elimination appears to compensate for the reduced renal excretion of patients with renal impairment. Nonetheless, some modification of dosage is recommended, particularly for patients with severe renal dysfunction. The following table provides a guideline for dosage adjustment of TEVA-CIPROFLOXACIN. 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/1.73 m^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 (< l0%) 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: $\frac{\text{Weight (kg) x (140 - age)}}{\text{49 x serum creatinine (μmol/L)}}$

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 TEVA-CIPROFLOXACIN tablets in individuals less than 18 years of age has not been established. TEVA-CIPROFLOXACIN is not recommended for use in pediatric patients and adolescents (see **WARNINGS AND PRECAUTIONS: Special Populations – Pediatrics (< 18 years of age)).**

Missed Dose
Take the normal dose as soon as possible and then continue as prescribed. However, if it is almost time for your next dose, do not take the missed dose and continue as usual. Do not take a double dose to make up for a forgotten dose. Be sure to complete your course of treatment.

OVERDOSAGE

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

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

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

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

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

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

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

Pharmacokinetics

(See **DETAILED PHARMACOLOGY: Human Pharmacology**)

Absorption

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

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

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

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

Metabolism
Small concentrations of four metabolites have been reported. They were identified as desethyleneciprofloxacin (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.

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

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

Special Populations and Conditions

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

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

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

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

STORAGE AND STABILITY

Bottles to be stored at room temperature (between 15-30^{o}C). Unit dose strips to be stored at room temperature (between 15-25^{o}C) and protected from high humidity.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Coated Tablets
TEVA-CIPROFLOXACIN tablets 250 mg - each white to off-white, round, film-coated tablet is engraved ‘novo’ on one side and ‘250' on the other and contains ciprofloxacin hydrochloride equivalent to 250 mg ciprofloxacin. Available in bottles of 100, 500 and 1000 tablets, and unit dose packages of 100 tablets.

TEVA-CIPROFLOXACIN tablets 500 mg - each white to off-white, capsule-shaped, film-coated tablet is engraved with ‘novo’ on one side and ‘500' on the other and contains ciprofloxacin hydrochloride equivalent to 500 mg ciprofloxacin. Available in bottles of 100, 500 and 1000 tablets, and unit dose packages of 100 tablets.

TEVA-CIPROFLOXACIN tablets 750 mg - each white to off white, capsule-shaped, film-coated tablet is engraved with ‘novo’ on one side and ‘750' on the other and contains ciprofloxacin hydrochloride equivalent to 750 mg ciprofloxacin. Available in bottles of 100, 500 and 1000 tablets, and unit dose packages of 100 tablets.

Composition
Ciprofloxacin Hydrochloride
Microcrystalline Cellulose
Sodium Starch Glycolate
Sodium Lauryl Sulfate
Crospovidone
Colloidal Silicon Dioxide
Magnesium Stearate
Hypromellose
Titanium Dioxide
Hydroxypropyl Cellulose
Polyethylene Glycol

PART II: SCIENTIFIC INFORMATION

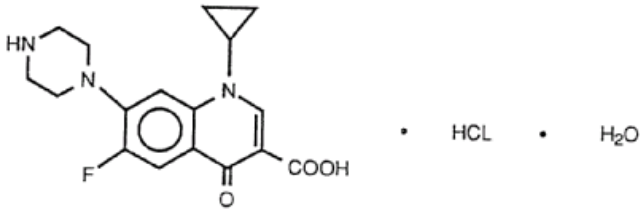
PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: Ciprofloxacin hydrochloride

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

Structural Formula:



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

Molecular Weight: 385.82 g/mol

Description: Ciprofloxacin hydrochloride can be described as faint yellowish to light-yellow crystals. It is freely soluble in water, slightly soluble in acetic acid and methanol, very slightly soluble in dehydrated alcohol, practically insoluble in acetone, acetonitrile, ethyl acetate, hexane and methylene chloride. It has a pH of 3.0-4.5.

CLINICAL TRIALS

Comparative Bioavailability Studies

A comparative two-way crossover bioavailability study was performed on two ciprofloxacin hydrochloride tablet products, TEVA-CIPROFLOXACIN 500 mg tablets and Cipro® 500 mg tablets, under fasting conditions.

The pharmacokinetic parameters of TEVA-CIPROFLOXACIN and Cipro® tablet formulations, following a single oral dose, under fasting conditions, is tabulated below:

Table 4: COMPARATIVE BIOAVAILABILITY DATA

TEVA-CIPROFLOXACIN Tablets (1 x 500 mg) **From measured data** **Geometric Mean** **Arithmetic Mean (CV%)**				
Parameters	**TEVA-CIPROFLOXACIN**	**Cipro®****	**Ratio of Geometric Means (%)**	**90% Confidence Interval**
AUC_T (ng X h/mL)	7081 7225 (20)	6778 6885 (18)	104	98.0% to 111.4%
AUC_I (ng X h/mL)	7529 7688 (21)	7189 7301 (18)	105	98.5% to 111.4%
C_{max} (ng X mL)	1776 1800 (17)	1722 1755 (20)	103	96.3% to 110.4%
T_{max}* (h)	1.14 (0.35)	1.12 (0.44)	-	-
$T_{1/2}$* (h)	3.9 (0.6)	3.8 (0.5)	-	-

*T_{max} and $T_{1/2}$ are expressed as arithmetic means (CV%) only.
**Cipro® 500 mg tablets (Miles Canada Inc., Canada); purchased in Canada.

DETAILED PHARMACOLOGY

Animal Pharmacology

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

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

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

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.

Human Pharmacology

Pharmacokinetics

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

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

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

Table 5: Pharmacokinetic Parameters Following a Single Oral Dose of Ciprofloxacin Tablets in Healthy Volunteers

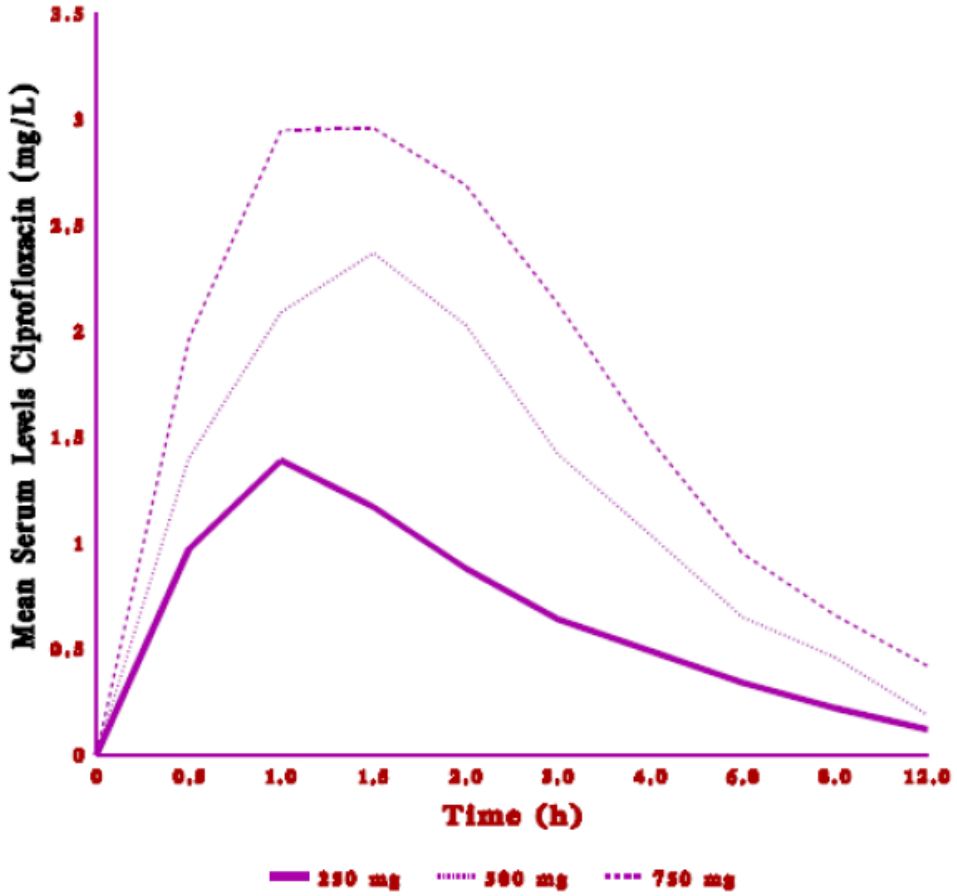
Dose	250 mg	500 mg	750 mg
C_{max} (mg/L)	1.42	2.60	3.41
$t_{½}$ (h)	4.19	4.87	5.34
$AUC_{0-\infty}$ (mg•h/L)	5.43	10.60	15.03
t_{max} (h)	1.11	1.11	1.56

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

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

Regimen	AUC_{0-12h} (mg·h/L)	C_{max} (mg/L)	T_{max} (h)
Ciprofloxacin 500 mg PO q12h	13.7	2.97	1.23

Figure 1: Mean Ciprofloxacin Serum Concentration after Single Oral Doses



Metabolism and Excretion

Ciprofloxacin is largely excreted unchanged both renally and, to a small extent, extra-renally. Small concentrations of 4 metabolites have been reported: Desethyleneciprofloxacin (M1) (1.8%), sulphociprofloxacin (M2) (5.0%), oxociprofloxacin (M3) (9.6%) and formylciprofloxacin (M4) (0.1%).

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

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

Table 7: Mean Urinary Excretion of Ciprofloxacin

Hours After Administration of a Single Tablet				
	0 - 2	**2 - 4**	**4 - 8**	**8 - 12**
Urine Concentration mg/L (± S.D.)				
250 mg PO	205 (±89)	163 (±145)	101 (±65)	32 (±28)
500 mg PO	255 (±204)	358 (±206)	117 (±86)	26 (±10)
750 mg PO	243 (±143)	593 (±526)	169 (±131)	55 (±36)
Amount Excreted mg (± S.D.)				
250 mg dose	54.38 (±36.22)	26.79 (±11.78)	22.84 (±6.79)	8.90 (±4.25)
500 mg dose	64.51 (±25.06)	47.37 (±15.65)	39.54 (±11.17)	15.52 (±5.39)
750 mg dose	68.90 (±41.85)	72.43 (±33.13)	61.07 (±21.68)	28.11 (±7.64)

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

Tissue Concentrations

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

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

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

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

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

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

Table 8: Distribution of Ciprofloxacin in Human Tissue/Fluid

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

Special Populations

Geriatrics

In 4 females and 6 males, (age: 67 ± 4 years, weight: 65 ± 6 kg) with normal renal function for their age, given a single oral dose of 250 mg, maximum ciprofloxacin serum concentrations and areas under the serum concentration time curves were significantly higher than in 10 male younger volunteers (age: 24 ± 3 years, weight: 72 ± 9 kg). The time to peak serum concentrations, overall elimination half-life and urinary recovery of ciprofloxacin were similar in both age groups.

Table 9: Comparison of Pharmacokinetic Parameters between Healthy Elderly and Healthy Younger Volunteers Following Oral Administration of a Single 250 mg Tablet

Parameter	Elderly Volunteers (Mean ± S.D.)	Younger Volunteers (Mean ± S.D.)
C_{max} (mg/L)	1.8 ± 0.5	1.3 ± 0.4
T_{max} (h)	1.2 ± 0.3	1.2 ± 0.1
$t_{½}$ (h)	3.7 ± 0.9	3.3 ± 0.6
Total AUC (mg•h/L)	7.25 ± 2.45	5.29 ± 1.21
% Dose Urinary Recovery after 24 hours	43	43

Renal Impairment

Ciprofloxacin is eliminated primarily by renal excretion. However, the drug is also metabolized and partially cleared through the biliary system of the liver and through the intestine. This alternate pathway of drug elimination appears to compensate for the reduced renal excretion of patients with

renal impairment. Nonetheless, some modification of dosage is recommended, particularly for patients with severe renal dysfunction.

The pharmacokinetics of ciprofloxacin following a single oral dose of 250 mg in 6 patients (5 male, 1 female, age: 51 ± 9 years) with normal renal function (see Group I, Table 10) were compared to 6 patients (3 male, 3 female, age: 63 ± 6 years) with renal impairment (see Group II, Table 10) and to 5 patients (2 male, 3 female, age: 63 ± 6 years) with end-stage renal failure, treated by haemodialysis (see Group III, Table 10). Patients with renal insufficiency had significantly increased AUCs, prolonged (about 2-fold) elimination half-lives, and decreased renal clearances.

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

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

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

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

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

Acinetobacter 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 (1) (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of ciprofloxacin powder. The MIC values should be interpreted according to the criteria outlined in Table 11.

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

Reports from the laboratory providing results of the standard single disk susceptibility test with a 5 μg ciprofloxacin disk should be interpreted according to the criteria outlined in Table 11. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for ciprofloxacin.

Table 11: Susceptibility Interpretative Criteria for Ciprofloxacin

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

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

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

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

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

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

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

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

g The current absence of data on resistant strains precludes defining any results other than "Susceptible". Strains 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 12. For diffusion technique, the 5 µg ciprofloxacin disk should provide the zone diameters outlined in Table 12.

Table 12: Quality Control for Susceptibility Testing

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

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

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

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

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

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

e These quality control limits are applicable only to tests conducted with *N. gonorrhoeae* ATCC 49226 performed by disk diffusion using GC agar base and 1% defined growth supplement.

TOXICOLOGY

Acute Toxicity

Species	Mode of administration	LD_{50} (mg/kg)
Mouse	PO	Approx. 5000
Rat	PO	Approx. 5000
Rabbit	PO	Approx. 2500
Mouse	IV	Approx. 290
Rat	IV	Approx. 145
Rabbit	IV	Approx. 125
Dog	IV	Approx. 250

Chronic Toxicity

Subacute Tolerability Studies Over 4 Weeks

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

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

changes are considered secondary inflammatory foreign-body reactions due to the precipitation of a crystalline complex in the distal renal tubule system.

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

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

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

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

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

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

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

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

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

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

Saccharomyces cerevisiae: Point Mutation Assay (Negative)
Mitotic Crossover and Gene Conversion Assay (Negative)
Rat Hepatocyte Primary Culture DNA Repair Assay (LIDS) (Positive)

Two of the eight tests were positive, but results of the following four *in vivo* test systems gave negative results:
Rat Hepatocyte DNA Repair Assay
Micronucleus Test (Mice)
Dominant Lethal Test (Mice)
Chinese Hamster Bone Marrow

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

Renal tolerability 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.

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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICATION

PATIENT MEDICATION INFORMATION

[Pr]TEVA-CIPROFLOXACIN
ciprofloxacin hydrochloride tablets, USP

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

Serious Warnings and Precautions

- Quinolone antibiotics, like TEVA-CIPROFLOXACIN, are related to disabling and possibly long lasting effects such as:
  - inflamed tendon (tendonitis), tendon rupture.
  - nerve damage (peripheral neuropathy).
  - problems in the brain such as:
    - convulsions
    - nervous breakdown
    - confusion
    - and other symptoms

- Quinolone antibiotics, like TEVA-CIPROFLOXACIN:
  - have lengthened the heartbeat (QT prolongation)
  - have led to serious allergic reactions, including death
  - may be related to increased tendonitis (inflamed tendon)
  - may worsen myasthenia gravis (a muscle disease)
  - may lead to seizures and nervous breakdowns. Tell your doctor if you have brain or spinal cord problems (such as epilepsy)
  - may cause liver injury which may lead to death

- For further information and symptoms see:
  - the "To help avoid side effects and ensure proper use,…" section
  - the "What are possible side effects from using TEVA-CIPROFLOXACIN?" section

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

What is TEVA-CIPROFLOXACIN used for?
TEVA-CIPROFLOXACIN is used to treat certain types of bacterial infections.

Antibacterial drugs like TEVA-CIPROFLOXACIN treat only bacterial infections. They do not treat viral infections such as the common cold. Although you may feel better early in treatment, TEVA-CIPROFLOXACIN should be taken exactly as directed. Misuse or overuse of TEVA-

CIPROFLOXACIN could lead to the growth of bacteria that will not be killed by TEVA-CIPROFLOXACIN (resistance). This means that TEVA-CIPROFLOXACIN may not work for you in the future. Do not share your medicine.

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

What are the ingredients in TEVA-CIPROFLOXACIN Tablets?
Medicinal ingredients: ciprofloxacin as ciprofloxacin hydrochloride

Non-medicinal ingredients: colloidal silicon dioxide, crospovidone, hydroxypropyl cellulose, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, sodium lauryl sulfate, sodium starch glycolate and titanium dioxide

TEVA-CIPROFLOXACIN Tablets come in the following dosage forms:
Tablets: 250 mg, 500 mg and 750 mg.

The 250 mg tablets are white to off-white, round, film-coated, engraved with ‘novo’ on one side and ‘250' on the other.

The 500 mg tablets are white to off white, capsule-shaped, film-coated, engraved with ‘novo’ on one side and ‘500' on the other.

The 750 mg tablets are white to off-white, capsule-shaped, film-coated, engraved with ‘novo’ on one side and ‘750' on the other.

Do not use TEVA-CIPROFLOXACIN if:
- you are allergic to ciprofloxacin or other quinolone antibiotics.
- you are allergic to any other ingredient in this product (see “What are the ingredients in TEVA-CIPROFLOXACIN Tablets?).
- you are taking tizanidine (ZANAFLEX®). Side effects such as drowsiness, sleepiness and low blood pressure may occur.
- you are currently taking agomelatine[a]. Agomelatine concentrations may increase and may cause further side effects such as liver toxicity.

[a] Currently not marketed in Canada.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take TEVA-CIPROFLOXACIN. Talk about any health conditions or problems you may have, including if you:
- have a history of seizures.
- have an irregular heart rhythm (such as QT prolongation).
- have low potassium blood levels.
- have liver or kidney disease or damage.
- are pregnant, planning to become pregnant, breast feeding or planning to breast feed.
- are less than 18 years of age.

- have a history of tendon problems (such as pain, swelling or rupture of a tendon) related to the use of quinolone antibiotics.
- have myasthenia gravis (a muscle disease).

Other warnings you should know about:
While taking TEVA-CIPROFLOXACIN:
- Avoid too much sunlight or artificial ultraviolet light (such as sunlamps).
    - ♦ Contact your doctor if a sunburn or rash occurs.
- Do not drive or use machinery if you feel dizzy or lightheaded.

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

The following may interact with TEVA-CIPROFLOXACIN:
- Theophylline or VIDEX® (didanosine) chewable/buffered tablets or pediatric powder. **Serious and fatal reactions have been reported in patients receiving ciprofloxacin, including TEVA-CIPROFLOXACIN and theophylline.**

- Antacids, multivitamins, and other dietary supplements containing magnesium, calcium, aluminum, iron or zinc (see "How to take TEVA-CIPROFLOXACIN:").
- Antidiabetic agents (such as glyburide, glibenclamide, glimepiride, insulin); the combination of any of these agents with ciprofloxacin may cause lower blood sugar.
- Nonsteroidal Anti-Inflammatory Drugs (NSAIDS)
- Caffeine (such as coffee) and other xanthine derivatives (such as pentoxifylline).
- Certain heart medications known as antiarrhythmics (such as quinidine, procainamide, amiodarone, sotalol).
- Other medications including:
    - ♦ oral anticoagulants (like warfarin and acenocoumarol),
    - ♦ phenytoin, duloxetine, methylxanthines, sevelamer,
    - ♦ sucralfate, clozapine, ropinirole, lidocaine, sildenafil, probenecid,
    - ♦ methotrexate, metoclopramide, cyclosporine, lanthanum carbonate, zolpidem.

How to take TEVA-CIPROFLOXACIN:
- TEVA-CIPROFLOXACIN should be taken as prescribed at almost the same times each day with food or on an empty stomach.

- TEVA-CIPROFLOXACIN should not be taken with dairy products (like milk or yogurt) or calcium-fortified juices alone; however, TEVA-CIPROFLOXACIN may be taken with a meal that contains these products (see "The following may interact with TEVA-CIPROFLOXACIN").

- You should avoid excessive caffeine consumption while taking TEVA-CIPROFLOXACIN.

- You should drink lots of water while taking TEVA-CIPROFLOXACIN.

- Swallow the TEVA-CIPROFLOXACIN tablets whole, with water as needed. **DO NOT SPLIT, CRUSH, OR CHEW THE TABLET.**

- If you are taking the following medicines, take them at least 2 hours before or 6 hours after TEVA-CIPROFLOXACIN:
    - ♦ antacids or mineral supplements containing magnesium or aluminum
    - ♦ sucralfate
    - ♦ supplements containing iron or zinc
    - ♦ any product (supplement or food) with more than 800 mg calcium
- Do not use TEVA-CIPROFLOXACIN for another condition or give it to others.

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

Usual dose:
Your doctor (healthcare provider) will tell you how much of the medicine to take and for how long.

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

Overdose:

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

Missed Dose:
Should you forget to take it at the usual time, you may take your dose later in the day. Do not take more than two doses of TEVA-CIPROFLOXACIN per day, even if you missed a dose.

What are possible side effects from using TEVA-CIPROFLOXACIN?
All medicines, including TEVA-CIPROFLOXACIN, can cause side effects, although not everyone gets them. These are not all the possible side effects you may feel when taking TEVA-CIPROFLOXACIN. If you have any side effects not listed here or if conditions worsen or do not improve then:

- contact your healthcare professional.
- see the "To help avoid side effects and ensure proper use,…" section.

Stop taking TEVA-CIPROFLOXACIN and contact your doctor if:

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

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

c) you have pain, swelling or rupture of a tendon. You should:
    - rest

- avoid physical exercise

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

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

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

f) you have mental problems such as:
   - confusion, headache, shaking
   - hallucinations, depression, agitation
   - difficulty sleeping, anxiety, nervousness, suicidal thoughts

   Contact your doctor if you have suicidal thoughts.

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

  Do not use TEVA-CIPROFLOXACIN if you have this condition.

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

Serious Side Effects and What to do About Them			
Symptom / Effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Rare			
Allergic Reaction: • rash, • hives (skin eruptions), • swelling of the face, lips, tongue or throat, • difficulty swallowing or breathing, • rapid heartbeat			✓
Central Nervous System Disorders: • seizures / convulsions,			✓

• confusion, • tremors, • hallucinations, • depression, • suicidal thoughts or psychotic reactions			
Photosensitivity Reaction: Sensitivity to light, blistering of skin			✓
Tendon pain, inflammation, or rupture			✓
Increased Blood Sugar: • frequent urination, • thirst, • hunger, • tiredness, • blurred vision, • headache, • trouble concentrating	✓		
Low Blood Sugar: • dizziness, • weakness, • headache, • sweating, • hunger	✓		
Unknown			
Severe Bowel Disorder (Clostridium difficile colitis): • persistent diarrhea, • bloody or watery diarrhea, • abdominal or stomach pain/cramping, • blood/mucus in stool			✓
Nerve Disorder (Neuropathy): Pain, burning, tingling, numbness, weakness			✓
Liver Disorder: Yellowing of the skin or eyes, dark urine, abdominal pain, nausea, vomiting, loss of appetite, pale stools		✓	
Heart Disorder (QT Prolongation): Irregular heartbeat		✓	

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

Reporting Side Effects

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

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

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

Storage:
Bottles to be stored at room temperature (between 15 – 30°C). Unit dose strips to be stored at room temperature (between 15 – 25°C) and protected from high humidity.

Keep out of reach and sight of children.

If you want more information about TEVA-CIPROFLOXACIN:

- Talk to your healthcare professional
- Find the full Product Monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (http://hc-sc.gc.ca/index-eng.php); the manufacturer's website http://www.tevacanada.com; or by calling 1-800-268-4127 ext. 3; or email druginfo@tevacanada.com.

This leaflet was prepared by Teva Canada Limited, Toronto, Ontario M1B 2K9

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