PRODUCT MONOGRAPH

[Pr]MYLAN-CIPROFLOXACIN XL

(Ciprofloxacin hydrochloride and Ciprofloxacin Extended Release Tablets)

Ciprofloxacin, 500 mg, 1000 mg

Antibacterial Agent

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Table 1: Product Information Summary

Route of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
Oral	Tablet, 500 mg, 1000 mg	Carnauba wax, colloidal silicon dioxide, croscarmellose sodium, dibasic calcium phosphate, magnesium stearate/sodium lauryl sulfate, hypromellose, macrogol, microcrystalline cellulose, polyvinyl alcohol-part hydrolyzed, povidone, pregelatinized starch, stearic acid, succinic acid, talc, and titanium dioxide.

INDICATIONS AND CLINICAL USE

MYLAN-CIPROFLOXACIN XL is indicated solely for the treatment of urinary tract infections, caused by susceptible strains of the designated microorganisms as listed below. MYLAN-CIPROFLOXACIN XL AND Mylan-Ciprofloxacin (IMMEDIATE RELEASE FORMULATION) ARE NOT INTERCHANGEABLE (see **DOSAGE AND ADMINISTRATION** for specific recommendations).

Uncomplicated Urinary Tract Infections (Acute Cystitis) in Females caused by:

Escherichia coli
Enterococcus faecalis
Proteus mirabilis
Staphylococcus saprophyticus

Complicated Urinary Tract Infections caused by:

Escherichia coli
Klebsiella pneumoniae
Enterococcus faecalis
Proteus mirabilis

Pseudomonas aeruginosa

Acute Uncomplicated Pyelonephritis caused by:

Escherichia coli

THE SAFETY AND EFFICACY OF CIPROFLOXACIN HYDROCHLORIDE EXTENDED RELEASE TABLETS IN TREATING INFECTIONS OTHER THAN URINARY TRACT INFECTIONS HAS NOT BEEN DEMONSTRATED.

Appropriate culture and susceptibility tests should be performed before treatment in order to isolate and identify organisms causing infection and to determine their susceptibility to ciprofloxacin. Therapy with MYLAN-CIPROFLOXACIN XL L may be initiated before results of these tests are known; once results become available, appropriate therapy should be continued.

Geriatrics:

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

Pediatrics (<18 years of age):

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

CONTRAINDICATIONS

- MYLAN-CIPROFLOXACIN XL extended release tablets are contraindicated in patients with a history of hypersensitivity to ciprofloxacin, or any member of the quinolone class of antibacterial agents or any of the excipients. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section.
- 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**).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- Ciprofloxacin hydrochloride and ciprofloxacin extended release tablets have 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 ciprofloxacin hydrochloride and ciprofloxacin extended release tablets (see **WARNINGS AND PRECAUTIONS: Immune**).

- Fluoroquinolones including ciprofloxacin hydrochloride and ciprofloxacin extended release tablets 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**).

- Fluroquinolones including MYLAN-CIPROFLOXACIN XL may exacerbate muscle weakness in persons with myasthenia gravis. Avoid using MYLAN-CIPROFLOXACIN XL 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 ciprofloxacin hydrochloride and ciprofloxacin extended release tablets. MYLAN-CIPROFLOXACIN XL 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 ciprofloxacin hydrochloride and ciprofloxacin extended release tablets (see **WARNINGS AND PRECAUTIONS: Hepatic/Biliary/Pancreatic**).

General

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

Cardiovascular

Ciprofloxacin hydrochloride and ciprofloxacin extended release tablets have been shown to prolong

the QT interval of the electrocardiogram in some patients. In general, elderly patients may be more susceptible to drug-associated effects on the QT interval. Precaution should be taken when using ciprofloxacin with concomitant drugs that can result in prolongation of the QT interval (eg, class IA or III antiarrhythmics) or in patients with risk factors for torsade de pointes (eg, known QT prolongation, uncorrected hypokalemia) (see **DRUG INTERACTIONS** and **ADVERSE REACTIONS**).

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 ciprofloxacin hydrochloride and ciprofloxacin extended release tablets (see **ADVERSE REACTIONS**).

Gastrointestinal

Clostridium Difficile-Associated Disease

Clostridium difficile-associated disease (CDAD) has been reported with the use of many antibacterial agents, including ciprofloxacin hydrochloride and ciprofloxacin extended release. CDAD may range in severity from mild diarrhea to fatal colitis. It is important to consider this diagnosis in patients who present with diarrhea or symptoms of colitis, pseudomembranous colitis, toxic megacolon, or perforation of the colon subsequent to the administration of any antibacterial agent. CDAD has been reported to occur over 2 months after the administration of antibacterial agents.

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

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

Hepatic/Biliary/Pancreatic

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

There can be an increase in transaminases, alkaline phosphatase, or cholestatic jaundice, especially in patients with previous liver damage, who are treated with ciprofloxacin hydrochloride and ciprofloxacin extended release (see **ADVERSE REACTIONS**).

Immune

Serious hypersensitivity and/or anaphylactic reactions have been reported in patients receiving quinolone therapy, including ciprofloxacin hydrochloride and ciprofloxacin extended release tablets (see **ADVERSE REACTIONS**). These reactions may occur following the first dose. 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.

MYLAN-CIPROFLOXACIN XL 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 (eg, 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 (see **CONTRAINDICATIONS**).

Musculoskeletal

Myasthenia Gravis

Fluoroquinolones, including ciprofloxacin hydrochloride and ciprofloxacin extended release, have neuromuscular blocking activity and may exacerbate muscle weakness in persons with myasthenia gravis. Postmarketing serious adverse events, including deaths and requirement for ventilatory support, have been associated with fluoroquinolone use in persons with myasthenia gravis. Avoid MYLAN-CIPROFLOXACIN XL 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 ciprofloxacin hydrochloride and ciprofloxacin extended release (see **ADVERSE REACTIONS**). MYLAN-CIPROFLOXACIN XL 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. MYLAN-CIPROFLOXACIN XL 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.

MYLAN-CIPROFLOXACIN XL 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 ciprofloxacin hydrochloride and ciprofloxacin extended release. Cases of status epilepticus have also been reported. Ciprofloxacin hydrochloride and ciprofloxacin extended release may also cause central nervous system (CNS) events including dizziness, tremors, restlessness, lightheadedness, confusion and 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 behavior, 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 MYLAN-CIPROFLOXACIN XL, the drug should be discontinued and appropriate measures instituted. MYLAN-CIPROFLOXACIN XL should be used with caution in patients with known or suspected CNS disorders which may predispose to seizures or lower the seizure threshold (eg, severe cerebral arteriosclerosis, epilepsy), or in the presence of other risk factors that may predispose to seizures or lower the seizure threshold (eg, 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 ciprofloxacin hydrochloride and ciprofloxacin extended release (see **ADVERSE REACTIONS**).

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.

In patients with reduced renal function, the half-life of ciprofloxacin is slightly prolonged. Since the total drug exposure attained with 500 mg ciprofloxacin hydrochloride and ciprofloxacin extended release tablets, does not exceed that achieved with 500 mg ciprofloxacin tablets, immediately release formulation, which is approved as a total daily dose for use in renally impaired patients, no dosage adjustment for renal disease is required with 500 mg ciprofloxacin hydrochloride and ciprofloxacin extended release tablets (see **DETAILED PHARMACOLOGY, Human Pharmacology**).

For complicated urinary tract infections or acute uncomplicated pyelonephritis, where 1000 mg is the appropriate dose, the dosage of MYLAN-CIPROFLOXACIN XL should be reduced to 500 mg MYLAN-CIPROFLOXACIN XL once daily in patients with creatinine clearance below 30 mL/min (see **DOSAGE AND ADMINISTRATION**).

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 (ie, sunburn-like skin reactions).

Vision Disorders

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

Special Populations

Pregnant Women

The safety of MYLAN-CIPROFLOXACIN XL in pregnancy has not yet been established. MYLAN-CIPROFLOXACIN XL should not be used in pregnant women unless the potential benefits outweigh the potential risk to the fetus.

Nursing Women

The safety of MYLAN-CIPROFLOXACIN XL in nursing women has not yet 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 whether to discontinue the drug, taking into account the importance of the drug to the mother and 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. MYLAN-CIPROFLOXACIN XL is not recommended in pediatric patients and adolescents.

Geriatrics

No dosage adjustment based on age alone is necessary for elderly patients. Since ciprofloxacin is substantially excreted by the kidney, the risk of adverse reactions may be greater in patients with impaired renal function. No significant accumulation of ciprofloxacin is anticipated in elderly subjects with renal impairment who take MYLAN-CIPROFLOXACIN XL 500 mg, therefore, no reductions in dosage are required.

However, in patients with renal impairment, where MYLAN-CIPROFLOXACIN XL 1000 mg once daily is the appropriate dose, dosage may need to be reduced to MYLAN-CIPROFLOXACIN XL 500 mg once daily (see **DOSAGE AND ADMINISTRATION, Special Populations, Renal Impairment**).

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 postmarket use of ciprofloxacin hydrochloride and ciprofloxacin extended release tablets.

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 and Ciprofloxacin extended release tablets 500 mg

In a phase III clinical trial involving 444 patients, the incidence of adverse drug reactions in patients

treated with 500 mg ciprofloxacin hydrochloride and ciprofloxacin extended release tablets (ciprofloxacin hydrochloride and ciprofloxacin extended release tablets) was 10%. Most adverse events reported in the trial were described as mild to moderate in severity and required no treatment. Ciprofloxacin hydrochloride and ciprofloxacin extended release tablets 500 mg was discontinued due to adverse reactions thought to be drug-related in 0.2% of patients.

Adverse reactions, judged by investigators to be at least possibly drug-related, occurring in greater than or equal to 1% of ciprofloxacin hydrochloride and ciprofloxacin extended release tablets 500 mg treated patients were nausea (3%) and headache (2%).

Additional uncommon adverse reactions, judged by investigators to be at least possibly drug related, that occurred in less than 1% of ciprofloxacin hydrochloride and ciprofloxacin extended release tablets 500 mg treated patients were:

Body as a Whole: abdominal pain, photosensitivity reaction

Cardiovascular: migraine

Digestive: constipation, decreased appetite and food intake, diarrhea, dyspepsia, flatulence, thirst, vomiting

Metabolic: hyperglycemia, hypoglycemia (see **WARNINGS AND PRECAUTIONS**, **Endocrine and Metabolism**)

Skin/Appendages: maculopapular rash, pruritus, rash, skin disorder, vesiculobullous rash

Special Senses: taste perversion

Urogenital: dysmenorrhea, vaginal candidiasis, vaginitis

Ciprofloxacin hydrochloride and Ciprofloxacin extended release tablets 1000 mg

In a phase III clinical trial involving 517 patients, the incidence of adverse drug reactions in patients treated with 1000 mg ciprofloxacin hydrochloride and ciprofloxacin extended release tablets was 13.2%. Most adverse events reported in the trial were described as mild to moderate in severity and required no treatment. Ciprofloxacin hydrochloride and ciprofloxacin extended release tablets 1000 mg was discontinued due to adverse reactions thought to be drug-related in 3.1% of patients.

Adverse reactions, judged by investigators to be at least possibly drug-related, occurring in greater than or equal to 1% of ciprofloxacin hydrochloride and ciprofloxacin extended release tablets 1000 mg treated patients, were nausea (3%), diarrhea (2%), headache (1%), dizziness (1%), dyspepsia (1%), and vaginal moniliasis (1%).

Additional uncommon adverse reactions, judged by investigators to be at least possibly drug-related, that occurred in less than 1% of ciprofloxacin hydrochloride and ciprofloxacin extended release tablets 1000 mg treated patients were:

Body as a Whole: abdominal pain, asthenia, malaise, moniliasis, photosensitivity reaction

Cardiovascular: bradycardia, migraine, syncope

Digestive: constipation, decreased appetite and food intake, dry mouth, flatulence, liver function tests abnormal, thirst, vomiting

Hemic/Lymphatic: prothrombin/international normalized ratio (INR) decreased

Nervous: abnormal dreams, depersonalization, depression, hypertonia, incoordination, insomnia, somnolence, tremor, vertigo

Metabolic: hyperglycemia, hypoglycemia (see **WARNINGS AND PRECAUTIONS, Endocrine and Metabolism**)

Skin/Appendages: dry skin, maculopapular rash, pruritus, rash, skin disorder, urticaria, vesiculobullous rash

Special Senses: diplopia, taste perversion

Urogenital: dysmenorrhea, hematuria, kidney function abnormal, vaginitis

Ciprofloxacin - Other Formulations

The following adverse drug reactions have been reported during clinical trials and subsequent postmarketing surveillance with other formulations of ciprofloxacin.

In patients treated orally with CIPRO (tablet and suspension), the most frequently reported events, possibly, probably drug-related were: nausea (1.3%), and diarrhea (1.0%). Comparatively, in patients treated with intravenous ciprofloxacin, the most frequently reported events, possibly, probably drug-related were: rash (1.8%), diarrhea (1.0%), and injection site pain (1.0%).

Events possibly or probably drug-related occurring at a frequency of less than 1% with CIPRO (ciprofloxacin tablets, immediate release formulation) oral and CIPRO I.V. treatment during clinical trials and subsequent postmarketing surveillance are as follows:

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

Cardiovascular: palpitation, phlebitis, tachycardia, thrombophlebitis. The following have been reported very rarely (< 0.01%): angina pectoris, atrial fibrillation, cardiac arrest, cerebrovascular disorder, electrocardiogram abnormality, hot flashes, hypertension, hypotension, 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 (> 0.01% - < 0.1%): moniliasis (oral), cholestatic jaundice, 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, leukopenia (granulocytopenia), leukocytopenia, leukocytosis, pancytopenia. The following have been reported rarely: abnormal prothrombin level/INR, thrombocytopenia, thrombocytemia (thrombocytosis). The following have been reported very rarely: hemolytic 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, vasculitis (petechia, haemorrhagic bullae, papules, crust formation), hepatitis, interstitial nephritis, petechia (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 failure), toxic epidermal necrolysis (Lyell Syndrome, potentially life-threatening).

I.V. Infusion Site: thrombophlebitis, injection site reaction. The following have been reported very rarely: burning, erythema, pain, paresthesia, and swelling.

Metabolic and Nutritional Disorder: creatinine increased. The following have been reported rarely: edema (face), hyperglycemia, hypoglycemia (see **WARNINGS AND PRECAUTIONS, Endocrine and Metabolism**).

Musculoskeletal: the following have been reported rarely in patients of all ages: achiness, arthralgia (joint pain), joint disorder (joint swelling), pain in the extremities, partial or completed tendon rupture (shoulder, hand, or Achilles tendon), tendinitis (predominantly achillotendinitis), myalgia (muscular pain). The following has 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 have been reported rarely: paresthesia (peripheral paralgesia), abnormal dreams (nightmares), anxiety, seizures (including status epilepticus) , depression (potentially culminating in self-injurious behavior, such as suicidal ideations/thoughts and attempted or completed suicide) (see **WARNINGS AND PRECAUTIONS, Neurologic**).

The following have been reported very rarely: apathy, ataxia, depersonalization, diplopia, hemiplegia, hyperesthesia, hypertonia, increase of intracranial pressure, meningism, migraine, nervousness, neuritis, polyneuritis, sleep disorder, twitching, grand mal convulsion, abnormal (unsteady) gait, psychotic reactions (potentially culminating in self-injurious behavior, such as suicidal ideations / thoughts and attempted or completed suicide), intracranial hypertension (including pseudotumor cerebri). In some instances, these reactions occurred after the first administration of ciprofloxacin. In these instances, ciprofloxacin is 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: dyspnea. The following have been reported very rarely: hiccup, hyperventilation, increased cough, larynx edema, lung edema, lung hemorrhage, pharyngitis, stridor, voice alteration.

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

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

Urogenital: 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: albuminuria, alkaline phosphatase increased, ALT increased, AST increased, bilirubinemia, BUN (urea) increased, cholestatic parameters increased, decreased creatinine clearance, gamma-GT increased, hypercholesteremia, hyperuricemia, increased sedimentation rate, lactic dehydrogenase increased, NPN increased, transaminases increased. The following have been reported rarely: acidosis, amylase increased, 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 postmarketing 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 color 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 have included 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 made as appropriate.

Cytochrome P450

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

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 (ie, those identified as contraindicated).

Table 2 – Established or Potential Drug-Drug Interactions

Proper Name	Ref	Effect	Clinical Comment
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**).

Proper Name	Ref	Effect	Clinical Comment
Caffeine and Other Xanthine Derivatives	CT	Ciprofloxacin has been shown to interfere with the metabolism of caffeine. This may lead to reduced clearance of caffeine and a prolongation of its serum half-life 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: Cardiovascular).**	Like other fluoroquinolones, precaution should be taken when using ciprofloxacin together with class IA (eg, quinidine, procainamide) or III (eg, 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.
Cyclosporine	CT	Some quinolones, including ciprofloxacin, have been associated with transient elevations 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 strong inhibitors of the CYP450 1A2 isozyme such as fluvoxamine, may result in an increase of AUC and C_{max} of duloxetine. Although no clinical data are available on a possible interaction with ciprofloxacin, similar effects can be expected upon concomitant administration.	Caution and careful monitoring of patients on concomitant therapy is recommended.
Ferrous Sulfate	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, MYLAN-CIPROFLOXACIN XL 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 MYLAN-CIPROFLOXACIN XL 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.

Proper Name	Ref	Effect	Clinical Comment
Lidocaine	CT	It was demonstrated in healthy subjects that concomitant use of lidocaine with ciprofloxacin, a moderate inhibitor of CYP450 1A2 isozyme, reduces clearance of intravenous lidocaine by 22%. Ciprofloxacin may increase the systemic toxicity of lidocaine.	Caution and careful monitoring of patients on concomitant therapy is recommended.
Methotrexate	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.

Proper Name	Ref	Effect	Clinical Comment
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, 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. When ciprofloxacin hydrochloride and ciprofloxacin extended release tablets given as a single 1000 mg dose, was administered 2 hours before or 4 hours after a magnesium/aluminum-containing antacid (900 mg aluminum hydroxide and 600 mg magnesium hydroxide as a single oral dose) to 18 healthy volunteers, there was a 4% and 19% reduction, respectively, in the mean C_{max} of ciprofloxacin. The reduction in the mean AUC was 24% and 26%, respectively Absorption of ciprofloxacin is significantly reduced by concomitant administration of multivalent cation- containing products. Although MYLAN-CIPROFLOXACIN XL may be taken with meals that include milk, concomitant administration with dairy products or with calcium- fortified juices alone should be avoided, since decreased absorption is possible. (see **DRUG INTERACTIONS**, Calcium-Fortified Products (including Food and Dairy Products)	MYLAN-CIPROFLOXACIN XL should be administered at least 2 hours before or 6 hours after antacids 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 **DOSAGE AND ADMINISTRATION**).
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.

Proper Name	Ref	Effect	Clinical Comment
Omeprazole	CT	Absorption of the ciprofloxacin hydrochloride and ciprofloxacin extended release tablets was slightly diminished (20%) when given concomitantly with omeprazole. When ciprofloxacin hydrochloride and ciprofloxacin extended release tablets given as a single 1000 mg dose, was administered concomitantly with omeprazole (40 mg once daily for three days) to 18 healthy volunteers, the mean AUC and C_{max} of ciprofloxacin were reduced by 20% and 23%, respectively. These differences are not considered clinically significant.	No dosage adjustment needed
Oral Anticoagulants	CT	Simultaneous administration of ciprofloxacin with an oral anticoagulant (eg, vitamin K antagonist) may augment its anticoagulant effects. There have been many reports of increases in oral anticoagulant activity in patients receiving antibacterial agents, including quinolones. The risk may vary with the underlying infection, age, and general status of the patient so that the contribution of ciprofloxacin to the increase in INR (international normalized ratio) is difficult to assess.	INR and/or prothrombin time should be monitored frequently during and shortly after co- administration of ciprofloxacin with an oral anticoagulant (eg, 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.	Caution and careful monitoring of patients on concomitant therapy is recommended.
Ropinirole	CT	In a clinical study it was shown that concomitant use of ropinirole with ciprofloxacin, a moderate 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.

Proper Name	Ref	Effect	Clinical Comment
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. Previous 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**,).

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

Serum Protein Binding

The binding of ciprofloxacin to serum proteins is 20% 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 hydrochloride and ciprofloxacin extended release tablets.

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

MYLAN-CIPROFLOXACIN XL AND MYLAN-CIPROFLOXACIN TABLETS (IMMEDIATE RELEASE FORMULATION) ARE NOT INTERCHANGEABLE. MYLAN-CIPROFLOXACIN XL should be administered once daily as described in the table below.

Table 3: Recommended Dosage

Indication	Unit Dose Mylan-Ciprofloxacin XL	Frequency	Recommended Duration
Uncomplicated Urinary Tract Infection (Acute Cystitis) in Females	500 mg	q 24 h	3 Days
Complicated Urinary Tract Infection	1000 mg[a]	q 24 h	7-14 Days
Acute Uncomplicated Pyelonephritis	1000 mg[a]	q 24 h	7-14 Days

a For severely renally impaired patients see **DOSAGE AND ADMINISTRATION, Special Populations, Renal Impairment** below.

MYLAN-CIPROFLOXACIN XL 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 MYLAN-CIPROFLOXACIN XL 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 MYLAN-CIPROFLOXACIN XL be administered at least 2 hours before or 6 hours after substantial calcium intake (>800 mg). MYLAN-CIPROFLOXACIN XL should be swallowed whole. Tablets should not be split, crushed or chewed (see **DRUG INTERACTIONS**).

Special Populations

Renal Impairment

MYLAN-CIPROFLOXACIN XL 500 mg

Based on pharmacokinetic data, no dosage adjustment is required with MYLAN-CIPROFLOXACIN XL 500 mg (see **DETAILED PHARMACOLOGY**, **Special Populations, Renal Impairment**).

MYLAN-CIPROFLOXACIN XL 1000 mg

For complicated urinary tract infections or acute uncomplicated pyelonephritis, where 1000 mg is the appropriate dose, the dosage of MYLAN-CIPROFLOXACIN XL should be reduced to 500 mg MYLAN-CIPROFLOXACIN XL once daily in patients with creatinine clearance below 30 mL/min. This recommendation is based on pharmacokinetic modeling. Clinical studies with ciprofloxacin hydrochloride and ciprofloxacin extended release have not been performed in patients with impaired renal function. For patients on hemodialysis or peritoneal dialysis, administer MYLAN-CIPROFLOXACIN XL after the dialysis procedure is completed (see **DETAILED PHARMACOLOGY**, **Human Pharmacology, Renal Impairment**).

Hepatic Impairment

Based on pharmacokinetic data, no dosage adjustment is required with MYLAN-CIPROFLOXACIN XL in patients with stable chronic cirrhosis (with mild to moderate hepatic impairment). The kinetics of ciprofloxacin in patients with acute hepatic insufficiency and stable chronic cirrhosis (with severe hepatic impairment), however, have not been elucidated (see **DETAILED PHARMACOLOGY**, **Human Pharmacology, Hepatic Impairment**).

Geriatrics

No dosage adjustment based on age alone is necessary in elderly patients. Since ciprofloxacin is substantially excreted by the kidney, the risk of adverse reactions may be greater in patients with impaired renal function. No significant accumulation of ciprofloxacin is anticipated in elderly subjects with renal impairment who take MYLAN-CIPROFLOXACIN XL 500 mg, therefore, no reductions in dosage are required.

However, in patients with renal impairment, where MYLAN-CIPROFLOXACIN XL 1000 mg once daily is the appropriate dose, dosage may need to be reduced to MYLAN-CIPROFLOXACIN XL 500 mg once daily (see **DOSAGE AND ADMINISTRATION, Special Populations, Renal Impairment**).

OVERDOSAGE

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

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

MYLAN-CIPROFLOXACIN XL extended release tablets contain ciprofloxacin, a synthetic broad-spectrum antimicrobial agent for oral administration. MYLAN-CIPROFLOXACIN XL tablets are coated, bi-layer tablets consisting of an immediate release layer and an erosion matrix type controlled-release layer. The tablets contain a combination of two types of ciprofloxacin drug substance, ciprofloxacin hydrochloride and ciprofloxacin (base).

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

Clinical pharmacology studies have compared the pharmacokinetics of ciprofloxacin hydrochloride and ciprofloxacin extended release tablets to ciprofloxacin tablets (immediate release formulation) (Ciprofloxacin hydrochloride and ciprofloxacin extended release tablets 500 mg vs ciprofloxacin immediate release tablets 250 mg bid and ciprofloxacin hydrochloride and ciprofloxacin extended release tablets 1000 mg vs ciprofloxacin immediate release tablets 500 mg bid, respectively), examined the effects of various meals on the pharmacokinetics of ciprofloxacin hydrochloride and ciprofloxacin extended release tablets, and investigated possible drug interactions.

Since the mean peak plasma concentration (C_{max}) of ciprofloxacin hydrochloride and ciprofloxacin extended release 500 mg tablets (1.59 mg/L) does not exceed that of ciprofloxacin 500 mg immediate release tablets (2.36 mg/L), the effect of ciprofloxacin hydrochloride and ciprofloxacin extended release 500 mg tablets with respect to special populations (elderly, renal impairment, hepatic impairment) (see **ACTION AND CLINICAL PHARMACOLOGY**, **Special Populations)** and drug-drug interactions is expected to be similar to that of ciprofloxacin 500 mg tablets, which has been extensively studied.

Since the ciprofloxacin hydrochloride and ciprofloxacin extended release tablets formulation entails only a slight modification of drug release, the overall performance of the ciprofloxacin

hydrochloride and ciprofloxacin extended release tablets 1000 mg formulation with respect to special populations and drug-drug and drug-disease interactions is expected to be similar to that of ciprofloxacin, which has been extensively studied.

Absorption

MYLAN-CIPROFLOXACIN XL tablets are formulated to release drug at a slower rate compared to Mylan-Ciprofloxacin tablets, which are immediate release. Approximately 35% of the ciprofloxacin dose in the MYLAN-CIPROFLOXACIN XL tablet is contained within an immediate release component, while the remaining 65% is contained in a slow-release matrix.

Ciprofloxacin hydrochloride and ciprofloxacin extended release tablets 500 mg

The C_{max} of once daily treatment with 500 mg ciprofloxacin hydrochloride and ciprofloxacin extended release tablets is 1.59 mg/L, which is 40% higher than the C_{max} of 250 mg ciprofloxacin tablets, immediate release formulation (1.14 mg/L). The mean area under the plasma-concentration time curve (AUC) over 24 hours at steady state following ciprofloxacin hydrochloride and ciprofloxacin extended release tablets 500 mg once daily is 7.97 mg*h/L, which is equivalent to the AUC of Ciprofloxacin 250 mg tablets bid (8.25 mg*h/L). Maximum plasma concentrations are attained between 1 and 2.5 hours after dosing of ciprofloxacin hydrochloride and ciprofloxacin extended release tablets 500 mg (median t_{max} = 1.5 h).

The following table (Table 4) compares the pharmacokinetic parameters obtained at steady state for ciprofloxacin hydrochloride and ciprofloxacin extended release 500 mg tablets and ciprofloxacin tablets 250 mg bid.

Table 4: Ciprofloxacin Pharmacokinetics (Mean ± SD) Following Ciprofloxacin 250 mg (Ciprofloxacin Tablets Immediate Release Formulation) BID and MYLAN-CIPROFLOXACIN XL 500 mg (Ciprofloxacin Hydrochloride and Ciprofloxacin Extended Release Tablets) Administration

	C_{max} (mg/L)	AUC_{0-24h} (mg* h/L)	$t_{1/2}$ (h)	t_{max} (h)[a]
ciprofloxacin hydrochloride and ciprofloxacin extended release tablets 500 mg	1.59 ± 0.43	7.97 ± 1.87	6.6 ± 1.4	1.5 (1.0-2.5)
ciprofloxacin tablets, immediate release formulation 250 mg tablets bid	1.14 ± 0.23	8.25 ± 2.15	4.8 ± 0.6	1.0 (0.5-2.5)

a Median (range)

Ciprofloxacin hydrochloride and Ciprofloxacin extended release tablets 1000 mg

The C_{max} of once daily treatment with 1000 mg ciprofloxacin hydrochloride and ciprofloxacin extended release tablets is 3.11 mg/L, which is 51% higher than the C_{max} of Ciprofloxacin 500 mg (ciprofloxacin tablets, immediate release formulation) (2.06 ± 0.41 mg/L). The mean area under the plasma-concentration time curve (AUC) over 24 hours at steady state following ciprofloxacin hydrochloride and ciprofloxacin extended release tablets 1000 mg once daily is 16.83 mg*h/L, which is equivalent to the AUC of 500 mg Ciprofloxacin tablets bid (17.04 mg* h/L). Maximum plasma concentrations are attained between 1 and 4 hours after dosing (median t_{max} = 2.0 h).

The following table (Table 5) compares the pharmacokinetic parameters obtained at steady state for 1000 mg ciprofloxacin hydrochloride and ciprofloxacin extended release tablets and 500 mg

Ciprofloxacin tablets bid.

Table 5: Ciprofloxacin Pharmacokinetics (Mean ± SD) Following Ciprofloxacin 500 mg (Ciprofloxacin Tablets Immediate Release formulation) BID and 1000 mg Ciprofloxacin Hydrochloride and Ciprofloxacin Extended Release Tablets Administration

	C_{max} (mg/L)	AUC_{0-24h} (mg* h/L)	$t_{1/2}$ (h)	t_{max} (h)[a]
Ciprofloxacin hydrochloride and ciprofloxacin extended release tablets 1000 mg	3.11 ± 1.08	16.83 ± 5.65	6.31 ± 0.72	2.0 (1 - 4)
Ciprofloxacin tablets, immediate release formulation 500 mg, bid	2.06 ± 0.41	17.04 ± 4.79	5.66 ± 0.89	2.0 (0.5 - 3.5)

a Median (range)

The relative bioavailability of ciprofloxacin hydrochloride and ciprofloxacin extended release Tablets 1000 mg compared to ciprofloxacin tablet 500 mg bid was examined in a crossover study of 20 healthy male volunteers under fasted conditions. Mean concentrations for Day 1 are shown in Figure 1.

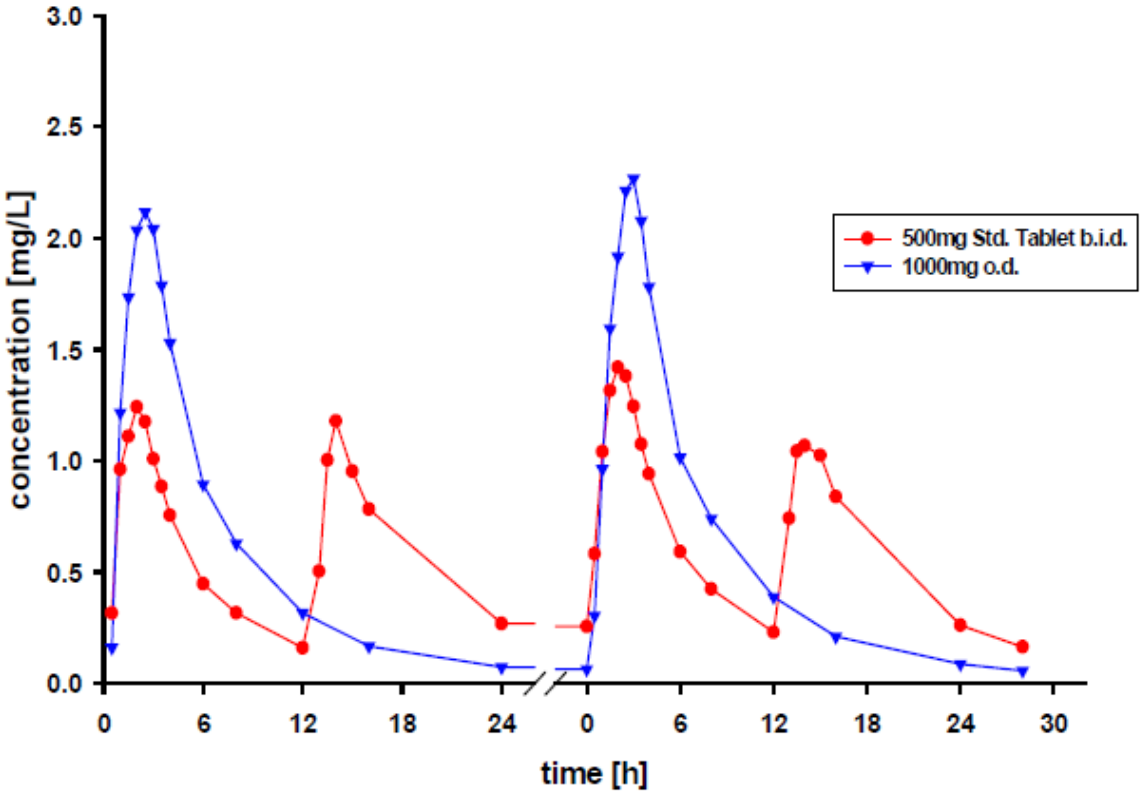


Figure 1: Relative Bioavailability of Ciprofloxacin Hydrochloride and Ciprofloxacin Extended Release Tablets 1000 mg vs. Ciprofloxacin tablets 500 mg BID

The pharmacokinetics of ciprofloxacin hydrochloride and ciprofloxacin extended release tablets are not altered by coadministration with food. AUC values were comparable following administration of ciprofloxacin hydrochloride and ciprofloxacin extended release tablets with a high-fat meal, a low fat meal, or under fasted conditions (see **DETAILED PHARMACOLOGY**, **Human Pharmacology**) (see **Table 6**).

Table 6: Pharmacokinetics of Ciprofloxacin Hydrochloride and Ciprofloxacin Extended Release 500 mg Tablets Under Fed and Fasted Conditions

Parameter	Fed	Fasted	Ratio (Fed/Fasted)	90% CI
AUC (mg*h/L)[a]	7.12 (21%)	7.05 (36%)	1.01	0.89 - 1.15
C_{max} (mg/L)[a]	1.30 (26%)	1.34 (42%)	0.97	0.79 - 1.18
t_{max} (h)[b]	3.5 (1.5 - 4.0)	1.5 (0.5 - 3.5)	Not evaluated	

a Geometric mean (% CV)
b Median (range)

Distribution

In one study, the apparent volume of distribution (Vd_{area}) of ciprofloxacin was estimated from kinetic data recorded after oral doses and found to be approximately 3.5 L/kg. Studies with the oral and intravenous forms of ciprofloxacin have demonstrated penetration of ciprofloxacin into a variety of tissues. A single dose study in healthy subjects has demonstrated penetration of ciprofloxacin into prostate tissue following administration of ciprofloxacin hydrochloride and ciprofloxacin extended release tablets 1000 mg. One and three hours after dosing, mean ciprofloxacin concentrations were greater than 4 µg/g. The binding of ciprofloxacin to serum proteins is 20% to 40%, which is not likely to be high enough to cause significant protein binding interactions with other drugs. Following administration of a single dose of ciprofloxacin hydrochloride and ciprofloxacin extended release tablets (500 mg or 1000 mg), ciprofloxacin concentrations in urine, collected up to 4 hours after dosing, averaged over 300 mg/L and over 500 mg/L, respectively; in urine excreted from 12 to 24 hours after dosing, ciprofloxacin concentration averaged 27 mg/L for ciprofloxacin hydrochloride and ciprofloxacin extended release tablets 500 mg and 58 mg/L for ciprofloxacin hydrochloride and ciprofloxacin extended release tablets 1000 mg (see **DETAILED PHARMACOLOGY, Human Pharmacology**).

Metabolism

Four metabolites of ciprofloxacin were identified in human urine. The primary metabolites are oxociprofloxacin (M3) and sulfociprofloxacin (M2), each accounting for roughly 3% to 8% of the total dose. Other minor metabolites are desethylene ciprofloxacin (M1) and formylciprofloxacin (M4). The relative proportion of drug and metabolite in serum corresponds to the composition found in urine. Excretion of these metabolites was essentially complete by 24 hours after dosing (see **DETAILED PHARMACOLOGY**, **Human Pharmacology**).

Excretion

The elimination kinetics of ciprofloxacin are similar for ciprofloxacin hydrochloride and ciprofloxacin extended release tablets and ciprofloxacin tablets (immediate release formulation).

The mean serum elimination half-life ($t_{1/2}$) of ciprofloxacin hydrochloride and ciprofloxacin extended release tablets is 6.6 (± 1.4) hours and 6.3 (± 0.7) hours, for the 500 mg and 1000 mg tablets, respectively (see **DETAILED PHARMACOLOGY**, **Human Pharmacology**). The major route of elimination of ciprofloxacin in humans is as unchanged drug in urine.

Special Populations

Renal Impairment

In patients with reduced renal function, the half-life of ciprofloxacin is slightly prolonged. Since the total drug exposure attained with ciprofloxacin hydrochloride and ciprofloxacin extended release tablets 500 mg does not exceed that achieved with ciprofloxacin 500 mg tablets (immediate release formulation), which is approved as a total daily dose for use in renally impaired patients, no dosage adjustment for renal disease is required with MYLAN-CIPROFLOXACIN XL 500 mg.

For complicated urinary tract infections or acute uncomplicated pyelonephritis, where 1000 mg is the appropriate dose, the dosage of MYLAN-CIPROFLOXACIN XL should be reduced to 500 mg MYLAN-CIPROFLOXACIN XL once daily in patients with creatinine clearance below 30 mL/min (see **DOSAGE AND ADMINISTRATION**, **Special Populations**, **Renal Impairment**).

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 elucidated. An increased incidence nausea, vomiting, headache and diarrhea were observed in this patient population (see **DETAILED PHARMACOLOGY**, **Human Pharmacology**).

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.

Geriatrics

No dosage adjustment based on age alone is necessary for elderly patients. Pharmacokinetic studies of the immediate-release oral tablet (single dose) and intravenous (single and multiple dose) forms of ciprofloxacin indicate that plasma concentrations of ciprofloxacin are higher in elderly subjects (>65 years) as compared to young adults. C_{max} is increased 16% to 40%, and mean AUC is increased approximately 30%, which can be at least partially attributed to decreased renal clearance in the elderly. Elimination half-life is only slightly (~20%) prolonged in the elderly (see **DETAILED PHARMACOLOGY**, **Human Pharmacology**).

Since ciprofloxacin is substantially excreted by the kidney, the risk of adverse reactions may be greater in patients with impaired renal function. No significant accumulation of ciprofloxacin is

anticipated in elderly subjects with renal impairment who take MYLAN-CIPROFLOXACIN XL 500 mg, therefore, no reductions in dosage are required.

However, in patients with renal impairment where MYLAN-CIPROFLOXACIN XL 1000 mg once daily is the appropriate dose, dosage may need to be reduced to MYLAN-CIPROFLOXACIN XL 500 mg once daily (see **DOSAGE AND ADMINISTRATION**, **Special Populations**, **Renal Impairment**).

STORAGE AND STABILITY

Store between 15°C and 30°C.

DOSAGE FORMS, COMPOSITION AND PACKAGING

MYLAN-CIPROFLOXACIN XL (ciprofloxacin hydrochloride and ciprofloxacin) 500 mg is available as a white, film-coated, modified capsule shaped, biconvex, beveled edge tablet debossed with M 1743 on one side of the tablet and blank on the other side. MYLAN-CIPROFLOXACIN XL 1000 mg available as a white, film-coated, capsule shaped, biconvex, beveled edge tablet debossed with M 1745 on one side of the tablet and blank on the other side. MYLAN-CIPROFLOXACIN XL 500 mg and 1000 mg tablets are available in bottles of 100s.

Composition

Each MYLAN-CIPROFLOXACIN XL (ciprofloxacin hydrochloride and ciprofloxacin) extended release 500 mg tablet contains 500 mg of ciprofloxacin as ciprofloxacin hydrochloride (287.5 mg, calculated as ciprofloxacin on the dried basis) and ciprofloxacin (212.6 mg, calculated on the dried basis). Each MYLAN-CIPROFLOXACIN XL (ciprofloxacin hydrochloride and ciprofloxacin) extended release 1000 mg tablet contains 1000 mg of ciprofloxacin as ciprofloxacin hydrochloride (669.6 mg, calculated as ciprofloxacin on the dried basis) and ciprofloxacin (425.2 mg, calculated on the dried basis).

The non-medicinal ingredients are carnauba wax, colloidal silicon dioxide, croscarmellose sodium, dibasic calcium phosphate, magnesium stearate/sodium lauryl sulfate, hypromellose, macrogol, microcrystalline cellulose, polyvinyl alcohol-part hydrolyzed, povidone, pregelatinized starch, stearic acid, succinic acid, talc, and titanium dioxide.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE

1) Ciprofloxacin Hydrochloride

Proper Name

Ciprofloxacin hydrochloride (USP)

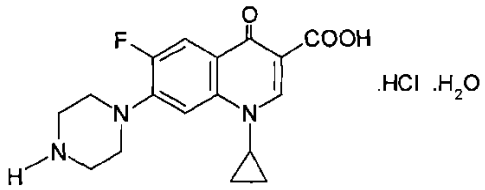
Chemical Names

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

1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolonecarboxylic acid, monohydrochloride, monohydrate

1-Cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)quinoline-3-carboxylic acid, monohydrochloride, monohydrate

Structural Formula



Molecular Formula

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

Molecular Weight

385.82 g/mol

Description

White to pale yellow crystalline granular powder.

Sparingly soluble in water; slightly soluble in acetic acid and in methanol; very slightly soluble in dehydrated alcohol; practically insoluble in acetone, in acetonitrile, in ethyl acetate, in hexane, and in methylene chloride.

pH and pKa values:

pH – 3.0 – 4.5

pKa – 6.43 ± 0.41 (free base)

pKa – 8.68 ± 0.10 (free base)

Other:
Partition coefficient: Log P = -1.7 (free base)

Melting point: 318-320°C

Optical Rotation: Ciprofloxacin does not contain a chiral center; therefore, optical rotation is not applicable.

UV absorption maxima: at about 228 nm and 313 nm

2) Ciprofloxacin

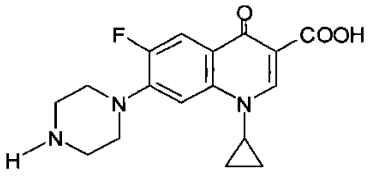
Proper Name

Ciprofloxacin, USP

Chemical Names

3-Quinolinecarboxylic acid, 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)
1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid
1-cyclopropyl-6-fluoro-4-oxo-7-(1-piperazin-1-yl)-1,4-dihydro quinoline-3-carboxylic acid
1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid

Structural Formula



Molecular Formula

$C_{17}H_{18}FN_3O_3$

Molecular Weight

331.34 g/mol

Description

White to pale yellow crystalline powder.

Sparingly soluble in water; slightly soluble in acetic acid and in methanol; very slightly soluble in dehydrated alcohol; practically insoluble in acetone, in acetonitrile, in ethyl acetate, in hexane, and in methylene chloride.

pH and pKa values:

pH – 7.6 at 0.1 g/L water at 20°C

pKa – 6.43 ± 0.41

pKa – 8.68 ± 0.10

Other:

Partition coefficient: Log P = -1.7

Melting point: about 255°C, with decomposition

Optical Rotation: Ciprofloxacin does not contain a chiral center; therefore, optical rotation is not applicable.

UV absorption maxima: at about 207 nm and 276 nm

CLINICAL TRIALS

Comparative Bioavailability Studies

A blinded, randomized, single oral dose, two-treatment, two period, crossover bioequivalence study comparing 1x 1000 mg MYLAN-CIPROFLOXACIN XL (ciprofloxacin hydrochloride and ciprofloxacin) extended release tablet (Mylan Pharmaceuticals ULC) and 1 x 1000 mg Cipro® XL™ (ciprofloxacin hydrochloride and ciprofloxacin) extended release tablet (Bayer Inc.) was performed in health adult male subjects (n=41) under fasting conditions.

A summary of the results is presented in the following table.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Ciprofloxacin (1 × 1000 mg) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test***	**Reference#**	**% Ratio of Geometric Means**	**90% Confidence Interval**
AUC_T (µg•hr/mL)	20.38 21.39 (27.07%)	21.40 22.02 (24.46%)	95.23%	88.09% - 102.94%
AUC_I (µg•hr/mL)	21.12 22.15 (27.43%)	22.14 22.79 (24.60%)	95.37%	88.52% - 102.76%
C_{max} (µg/mL)	3.14 3.26 (25.62%)	2.94 3.03 (25.50%)	106.99%	99.64% - 114.89%
T_{max}§ (h)	2.50 (1.00 – 3.00)	2.50 (1.00-5.00)	--	--
$T_{½}$€ (h)	6.43 (12.80%)	6.47 (12.90%)	--	--

* Mylan-Ciprofloxacin XL 1000 mg extended release tablets (Mylan Pharmaceuticals ULC)
# Cipro® XL™ 1000 mg extended release tablets (Bayer Inc.) were purchased in Canada
§ Expressed as the median (range) only;
€ Expressed as the arithmetic mean (CV%) only

A blinded, randomized, single oral dose, two-treatment, two-period, crossover bioequivalence study comparing 1 x 1000 mg MYLAN-CIPROFLOXACIN XL (ciprofloxacin and ciprofloxacin hydrochloride) extended release tablet (Mylan Pharmaceuticals ULC) and 1 x 1000 mg Cipro® XL™ (ciprofloxacin and ciprofloxacin hydrochloride) extended release tablet (Bayer Inc.) was performed in healthy adult male subjects (n=17) under fed conditions.

A summary of the results is presented in the following table.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Ciprofloxacin (1 × 1000 mg) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test***	**Reference#**	**% Ratio of Geometric Means**	**90% Confidence Interval**
AUC_T (µg•hr/mL)	15.77 16.08 (18.99%)	16.64 16.87 (16.89%)	94.74%	89.79% - 99.95%
AUC_I (µg•hr/mL)	16.34 16.65 (18.88%)	17.26 17.49 (16.63%)	94.63%	89.69% - 99.85%
C_{max} (µg/mL)	3.28 3.36 (19.89%)	2.97 3.04 (19.45%)	110.37%	99.78% - 122.08%
T_{max}§ (h)	2.00 (1.50 – 2.50)	2.00 (1.00-3.50)	--	--
$T_{½}$€ (h)	6.94 (15.07%)	6.55 (18.73%)	--	--

* Mylan-Ciprofloxacin XL 1000 mg extended release tablets (Mylan Pharmaceuticals ULC)
# Cipro® XL™ 1000 mg extended release tablets (Bayer Inc.) were purchased in Canada
§ Expressed as the median (range) only
€ Expressed as the arithmetic mean (CV%) only

A blinded, randomized, single oral dose, two-treatment, two-period, crossover bioequivalence study comparing 1 x 500 mg MYLAN-CIPROFLOXACIN XL (ciprofloxacin and ciprofloxacin hydrochloride) extended release tablet (Mylan Pharmaceuticals ULC) and
1 x 500 mg Cipro® XL™ (ciprofloxacin and ciprofloxacin hydrochloride) extended release tablet (Bayer Inc.) was performed in healthy adult male subjects (n=41) under fasting conditions.

A summary of the results is presented in the following table.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Ciprofloxacin (1 × 500 mg) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test***	**Reference#**	**% Ratio of Geometric Means**	**90% Confidence Interval**
AUC_T (µg•hr/mL)	10.06 10.46 (26.40%)	10.19 10.43 (20.77%)	98.73%	91.58% - 106.43%
AUC_I (µg•hr/mL)	10.59 10.98 (25.54%)	10.72 10.96 (20.35%)	98.73%	91.85% - 106.13%
C_{max} (µg/mL)	1.71 1.78 (28.75%)	1.70 1.74 (21.57%)	100.46%	91.90% - 109.82%
T_{max}§ (h)	2.00 (0.75 – 3.00)	2.00 (0.75-4.00)	--	--
$T_{½}$€ (h)	5.91 (16.30%)	6.12 (16.76%)	--	--

* Mylan-Ciprofloxacin XL 500 mg extended release tablets (Mylan Pharmaceuticals ULC)
# Cipro® XL™ 500 mg extended release tablets (Bayer Inc.) were purchased in Canada
§ Expressed as the median (range) only;
€ Expressed as the arithmetic mean (CV%) only

Uncomplicated Urinary Tract Infections (acute cystitis)

Ciprofloxacin hydrochloride and ciprofloxacin extended release was evaluated for the treatment of uncomplicated urinary tract infections (acute cystitis) in females in a prospective, randomized, double-blind, multicentre, clinical trial. This study compared ciprofloxacin hydrochloride and ciprofloxacin extended release (500 mg once daily for three days) with ciprofloxacin (250 mg bid for three days). Of the 905 patients enrolled, 452 were randomly assigned to the ciprofloxacin hydrochloride and ciprofloxacin extended release treatment group and 453 were randomly assigned to the control group. The primary efficacy variable was bacteriologic eradication at Test of Cure (TOC; Day 4-11 Post Therapy).

The bacteriologic eradication and clinical success rates were similar between ciprofloxacin hydrochloride and ciprofloxacin extended release and the control group. The eradication and clinical success rates and their corresponding 95% confidence intervals for the differences between rates (ciprofloxacin hydrochloride and ciprofloxacin extended release minus control ciprofloxacin group) are given in **Table 7** below:

Table 7: Clinical and Bacteriologic Response at Test of Cure

	Ciprofloxacin hydrochloride and ciprofloxacin extended release 500 mg Once Daily x 3 Days	**Ciprofloxacin 250 mg bid x 3 Days**
Randomized Patients	452	453
Per Protocol Patients[a]	199	223
Clinical Success at TOC (n/N)[b]	189/199 (95.0%)	204/ 223 (91.5%)
	CI [-1.6%, 7.1%]	
Bacteriologic Eradication at TOC (n/N)[b]	188/199 (94.5%)	209/223 (93.7%)
	CI [-3.5%, 5.1%]	
Bacteriologic Eradication (by organism) at TOC (n/N)[b]		
E coli	156/160 (97.5%)	176/181 (97.2%)
E faecalis	10/11 (90.9%)	17/21 (81.0%)
P mirabilis	11/12 (91.7%)	7/7 (100%)
S saprophyticus	5/6 (83.3)	7/7 (100%)
K pneumoniae	7/9 (77.8%)[c]	11/14 (78.6%)[c]

a The presence of a pathogen at a level of $\geq 10^5$ CFU/mL was required for microbiological evaluability criteria.
b n/N = patients with pathogen eradicated/total number of patients
c Eradication rate at Follow-up was 3/6 (50%) for ciprofloxacin hydrochloride and ciprofloxacin extended release and 6/10 (60%) for ciprofloxacin. This was due primarily to eradication with recurrence for this organism in both treatment groups.

Complicated Urinary Tract Infections and Acute Uncomplicated Pyelonephritis

Ciprofloxacin hydrochloride and ciprofloxacin extended release 1000 mg was evaluated for the treatment of complicated urinary tract infections and acute uncomplicated pyelonephritis in a large, randomized, double-blind, controlled clinical trial. This study compared ciprofloxacin hydrochloride and ciprofloxacin extended release (1000 mg once daily for 7 to 14 days) with ciprofloxacin (500 mg twice daily for 7 to 14 days). Of the 1,042 patients enrolled, 521 were randomly assigned to the ciprofloxacin hydrochloride and ciprofloxacin extended release treatment group and 521 were randomly assigned to the control group. The primary efficacy variable was bacteriological eradication at Test of Cure (TOC; Day 5-11 Post Therapy).

The bacteriological eradication and clinical success rates were similar between ciprofloxacin hydrochloride and ciprofloxacin extended release 1000 mg and the control group. The eradication and clinical success rates and their corresponding 95% confidence intervals for the differences between rates (ciprofloxacin hydrochloride and ciprofloxacin extended release 1000 mg minus control ciprofloxacin group) are given in **Table 8**.

Table 8: Clinical and Bacteriologic Response at Test of Cure

	Ciprofloxacin hydrochloride and ciprofloxacin extended release 1000 mg Once Daily x 7-14 Days	**Ciprofloxacin 500 mg bid x 7-14 Days**
Randomized Patients	521	521
Per Protocol Patients[a]	206	229
Clinical Success at TOC in cUTI and AUP combined (n/N)[b]	198/206 (96.1%)	211/ 229 (92.1%)
	CI [-1.2%, 6.9%]	
Bacteriologic Eradication at TOC in cUTI and AUP combined (n/N)[c]	183/206 (88.8%)	195/229 (85.2%)
	CI [-2.4%, 10.3%]	
cUTI		
Clinical Success in cUTI at TOC (n/N)[b]	159/166 (95.8%)	161/177 (91.0%)
Bacteriologic Eradication (by organism) in cUTI at TOC (n/N)[d]		
E coli	91/94 (96.8%)	90/92 (97.8%)
K pneumoniae	20/21 (95.2%)	19/23 (82.6%)
E faecalis	17/17 (100%)	14/21 (66.7%)
P mirabilis	11/12 (91.6%)	10/10 (100%)
P aeroginosa	3/3 (100%)	3/3 (100%)
Bacteriologic Eradication Overall in cUTI at TOC[e]	148/166 (89.2%)	144/177 (81.4%)
AUP		
Clinical Success in AUP at TOC (n/N)[b]	39/40 (97.5%)	50/52 (96.2%)
Bacteriologic Eradication of *E coli* in AUP at TOC (n/N)[d]	35/36 (97.2%)	41/41 (100%)

a Patients excluded from the Per Protocol population were primarily those with no causative organism(s) at baseline or no organism present at ≥ 105 CFU/mL at baseline, inclusion criteria violation, no valid test-of-cure urine culture within the TOC window, an organism resistant to study drug, premature discontinuation due to an adverse event, lost to follow-up, or noncompliance with dosage regimen (among other criteria).
b n/N - patients with clinical success or pathogen eradicated/total number of patients
c n/N - patients with bacteriological eradication and no new infection /total number of patients
d n/N - patients with specified baseline organism eradicated/patients with specified baseline organism e n/N - patients with specified baseline organism(s) eradicated and no new infections or superinfections/total number of patients

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/h and dehydrobenzperidol 0.25 mg/kg/h) at a single dose of 3, 10 or 30 mg/kg. Ciprofloxacin treatment resulted in circulatory changes similar to those caused by histamine release. These were reductions in blood pressure, cardiac output and maximum rate of pressure increase in the left ventricle (dp/dt max), and increase in heart rate. This histamine-liberating effect was counteracted by the simultaneous intravenous administration of 0.01 mg/kg pyrilamine maleate. No signs of histamine liberation were observed on conscious animals.

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

Bronchodilatory Effects

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

Central Nervous System (CNS) Effects

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

Gastrointestinal Effects

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

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

Effect on Blood Glucose and Serum Triglycerides

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

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

Human Pharmacology

Pharmacokinetics

Absorption:

MYLAN-CIPROFLOXACIN XL extended release tablets are formulated to release drug at a slower rate compared to ciprofloxacin and ciprofloxacin hydrochloride tablets, which are immediate release tablets. Approximately 35% of the ciprofloxacin dose in MYLAN-CIPROFLOXACIN XL is contained within an immediate release component, while the remaining 65% is contained in a slow-release matrix.

The relative bioavailability of MYLAN-CIPROFLOXACIN XL as compared to MYLAN-CIPROFLOXACIN, and also the effect of food on the pharmacokinetics of MYLAN-CIPROFLOXACIN XL, have been discussed under Action and Clinical Pharmacology (see **ACTION AND CLINICAL PHARMACOLOGY**: **Pharmacokinetics: Absorption**).

Distribution

In one study, the apparent volume of distribution (Vd_{area}) of ciprofloxacin was estimated from kinetic data recorded after oral doses and found to be approximately 3.5 L/kg. Studies with the oral and intravenous forms of ciprofloxacin have demonstrated penetration of ciprofloxacin into a variety of tissues. A single dose study in healthy subjects has demonstrated penetration of ciprofloxacin into prostate tissue following administration of ciprofloxacin hydrochloride and ciprofloxacin extended release 1000 mg. One and three hours after dosing, mean ciprofloxacin concentrations in the prostate were 4.75 ± 1.3 μg/g and 4.29 ± 1.61 μg/g, respectively. The binding of ciprofloxacin to serum proteins is 20% to 40%, which is not likely to be high enough to cause significant protein binding interactions with other drugs. Following administration of a single dose of ciprofloxacin hydrochloride and ciprofloxacin extended release (500 mg or 1000 mg), ciprofloxacin concentrations in urine, collected up to 4 hours after dosing, averaged over 300 mg/L and over 500 mg/L, respectively; in urine excreted from 12 to 24 hours after dosing, ciprofloxacin concentration averaged 27 mg/L for ciprofloxacin hydrochloride and ciprofloxacin extended release 500 mg and 58 mg/L for ciprofloxacin hydrochloride and ciprofloxacin extended release 1000 mg.

The following table (**Table 9**) compares the mean concentrations in urine at steady state during different collection intervals for ciprofloxacin hydrochloride and ciprofloxacin and ciprofloxacin bid.

Table 9: Concentration of Ciprofloxacin in Urine at Steady State

	Mean Concentration (Range) (mg/L)	
Collection Interval	**Ciprofloxacin hydrochloride and ciprofloxacin extended release 500 mg**	**Ciprofloxacin bid 250 mg**
0 - 4 h	368 (73 - 968)	196 (49 - 371)
4 - 8 h	166 (30 - 298)	82 (19 - 231)
8 - 12 h	53 (15 - 143)	31 (6 - 77)
12 - 24 h	30 (8 - 71)	128 (43 - 231)
Collection Interval	**Ciprofloxacin hydrochloride and ciprofloxacin extended release 1000 mg**	**Ciprofloxacin bid 500 mg**
0 - 4 h	589 (108 - 3030)	272 (98 - 762)
4 - 8 h	359 (26 - 1991)	136 (34 - 288)
8 - 12 h	160 (36 - 843)	59 (20 - 151)
12 - 24 h	65 (5 - 204)	231 (80 - 864)

Metabolism

Four metabolites of ciprofloxacin were identified in human urine. The primary metabolites are oxociprofloxacin (M3) and sulfociprofloxacin (M2), each accounting for roughly 3% to 8% of the total dose. Other minor metabolites are desethylene ciprofloxacin (M1), and formylciprofloxacin (M4). The relative proportion of drug and metabolite in serum corresponds to the composition found in urine. Excretion of these metabolites was essentially complete by 24 hours after dosing.

Following the oral administration of a single 259 mg dose of ^{14}C-labeled 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%.

Elimination

The elimination kinetics of ciprofloxacin are similar for ciprofloxacin hydrochloride and ciprofloxacin extended release and ciprofloxacin (immediate release formulation). The mean serum elimination half-life ($t_{1/2}$) of ciprofloxacin hydrochloride and ciprofloxacin extended release tablet is 6.6 (± 1.4) hours, and 6.3 (±0.7) hours for the 500 mg and 1000 mg tablets, respectively. The major route of elimination of ciprofloxacin in humans is as unchanged drug in urine.

In studies comparing the ciprofloxacin hydrochloride and ciprofloxacin extended release and ciprofloxacin bid regimens (ciprofloxacin hydrochloride and ciprofloxacin extended release 500 mg vs ciprofloxacin 250 mg bid and ciprofloxacin hydrochloride and ciprofloxacin extended release 1000 mg vs ciprofloxacin 500 mg bid), approximately 35% of an orally administered dose was excreted in the urine as unchanged drug for both formulations. The urinary excretion of ciprofloxacin is virtually complete within 24 hours after dosing. The renal clearance of ciprofloxacin, which is approximately 300 mL/minute, exceeds the normal glomerular filtration rate of 120 mL/minute. Thus, active tubular secretion would seem to play a significant role in its elimination. Co-administration of probenecid with immediate release ciprofloxacin results in about a 50% reduction in the ciprofloxacin renal clearance and a 50% increase its concentration in the systemic circulation.

Although bile concentrations of ciprofloxacin are several folds higher than serum concentrations after oral dosing with the immediate release tablet, only a small amount of the dose administered is recovered from the bile as unchanged drug. An additional 1% to 2% of the dose is recovered from the bile in the form of metabolites. Approximately 20% to 35% of an oral dose of immediate release ciprofloxacin is recovered from the feces within 5 days after dosing. This may arise from either biliary clearance or transintestinal elimination**.**

Special Populations

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. These alternate pathways of drug elimination appear to compensate for the reduced renal excretion in patients with renal impairment. In patients with reduced renal function, the half-life of ciprofloxacin is slightly prolonged. Since the total drug exposure attained with ciprofloxacin hydrochloride and ciprofloxacin extended release 500 mg does not exceed that achieved with ciprofloxacin 500 mg (immediate release formulation) which is approved as a total daily dose for use in renally impaired patients, no dosage adjustment for renal disease is required for ciprofloxacin hydrochloride and ciprofloxacin extended release 500 mg.

For complicated urinary tract infections or acute uncomplicated pyelonephritis, where 1000 mg is the appropriate dose, the dosage of MYLAN-CIPROFLOXACIN XL should be reduced to 500 mg MYLAN-CIPROFLOXACIN XL once daily in patients with creatinine clearance below 30 mL/min.

Since ciprofloxacin is eliminated primarily by the kidney, a change in pharmacokinetics is to be expected depending on the degree of impairment of renal function.

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 a Single 250 mg Oral Dose in Healthy Volunteers and in Patients With Renal Insufficiency

Group	Creatinine Clearance (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	> 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	< 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 preliminary studies in patients with stable chronic liver cirrhosis (with mild to moderate

hepatic impairment), no significant changes in ciprofloxacin pharmacokinetics have been observed. No dosage adjustment is required with MYLAN-CIPROFLOXACIN XL in patients with stable chronic cirrhosis (with mild to moderate hepatic impairment). The kinetics of ciprofloxacin in patients with acute hepatic insufficiency and stable chronic cirrhosis (with severe hepatic impairment), however, have not been elucidated.

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.

Elderly

No dosage adjustment based on age alone is necessary for elderly patients. Pharmacokinetic studies of immediate release oral tablet (single dose) and intravenous (single and multiple dose) forms of ciprofloxacin indicate that plasma concentrations of ciprofloxacin are higher in elderly subjects (> 65 years) as compared to young adults. C_{max} is increased 16% to 40% and mean AUC is increased approximately 30%, which can be at least partially attributed to decreased renal clearance in the elderly. Elimination half-life is only slightly (–20%) prolonged in the elderly.

Ciprofloxacin is substantially excreted by the kidney and the risk of adverse reactions may be greater in patients with impaired renal function. No significant accumulation of ciprofloxacin is anticipated in elderly subjects with renal impairment who take ciprofloxacin hydrochloride and ciprofloxacin extended release tablets 500 mg, therefore, no reductions in dosage are required.

However, in patients with renal impairment, where MYLAN-CIPROFLOXACIN XL 1000 mg once daily is the appropriate dose, dosage may need to be reduced to MYLAN-CIPROFLOXACIN XL 500 mg once daily (see **PART I: HEALTH PROFESSIONAL INFORMATION, DOSAGE AND ADMINISTRATION, Special Populations, Renal Impairment**).

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 ciprofloxacin 250 mg, maximum ciprofloxacin serum concentrations and areas under the serum concentration time curves were significantly higher than in 10 male younger volunteers (age: 24 ± 3 years, weight: 72 ± 9 kg). The time to peak serum concentrations, overall elimination half-life and urinary recovery of ciprofloxacin were similar in both age groups (see **Table 11**).

Table 11: Comparison of Pharmacokinetic Parameters Between Healthy Elderly and Healthy Younger Volunteers With Ciprofloxacin 250 mg

Parameter	Elderly Volunteers (Mean ± SD)	Younger Volunteers (Mean ± SD)
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

Serum Protein Binding

Serum protein binding of ciprofloxacin is between 20% to 40%.

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.

MICROBIOLOGY

Mechanism of Action

The bactericidal action of ciprofloxacin 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.

Drug Resistance

The mechanism of action of fluoroquinolones, including ciprofloxacin, is different from that of other antimicrobial agents such as beta-lactams, macrolides, tetracyclines, or aminoglycosides; therefore, microorganisms resistant to these classes of drugs may be susceptible to ciprofloxacin. There is no known cross-resistance between ciprofloxacin and other classes of antimicrobials. Resistance to ciprofloxacin *in vitro* develops slowly (multiple-step mutation). 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-negative and gram-positive 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 (see **PART I – HEALTH PROFESSIONAL INFORMATION, INDICATIONS AND CLINICAL USE**).

Aerobic gram-positive microorganisms
Enterococcus faecalis (Many strains are only moderately susceptible.)
Staphylococcus saprophyticus

Aerobic gram-negative microorganisms
Escherichia coli Klebsiella pneumoniae Proteus mirabilis Pseudomonas aeruginosa

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-negative microorganisms
Citrobacter koseri
Citrobacter freundii
Edwardsiella tarda
Enterobacter aerogenes
Enterobacter cloacae
Klebsiella oxytoca
Morganella morganii
Proteus vulgaris
Providencia rettgeri
Providencia stuartii
Serratia marcescens

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. The MIC values should be interpreted according to the criteria outlined in **Table 12**.

Diffusion Techniques: Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure (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 12**. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for ciprofloxacin.

Table 12: Susceptibility Interpretive 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
Pseudomonas aeruginosa	≤1	2	≥4	≥21	16-20	≤15
Staphylococcus saprophyticus	≤1	2	≥4	≥21	16-20	≤15

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

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

Quality Control: Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. For dilution technique, standard ciprofloxacin powder should provide the MIC values according to criteria outlined in **Table 13**. For diffusion technique, the 5 µg ciprofloxacin disk should provide the zone diameters outlined in **Table 13**.

Table 13: 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
Pseudomonas aeruginosa ATCC 27853	0.25-1.0	25-33
Staphylococcus aureus ATCC 29212	0.12-0.5	-
Staphylococcus aureus ATCC 25923	-	22-30

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

TOXICOLOGY

Acute Toxicity

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

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

Chronic Toxicity

Subacute Tolerability Studies Over 4 Weeks

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

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

Subchronic Tolerability Studies Over 3 Months

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

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

Chronic Tolerability Studies Over 6 Months

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

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

Carcinogenicity

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

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 cerev.: 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

Although two of the eight in vitro assays (ie, the Mouse Lymphona Cell Forward Mutation

Assay and the Rat Hepatocyte Primary Culture DNA Repair Assay [LIDS]) were positive, all of the in vivo test systems covering all relevant endpoints gave negative results.

Special Tolerability Studies

It is known from comparative studies in animals, both with the older gyrase inhibitors (eg, nalidixic and pipemidic acid) and the more recent ones (eg, norfloxacin and ofloxacin), 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.

REFERENCES

1. CLSI (Clinical and Laboratory Standards Institute). Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard. CLSI Document M7-A8, Vol. 29, No. 2. Eighth Edition ed. CLSI, Wayne, PA2009.

2. CLSI (Clinical and Laboratory Standards Institute). Performance Standards for Antimicrobial Disk Susceptibility Tests; Approved Standard. CLSI Document M2-A10 Vol. 29, No. 1. Tenth Edition ed. CLSI, Wayne, PA2009.

3. Aldridge KE, Schiro DD, Tsai L, Janney A, Sanders CV, Marier RL. Ciprofloxacin (BAY o 9867) and in vitro comparison with other broad spectrum antibiotics. Curr Ther Res. 1985;37(4):754-62.

4. Bauernfeind A, Petermuller C. In vitro activity of ciprofloxacin, norfloxacin and nalidixic acid. Eur J Clin Microbiol. 1983 Apr;2(2):111-5.

5. Bayer A, Gajewska A, Stephens M, Stark JM, Pathy J. Pharmacokinetics of ciprofloxacin in the elderly. Respiration. 1987;51(4):292-5.

6. Bayer Inc. CIPRO® Tablets and CIPRO® ORAL SUSPENSION Product Monograph.

7. Crump B, Wise R, Dent J. Pharmacokinetics and tissue penetration of ciprofloxacin. Antimicrob Agents Chemother. 1983 Nov;24(5):784-6.

8. Fass RJ. Efficacy and safety of oral ciprofloxacin for treatment of serious urinary tract infections. Antimicrob Agents Chemother. 1987 Feb;31(2):148-50.

9. Gasser TC, Ebert SC, Graversen PH, Madsen PO. Ciprofloxacin pharmacokinetics in patients with normal and impaired renal function. Antimicrob Agents Chemother. 1987 May;31(5):709-12.

10. Gonzalez MA, Moranchel AH, Duran S, Pichardo A, Magana JL, Painter B, et al. Multiple-dose ciprofloxacin dose ranging and kinetics. Clin Pharmacol Ther. 1985 Jun;37(6):633-7.

11. Henry DC, Jr., Bettis RB, Riffer E, Haverstock DC, Kowalsky SF, Manning K, et al. Comparison of once-daily extended-release ciprofloxacin and conventional twice-daily ciprofloxacin for the treatment of uncomplicated urinary tract infection in women. Clin Ther. 2002 Dec;24(12):2088-104.

12. Karlowsky JA, Jones ME, Thornsberry C, Critchley I, Kelly LJ, Sahm DF. Prevalence of antimicrobial resistance among urinary tract pathogens isolated from female outpatients across the US in 1999. Int J Antimicrob Agents. 2001 Aug;18(2):121-7.

13. Klecak G, Urbach F, Urwyler H. Fluoroquinolone antibacterials enhance UVA-induced skin tumors. J Photochem Photobiol B. 1997 Feb;37(3):174-81.

14. National Committee for Clinical Laboratory Standards. Performance standards for antimicrobial disk susceptibility tests, 8th edition. Wayne, PA2003.

15. National Committee for Clinical Laboratory Standards. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically. 6th ed. . Wayne, PA2003.

16. Raoof S, Wollschlager C, Khan FA. Ciprofloxacin increases serum levels of theophylline. Am J Med. 1987 Apr 27;82(4A):115-8.

17. Ratcliffe NT, Smith JT. Effects of magnesium on the activity of 4-quinolone antibacterial agents. J Pharm Pharmacol. 1983;35(Suppl):61.

18. Sahm DF, Thornsberry C, Kelly LJ, Jones ME, Karlowsky JA. In vitro activities of commonly used antibiotics against prevalent uropathogens: implications for empiric therapy. . Infect Urol. 2001;14(3):59-67.

19. Schacht P, Arcieri G, Branolte J, Bruck H, Chysky V, Griffith E, et al. Worldwide clinical data on efficacy and safety of ciprofloxacin. Infection. 1988;16 Suppl 1:S29-43.

20. Smith JT. The mode of action of 4-quinolones and possible mechanisms of resistance. J Antimicrob Chemother. 1986 Nov;18 Suppl D:21-9.

21. Talan DA, Klimberg IW, Nicolle LE, Song J, Kowalsky SF, Church DA. Once daily, extended release ciprofloxacin for complicated urinary tract infections and acute uncomplicated pyelonephritis. J Urol. 2004 Feb;171(2 Pt 1):734-9.

22. Wolfson JS, Hooper DC. The fluoroquinolones: structures, mechanisms of action and resistance, and spectra of activity in vitro. Antimicrob Agents Chemother. 1985 Oct;28(4):581-6.

23. Zeiler HJ. Evaluation of the in vitro bactericidal action of ciprofloxacin on cells of Escherichia coli in the logarithmic and stationary phases of growth. Antimicrob Agents Chemother. 1985 Oct;28(4):524-7.

24. CIPRO® XL™ Product Monograph, Bayer Inc., Control No: 180658. Date of Revision: March 9, 2015.

PART III: CONSUMER INFORMATION

[Pr]MYLAN-CIPROFLOXACIN XL
(Ciprofloxacin hydrochloride and Ciprofloxacin Extended Release Tablets)
Ciprofloxacin, 500 mg, 1000 mg
Professed Standard

This leaflet is part III of a three-part "Product Monograph" published when MYLAN-CIPROFLOXACIN XL was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about MYLAN-CIPROFLOXACIN XL. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

MYLAN-CIPROFLOXACIN XL is used to treat bacterial urinary tract infections and inflammation of the kidneys.

What it does:

MYLAN-CIPROFLOXACIN XL is an antibiotic that kills the bacteria causing infection in the urinary tract.

When it should not be used:

Do not use MYLAN-CIPROFLOXACIN XL if you:

- are allergic to ciprofloxacin, other quinolone antibiotics or to any nonmedicinal ingredients in this product (see What the nonmedicinal ingredients are).
- are currently taking tizanidine (ZANAFLEX®) for the management of spasticity. Tizanidine concentrations may increase and cause further side effects such as drowsiness, sleepiness and low blood pressure.

What the medicinal ingredient is:

Ciprofloxacin.

What the nonmedicinal ingredients are:
Carnauba wax, colloidal silicon dioxide, croscarmellose sodium, dibasic calcium phosphate, magnesium stearate/sodium lauryl sulfate, hypromellose, macrogol, microcrystalline cellulose, polyvinyl alcohol-part hydrolyzed, povidone, pregelatinized starch, stearic acid, succinic acid, talc, and titanium dioxide.

What dosage forms it comes in:
MYLAN-CIPROFLOXACIN XL (ciprofloxacin hydrochloride and ciprofloxacin) 500 mg is available as a white, film-coated, modified capsule shaped, biconvex, beveled edge tablet debossed with M 1743 on one side of the tablet and blank on the other side. MYLAN-CIPROFLOXACIN XL 1000 mg available as a white, film-coated, capsule shaped, biconvex, beveled edge tablet debossed with M 1745 on one side of the tablet and blank on the other side. MYLAN-CIPROFLOXACIN XL 500 mg and 1000 mg tablets are available in bottles of 100.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- **MYLAN-CIPROFLOXACIN XL has been shown to lengthen the heartbeat on an electrocardiogram test (QT interval prolongation).**
- **Serious hypersensitivity (allergic) reactions have been reported in some patients receiving quinolone therapy, including MYLAN-CIPROFLOXACIN XL.**
- **If you have myasthenia gravis, treatment with MYLAN-CIPROFLOXACIN XL may make your condition worse. Do not use MYLAN-CIPROFLOXACIN XL if you have this condition.**
- **Quinolones, including MYLAN-CIPROFLOXACIN XL, are associated with an increased risk of tendinitis and tendon rupture in all ages. Speak to your doctor to determine if this medication is suitable for you.**
- **Seizures and toxic psychoses may occur with quinolone therapy. Tell your doctor if you have any central nervous system problems (ie, epilepsy). Your doctor will determine whether you should use this medication.**
- **MYLAN-CIPROFLOXACIN XL can cause liver injury which may be fatal.**

BEFORE you use MYLAN-CIPROFLOXACIN XL talk to your doctor or pharmacist if you:

- Have a history of seizures
- Have a heart condition known as “QT prolongation”
- Have low levels of potassium in your blood
- Have liver or kidney disease or damage
- Are pregnant, planning to become pregnant, breast feeding or planning to breast feed MYLAN-CIPROFLOXACIN XL is not recommended for use during pregnancy or nursing, as the effects on the unborn child or nursing infant are unknown.
- Are less than 18 years of age.
- Have a history of tendon problems associated with the use of a quinolone antibiotic.
- Have a condition known as myasthenia gravis.

You may become sensitive to the sun and ultraviolet light while taking MYLAN-CIPROFLOXACIN XL. Exposure to sunlight and ultraviolet light, such as that used in tanning salons, should be

minimized until you know how you respond.

Driving and using machines: Before you perform tasks which may require special attention, wait until you know how you respond to MYLAN-CIPROFLOXACIN XL as it can cause dizziness.

INTERACTIONS WITH THIS MEDICATION

As with most medicines, interactions with other drugs are possible. Tell your doctor, nurse, or pharmacist about all the medicines you take, including drugs prescribed by other doctors, vitamins, minerals, natural supplements, or alternative medicines.

Drugs that may interact with MYLAN-CIPROFLOXACIN XL include:

- Theophylline or VIDEX® (didanosine) chewable/buffered tablets or pediatric powder. **Serious and fatal reactions have been reported in patients receiving ciprofloxacin, including ciprofloxacin hydrochloride and ciprofloxacin extended release tablets and theophylline**.
- Antacids, multivitamins, and other dietary supplements containing magnesium, calcium, aluminum, iron or zinc, all of which can interfere with the absorption of MYLAN-CIPROFLOXACIN XL and may prevent it from working. You should take MYLAN-CIPROFLOXACIN XL either 2 hours before or 6 hours after taking these products.
- Antidiabetic agents (eg, glyburide, glibenclamide, glimepiride, insulin) as the combination of ciprofloxacin with any of these agents may cause lower blood sugar.
- Nonsteroidal Anti-Inflammatory Drugs (NSAIDS).
- Caffeine (e.g. coffee) and other xanthine derivatives (e.g. pentoxifylline). Excessive caffeine intake should be avoided while taking MYLAN-CIPROFLOXACIN XL.
- Certain heart medications known as antiarrhythmics (e.g. quinidine, procainamide, amiodarone, sotalol).
- Other medications including oral anticoagulants (like warfarin and acenocoumarol), phenytoin, duloxetine, tizanidine, methylxanthines, sevelamer, sucralfate, clozapine, ropinirole, lidocaine, sildenafil, probenecid, methotrexate, metoclopramide, cyclosporine, lanthanum carbonate.

PROPER USE OF THIS MEDICATION

- MYLAN-CIPROFLOXACIN XL should be taken as prescribed at approximately the same time each day with food or on an empty stomach.
- MYLAN-CIPROFLOXACIN XL should not be taken with dairy products (like milk or yogurt) or calcium-fortified juices alone; however, MYLAN-CIPROFLOXACIN XL may be taken with a meal that contains these products. (see "Interactions with this Medication")
- You should avoid excessive caffeine consumption while taking MYLAN-CIPROFLOXACIN XL.
- You should drink lots of water while taking MYLAN-CIPROFLOXACIN XL
- Swallow the MYLAN-CIPROFLOXACIN XL tablet whole, with water as needed. **DO NOT SPLIT, CRUSH, OR CHEW THE TABLET.**

Usual adult dose:

Urinary tract infections: One tablet once a day for 3 days as prescribed.

Inflammation of the kidneys: One tablet once a day for 7 to 14 days as prescribed.

You should take MYLAN-CIPROFLOXACIN XL 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.

Remember:

- Take your dose of MYLAN-CIPROFLOXACIN XL once a day.
- Complete the course of MYLAN-CIPROFLOXACIN XL even if you are feeling better.
- Do not use MYLAN-CIPROFLOXACIN XL for another condition or give it to others.

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

OVERDOSE

In case of drug overdose, contact a health care practitioner, 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 one dose of MYLAN-CIPROFLOXACIN XL per day, even if you missed a dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Side effects may include:

- Nausea and vomiting
- Diarrhea
- Headache

- Rash, blistering of skin
- Stomach pain/discomfort, gas, indigestion
- Cramping
- Coordination problems (unsteady walk) Dizziness, fainting
- Feeling unwell
- Increased muscle tone, inflammation of joints, muscle pain
- Loss of appetite
- Loss of hearing (tinnitus) Migraine
- Sleeping problems
- Problems with smell and taste
- Sweating
- Visual disturbances (eyesight problems)

If your eyesight worsens or changes in any way, consult your doctor and eye specialist immediately.

If you experience symptoms such as severe diarrhea (bloody or watery) with or without fever, abdominal pain, or tenderness, you may have Clostridium difficile colitis bowel inflammation). If this occurs, stop taking MYLAN-CIPROFLOXACIN XL and contact your healthcare professional immediately.

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

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Frequency	Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and seek immediate emergency medical attention
		Only if severe	In all cases	
Common	**Vaginal Yeast Infection:** Itching, burning, thick white discharge		✓	
Rare	**Allergic Reaction:** rash, hives (skin eruptions), swelling of the face, lips, tongue or throat, difficulty swallowing or breathing, rapid heartbeat			✓

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Frequency	Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and seek immediate emergency medical attention
		Only if severe	In all cases	
	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, and hunger, tiredness, blurred vision, headache, trouble concentrating	✓		
	Low Blood Sugar: dizziness, weakness, headache, sweating, hunger	✓		

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Frequency	Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and seek immediate emergency medical attention
		Only if severe	In all cases	
Unknown	**Severe Bowel Disorder:** Persistent diarrhea, bloody or watery diarrhea, abdominal or stomach pain/cramping, blood/mucus in stool			✓
	Nerve Disorder (Neuropathy): Pain, burning, tingling, numbness, weakness		✓	
	Liver Disorder: yellowing of the skin or eyes, dark urine, abdominal pain, nausea, vomiting, loss of appetite, pale stools		✓	
	Heart Disorder (QT Prolongation): Irregular heartbeat		✓	

This is not a complete list of side effects. For any unexpected effects while taking MYLAN-CIPROFLOXACIN XL, contact your doctor or pharmacist.

HOW TO STORE IT

Store at 15°C to 30°C.
Keep out of reach and sight of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:
- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 0701E
    Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of the side effect, please contact your health care provider before notifying Canada Vigilance. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document can be found at: www.mylan.ca.

The full Product Monograph prepared for health professionals can be obtained by contacting the sponsor, Mylan Pharmaceuticals ULC at: 1-800-575-1379

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