CIPLOX Tablets (Ciprofloxacin hydrochloride)

To be sold on retail on prescription of RMP only

Black Box Warning

Serious adverse reactions, including tendinitis, tendon rupture, peripheral neuropathy, central nervous system (CNS) effects and exacerbation of myasthenia gravis

Fluoroquinolones, including ciprofloxacin have been associated with disabling and potentially irreversible serious adverse reactions that have occurred together, including the following:

• Tendinitis and tendon rupture
• Peripheral neuropathy
• CNS effects

Discontinue ciprofloxacin immediately and avoid the use of fluoroquinolones, including ciprofloxacin, in patients who experience any of these serious adverse reactions

• Fluoroquinolones, including ciprofloxacin, may exacerbate muscle weakness in patients with myasthenia gravis. Avoid ciprofloxacin in patients with known history of myasthenia gravis.
• Because fluoroquinolones, including ciprofloxacin, have been associated with serious adverse reactions, reserve ciprofloxacin for use in patients who have no alternative treatment options for for the following indications:
• Acute exacerbation of chronic bronchitis
• Acute uncomplicated cystitis
• Acute sinusitis

This drug may cause low blood sugar and mental health-related side effects.

Qualitative and Quantitative Composition

CIPLOX-250 Tablets
Each film-coated tablet contains:

Ciprofloxacin Hydrochloride, IP (equivalent to Ciprofloxacin, IP) ..... 250 mg

CIPLOX-500 Tablets
Each film-coated tablet contains:

Ciprofloxacin Hydrochloride, IP (equivalent to Ciprofloxacin, IP) .....500 mg

Dosage Form(S) and Strength(S)

Film-coated, oral tablet; 250 mg and 500 mg

Clinical Particulars

Therapeutic Indications

Ciprofloxacin tablets are indicated for the treatment of a wide variety of infections caused by susceptible gram-positive and gram-negative organisms, including mixed infections caused two or more organisms. It may also use for infections caused by multidrug-resistant bacteria. Ciprofloxacin is indicated for the treatment of the following infections caused by susceptible bacteria.

- ***Respiratory Tract Infections:*** Acute bronchitis, exacerbation of chronic obstructive airways disease, empyema, lung abscess, infected bronchiectasis, cystic fibrosis and pneumonia.
- ***Urinary Tract Infections (UTIs):*** Acute and chronic pyelonephritis, prostatitis, cystitis, epididymitis and chronic complicated or recurrent UTI caused by multi-resistant organisms and/or *Pseudomonas aeruginosa*
- ***Skin and Soft Tissue Infections:*** In surgical and post-operative wound infections, due to gram-negative organisms such as *Enterobacteriaceae* and *Pseudomonas aeruginosa*. Also, useful in infections caused by resistant staphylococci.
- ***Surgical Infections:*** Peritonitis, intra-abdominal abscess, cholangitis, cholecystitis, empyema of gall bladder
- ***Bone and Joint infections:*** Since ciprofloxacin achieves adequate tissue concentrations in bone, it is useful in the management of acute and chronic osteomyelitis
- ***Gynecological Infections:*** Severe pelvic infections caused by susceptible bacteria
- ***Sexually Transmitted Diseases:*** Gonorrhea, including that caused y-beta-lactamase-producing strains. Chancroid caused by *Haemophilus ducreyi*.
- ***Gastrointestinal Infections:*** Effective in the treatment of typhoid and may also eradicate carrier stage. Useful in resistant *Salmonella typhi* infections.
- ***Severe Systemic Infections:*** Septicemia and bacteremia infections in immunocompromised patients.

Posology and Method of Administration

Indications	**Daily Dose (mg)**	**Total Duration of Treatment**
Infections of the lower respiratory tract	500 mg to 750 mg twice daily	7 to 14 days

UTIs	Acute uncomplicated cystitis	250 mg twice daily	3 days
		In pre-menopausal women, 500 mg single dose may be used	
	Complicated cystitis	500 mg twice daily	7 days
	Uncomplicated pyelonephritis	500 mg twice daily	7 days
	Acute complicated pyelonephritis	500 mg to 750 mg twice daily	At least 10 days, it can be continued for longer than 21 days in some specific circumstances (such as abscesses)
	Prostatitis	500 mg to 750 mg twice daily	2 to 4 weeks (acute) to 4 to 6 weeks (chronic)
	Epididymitis	500 mg to 750 mg twice daily	at least 14 days
Genital tract infections	Gonococcal uretritis and cervicitis due to susceptible *Neisseria gonorrhoeae*	250 mg or 500 mg as a single dose	1 day (single dose)
	Pelvic inflammatory diseases	500 mg to 750 mg twice daily	at least 14 days
Gastrointestinal tract infections	Complicated intra–abdominal	500 mg twice daily	7 to 14 days
	Typhoid fever	500 mg twice daily	7 to 10 days
	Infectious diarrhea	500 mg twice daily	5 to 7 days
Infections of the skin and soft tissue		500 mg to 750 mg twice daily	7 to 14 days
Bone and joint infections		500 mg to 750 mg twice daily	Max of 3 months or 4 to 8 weeks
Septicemia, bacteremia and surgical infections: Initial intravenous (I.V.) ciprofloxacin therapy may be followed by oral ciprofloxacin 500 mg to 750 mg twice daily			

Usage

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

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 Ciprofloxacin may be initiated before results of these tests are known; once results become available, appropriate therapy should be continued. As with other drugs, some isolates of *Pseudomonas aeruginosa* may develop resistance fairly rapidly during treatment with ciprofloxacin. Culture and susceptibility testing performed periodically during therapy will provide information not

only on the therapeutic effect of the antimicrobial agent but also on the possible emergence of bacterial resistance.

Important Administration Instructions

With Multivalent Cations

Administer ciprofloxacin at least 2 hours before or 6 hours after magnesium/aluminum antacids; polymeric phosphate binders (for example, sevelamer, lanthanum carbonate) or sucralfate; (didanosine) chewable/buffered tablets or pediatric powder for oral solution; other highly buffered drugs; or other products containing calcium, iron or zinc.

With Dairy Products

Concomitant administration of ciprofloxacin with dairy products (such as milk or yogurt) or calcium-fortified juices alone should be avoided since decreased absorption is possible; however, ciprofloxacin may be taken with a meal that contains these products.

Hydration of Patients Receiving Ciprofloxacin

Assure adequate hydration of patients receiving ciprofloxacin to prevent the formation of highly concentrated urine. Crystalluria has been reported with quinolones. Instruct the patient about the appropriate ciprofloxacin administration.

Use in Special Populations

Geriatric Patients

Elderly patients should receive a dose selected according to the severity of the infection and the patient's creatinine clearance.

Patients with Renal Impairment

The total daily dosage should be halved in patients with severe renal impairment (creatinine clearance ≤20 mL/min).

In patients with complicated UTI (cUTI) and acute uncomplicated pyelonephritis with a creatinine clearance of ≤30 mL/min, the dose of **CIPLOX Tablets** should be reduced from 1,000 mg to 500 mg daily.

For patients on hemodialysis or peritoneal dialysis, administer **CIPLOX Tablets** after the dialysis procedure is completed (maximum dose should be ciprofloxacin 500 mg every 24 hours).

For patients on continuous ambulatory peritoneal dialysis (CAPD), the maximum dose should be 500 mg every 24 hours

Recommended starting and maintenance doses for patients with renal impairment

Creatinine Clearance [mL/min/1.73 m^2]	**Serum Creatinine [µmol/L]**	**Oral Dose [mg]**
>60	<124	See Usual Dosage
30 to 60	124 to 168	250 to 500 mg every 12 h

≤30	≥169	250 to 500 mg every 24 h
Patients on hemodialysis	>169	250 to 500 mg every 24 h (after dialysis)
Patients on peritoneal dialysis	>169	250 to 500 mg every 24 h

h = hour

In patients with hepatic impairment, no dose adjustment is required. Dosing in children with impaired renal and/or hepatic function has not been studied.

Administration

CIPLOX Tablets should be taken whole and not split, crushed, or chewed.

If taken on an empty stomach, the active substance is absorbed more rapidly.

CIPLOX Tablets should be administered at least 2 hours before or 6 hours after antacids containing magnesium or aluminum, polymeric phosphate binders (for example, sevelamer, lanthanum carbonate), as well as sucralfate, didanosine chewable/buffered tablets or pediatric powder, other highly buffered drugs, metal cations such as iron, and multivitamin preparations with zinc

Concomitant administration of **CIPLOX Tablets** with dairy products (such as milk or yogurt) or mineral-fortified fruit-juice (e.g. calcium-fortified orange juice) or with calcium-fortified products alone should be avoided since decreased absorption is possible.

Adequate hydration of patients receiving **CIPLOX Tablets** should be maintained to prevent the formation of highly concentrated urine. Crystalluria has been reported with quinolones

Contraindications

- Ciprofloxacin is contraindicated in individual with history of hypersensitivity to ciprofloxacin or any other quinolone derivative/any member of the quinolone class of antibacterials, or any of the product components.
- Concomitant administration with tizanidine is contraindicated.
- Not recommended in children below the age of 18 years.

Special Warnings and Precautions for Use

The use of ciprofloxacin should be avoided in patients who have experienced serious adverse reactions in the past when using quinolone- or fluoroquinolone-containing products. Treatment of these patients with ciprofloxacin should only be initiated in the absence of alternative treatment options and after careful benefit/risk assessment.

Disabling and Potentially Irreversible Serious Adverse Reactions, Including Tendinitis and Tendon Rupture, Peripheral Neuropathy, and CNS Effects

Fluoroquinolones, including ciprofloxacin, have been associated with disabling and potentially irreversible serious adverse reactions from different body systems that can occur together in the same patient. Commonly seen adverse reactions include tendinitis, tendon rupture, arthralgia, myalgia, peripheral neuropathy, and CNS effects (hallucinations, anxiety, depression, insomnia, severe headaches, and confusion). These reactions can occur within hours to weeks after starting ciprofloxacin. Patients of any age or without pre-existing risk factors have experienced these adverse

reactions

Discontinue ciprofloxacin immediately at the first signs or symptoms of any serious adverse reaction. In addition, avoid the use of fluoroquinolones, including ciprofloxacin, in patients who have experienced any of these serious adverse reactions associated with fluoroquinolones.

Severe Infections and Mixed Infections with Gram-Positive and Anaerobic Pathogens

Ciprofloxacin monotherapy is not suited for treatment of severe infections and infections that might be due to gram-positive or anaerobic pathogens. In such infections ciprofloxacin, must be co-administered with other appropriate antibacterial agents.

Streptococcal Infections (Including Streptococcus pneumonia)

Ciprofloxacin is not recommended for the treatment of streptococcal infections due to inadequate efficacy.

Genital Tract Infections

Gonococcal uretritis, cervicitis, epididymo-orchitis and pelvic inflammatory disease may be caused by fluoroquinolones resistant *Neisseria gonorrhoeae* isolates. Therefore, ciprofloxacin should be administered for the treatment of gonococcal uretritis or cervicitis only if ciprofloxacin resistant *Neisseria gonorrhoeae* can be excluded. For epididymo-orchitis and pelvic inflammatory diseases, empirical ciprofloxacin should only be considered in combination with another appropriate antibacterial agent (e.g. a cephalosporin) unless ciprofloxacin-resistant *Neisseria gonorrhoeae* can be excluded. If clinical improvement is not achieved after 3 days of treatment, the therapy should be reconsidered.

UTIs

Resistance to fluoroquinolones of *Escherichia coli* – the most common pathogen involved in urinary tract infections – varies across the European Union. Prescribers are advised to take into account the local prevalence of resistance in *Escherichia coli* to fluoroquinolones. The single dose of ciprofloxacin that may be used in uncomplicated cystitis in pre-menopausal women is expected to be associated with lower efficacy than the longer treatment duration. This is all the more to be taken into account as regards the increasing resistance level of *Escherichia coli* to quinolones.

Inhalational Anthrax

Use in humans is based on *in vitro* susceptibility data and on animal experimental data together with limited human data. Treating physicians should refer to national and/or international consensus documents regarding the treatment of anthrax.

Broncho-Pulmonary Infections in Cystic Fibrosis

Clinical trials have included children and adolescents aged 5 to 17 years. More limited experience is available in treating children between 1 and 5 years of age.

Complicated UTIs and Pyelonephritis

Ciprofloxacin treatment of UTIs should be considered when other treatments cannot be used, and should be based in the results of the microbiological documentation. Clinical trials have included children and adolescents aged 1 to 17 years.

Tendinitis and Tendon Rupture

Fluoroquinolones, including ciprofloxacin, have been associated with an increased risk of tendinitis and tendon rupture in all ages. This adverse reaction most frequently involves the Achilles tendon, and has also been reported with the rotator cuff (the shoulder), the hand, the biceps, the thumb, and other tendons. Tendinitis or tendon rupture can occur, within hours or days of starting ciprofloxacin, or as long as several months after completion of fluoroquinolone therapy. Tendinitis and tendon rupture can occur bilaterally.

The risk of developing fluoroquinolone-associated tendinitis and tendon rupture is increased in patients over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants. Other factors 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.

Discontinue ciprofloxacin immediately if the patient experiences pain, swelling, inflammation or rupture of a tendon. Avoid fluoroquinolones, including ciprofloxacin, in patients who have a history of tendon disorders or have experienced tendinitis or tendon rupture.

Peripheral Neuropathy

Fluoroquinolones, including ciprofloxacin have been associated with an increased risk of peripheral neuropathy. Cases of sensory or sensorimotor axonal polyneuropathy affecting small and/or large axons resulting in paresthesias, hypesthesias, dysesthesias and weakness have been reported in patients receiving fluoroquinolones, including ciprofloxacin. Symptoms may occur soon after initiation of ciprofloxacin and may be irreversible in some patients.

Discontinue ciprofloxacin immediately if the patient experiences symptoms of peripheral neuropathy, including pain, burning, tingling, numbness, and/or weakness, or other alterations in sensations including light touch, pain, temperature, position sense and vibratory sensation, and/or motor strength in order to minimize the development of an irreversible condition. Avoid fluoroquinolones, including ciprofloxacin, in patients who have previously experienced peripheral neuropathy.

CNS Effects

Psychiatric Adverse Reactions

Fluoroquinolones, including ciprofloxacin, have been associated with an increased risk of psychiatric adverse reactions, including toxic psychosis, psychotic reactions progressing to suicidal ideations/thoughts, hallucinations, or paranoia; depression, or self-injurious behavior such as attempted or completed suicide; anxiety, agitation, or nervousness; confusion, delirium, disorientation, or disturbances in attention; insomnia or nightmares; memory impairment. These reactions may occur following the first dose. Advise patients receiving ciprofloxacin to inform their healthcare provider immediately if these reactions occur, discontinue the drug, and institute appropriate care.

Other Adverse Reactions

Fluoroquinolones, including ciprofloxacin, have been associated with an increased risk of seizures (convulsions), increased intracranial pressure (pseudotumor cerebri), dizziness, and tremors. Ciprofloxacin, like other fluoroquinolones, is known to trigger seizures or lower the seizure

threshold. Cases of status epilepticus have been reported. As with all fluoroquinolones, use ciprofloxacin with caution in epileptic patients and patients with known or suspected CNS disorders that may predispose to seizures or lower the seizure threshold (e.g., severe cerebral arteriosclerosis, previous history of convulsion, reduced cerebral blood flow, altered brain structure, or stroke), or in the presence of other risk factors that may predispose to seizures or lower the seizure threshold (e.g., certain drug therapy, renal dysfunction). If seizures occur, discontinue ciprofloxacin and institute appropriate care.

Exacerbation of Myasthenia Gravis

Fluoroquinolones, including ciprofloxacin, have neuromuscular-blocking activity and may exacerbate muscle weakness in patients with myasthenia gravis. Postmarketing serious adverse reactions, including deaths and requirement for ventilatory support, have been associated with fluoroquinolone use in patients with myasthenia gravis. Avoid ciprofloxacin in patients with known history of myasthenia gravis.

Other Serious, and Sometimes Fatal, Adverse Reactions

Other serious, and sometimes fatal, adverse reactions, some due to hypersensitivity, and some due to uncertain etiology, have been reported in patients receiving therapy with quinolones, including ciprofloxacin. These events may be severe and generally occur following the administration of multiple doses. Clinical manifestations may include one or more of the following:

- Fever, rash, or severe dermatologic reactions (e.g., toxic epidermal necrolysis, Stevens-Johnson syndrome)
- Vasculitis; arthralgia; myalgia; serum sickness
- Allergic pneumonitis
- Interstitial nephritis; acute renal insufficiency or failure
- Hepatitis; jaundice; acute hepatic necrosis or failure
- Anemia, including hemolytic and aplastic; thrombocytopenia, including thrombotic thrombocytopenic purpura; leukopenia; agranulocytosis; pancytopenia; and/or other hematologic abnormalities.

Discontinue ciprofloxacin immediately at the first appearance of a skin rash, jaundice, or any other sign of hypersensitivity and supportive measures instituted

Hypersensitivity Reactions

Serious, and occasionally fatal, hypersensitivity (anaphylactic) reactions, some following the first dose, have been reported in patients receiving fluoroquinolone therapy, including ciprofloxacin. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, tingling, pharyngeal or facial edema, dyspnea, urticaria, and itching. Only a few patients had a history of hypersensitivity reactions. Serious anaphylactic reactions require immediate emergency treatment with epinephrine and other resuscitation measures, including oxygen, I.V. fluids, intravenous antihistamines, corticosteroids, pressor amines, and airway management, including intubation, as indicated.

Hepatotoxicity

Cases of severe hepatotoxicity, including hepatic necrosis, life-threatening hepatic failure, and fatal events, have been reported with ciprofloxacin. Acute liver injury is rapid in onset (range: 1 to 39 days), and is often associated with hypersensitivity. The pattern of injury can be hepatocellular,

cholestatic, or mixed. Most patients with fatal outcomes were older than 55 years. In the event of any signs and symptoms of hepatitis (such as anorexia, jaundice, dark urine, pruritus, or tender abdomen), discontinue treatment immediately.

There can be a temporary increase in transaminases, alkaline phosphatase or cholestatic jaundice, especially in patients with previous liver damage, who are treated with ciprofloxacin.

Risk of Aortic Aneurysm and Dissection

Epidemiologic studies report an increased risk of aortic aneurysm and dissection after intake of fluoroquinolones, particularly in the older population. Therefore, fluoroquinolones should only be used after careful benefit–risk assessment and after consideration of other therapeutic options in patients with positive family history of aneurysm disease, or in patients diagnosed with pre-existing aortic aneurysm and/or aortic dissection, or in presence of other risk factors or conditions predisposing for aortic aneurysm and dissection (e.g., Marfan syndrome, vascular Ehlers-Danlos syndrome, Takayasu arteritis, giant cell arteritis, Behcet's disease, hypertension, known atherosclerosis). In case of sudden abdominal, chest or back pain, patients should be advised to immediately consult a physician in an emergency department.

Serious Adverse Reactions with Concomitant Theophylline Use

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. Instances of nausea, vomiting, tremor, irritability, or palpitation have also occurred.

Although similar serious adverse reactions have been reported in patients receiving theophylline alone, the possibility that these reactions may be potentiated by ciprofloxacin cannot be eliminated. If concomitant use cannot be avoided, monitor serum levels of theophylline and adjust dosage as appropriate

Clostridium difficile-associated Diarrhea

Clostridium difficile (*C. difficile*)-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including ciprofloxacin, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

C. difficile produces toxins A and B, which contribute to the development of CDAD. Hypertoxin-producing isolates of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibacterial use. Careful medical history is necessary since CDAD has been reported to occur over 2 months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibacterial use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibacterial treatment of *C. difficile*, and institute surgical evaluation as clinically indicated.

Glucose-6-Phosphate Dehydrogenase Deficiency

Hemolytic reactions have been reported with ciprofloxacin in patients with glucose-6-phosphate dehydrogenase deficiency. Ciprofloxacin should be avoided in these patients unless the potential

benefit is considered to outweigh the possible risk. In this case, potential occurrence of hemolysis should be monitored.

Prolongation of the QT Interval

Some fluoroquinolones, including ciprofloxacin, have been associated with prolongation of the QT interval on the electrocardiogram and cases of arrhythmia. Cases of *torsades de pointes* have been reported during postmarketing surveillance in patients receiving fluoroquinolones, including ciprofloxacin.

Avoid ciprofloxacin in patients with known prolongation of the QT interval, risk factors for QT prolongation or *torsades de pointes* (e.g., congenital long QT syndrome, uncorrected electrolyte imbalance, such as hypokalemia or hypomagnesemia and cardiac disease, such as heart failure, myocardial infarction, or bradycardia), and patients receiving Class IA antiarrhythmic agents (quinidine, procainamide), or Class III antiarrhythmic agents (amiodarone, sotalol), tricyclic antidepressants, macrolides, and antipsychotics. Elderly patients may also be more susceptible to drug-associated effects on the QT interval.

Musculoskeletal Disorders in Pediatric Patients and Arthropathic Effects in Animals

Ciprofloxacin is indicated in pediatric patients (less than 18 years of age) only for cUTI, prevention of inhalational anthrax (post-exposure), and plague. An increased incidence of adverse reactions compared to controls, including reactions related to joints and/or surrounding tissues, has been observed.

In pre-clinical studies, oral administration of ciprofloxacin caused lameness in immature dogs. Histopathological examination of the weight-bearing joints of these dogs revealed permanent lesions of the cartilage. Related quinolone-class drugs also produce erosions of cartilage of weight-bearing joints and other signs of arthropathy in immature animals of various species.

Photosensitivity/Phototoxicity

Moderate-to-severe photosensitivity/phototoxicity reactions, the latter of which may manifest as exaggerated sunburn reactions (e.g., burning, erythema, exudation, vesicles, blistering, edema) involving areas exposed to light (typically the face, “V” area of the neck, extensor surfaces of the forearms, dorsa of the hands), can be associated with the use of quinolones including ciprofloxacin after sun or ultraviolet (UV) light exposure. Therefore, avoid excessive exposure to these sources of light. Discontinue ciprofloxacin if phototoxicity occurs.

Development of Drug-resistant Bacteria

Prescribing ciprofloxacin tablets in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Resistance

During or following a course of treatment with ciprofloxacin bacteria that demonstrate resistance to ciprofloxacin may be isolated, with or without a clinically apparent superinfection. There may be a particular risk of selecting for ciprofloxacin resistant bacteria during extended durations of treatment and when treating nosocomial infections and/or infections caused by *Staphylococcus* and *Pseudomonas* species.

Potential Risks with Concomitant Use of Drugs Metabolized by Cytochrome (CY) P450 1A2 Enzymes

Ciprofloxacin is an inhibitor of the hepatic CYP1A2 enzyme pathway. Co-administration of ciprofloxacin and other drugs primarily metabolized by CYP1A2 (e.g., theophylline, methylxanthines, caffeine, tizanidine, ropinirole, clozapine, olanzapine and zolpidem) results in increased plasma concentrations of the co-administered drug and could lead to clinically significant pharmacodynamic adverse reactions of the co-administered drug.

Interference with Timely Diagnosis of Syphilis

Ciprofloxacin has not been shown to be effective in the treatment of syphilis. Antimicrobial agents used in high dose for short periods of time to treat gonorrhea may mask or delay the symptoms of incubating syphilis. Perform a serologic test for syphilis in all patients with gonorrhea at the time of diagnosis. Perform follow-up serologic test for syphilis three months after ciprofloxacin treatment.

Crystalluria

Crystals of ciprofloxacin have been observed rarely in the urine of human subjects but more frequently in the urine of laboratory animals, which is usually alkaline. Crystalluria related to ciprofloxacin has been reported only rarely in humans because human urine is usually acidic. Avoid alkalinity of the urine in patients receiving ciprofloxacin. Hydrate patients well to prevent the formation of highly concentrated urine.

Blood Glucose Disturbances

Fluoroquinolones, including ciprofloxacin, have been associated with disturbances of blood glucose, including symptomatic hyperglycemia and hypoglycemia, usually in diabetic patients receiving concomitant treatment with an oral hypoglycemic agent (e.g., glyburide) or with insulin. In these patients, careful monitoring of blood glucose is recommended.

Severe cases of hypoglycemia resulting in coma or death have been reported. If a hypoglycemic reaction occurs in a patient being treated with ciprofloxacin, discontinue ciprofloxacin and initiate appropriate therapy immediately.

Interaction with Tests

The *in vitro* activity of ciprofloxacin against *Mycobacterium tuberculosis* might give false-negative bacteriological test results in specimens from patients currently taking ciprofloxacin.

Vision Disorders

If vision becomes impaired or any effects on the eyes are experienced, an eye specialist should be consulted immediately

Drug Interactions

Ciprofloxacin is an inhibitor of human CYP450 1A2 (CYP1A2)-mediated metabolism. Co-administration of ciprofloxacin with other drugs primarily metabolized by CYP1A2 results in increased plasma concentrations of these drugs and could lead to clinically significant adverse events of the co-administered drug.

Drugs Known to Prolong QT Interval

Ciprofloxacin, like other fluoroquinolones, should be used with caution in patients receiving drugs known to prolong the QT interval (e.g., Class IA and III anti-arrhythmics, tricyclic antidepressants, macrolides, antipsychotics)

Chelation Complex Formation

The simultaneous administration of ciprofloxacin (oral) and multivalent cation-containing drugs and mineral supplements (e.g., calcium, magnesium, aluminium, iron), polymeric phosphate binders (e.g., sevelamer or lanthanum carbonate), sucralfate or antacids, and highly buffered drugs (e.g., didanosine tablets) containing magnesium, aluminium, or calcium reduces the absorption of ciprofloxacin. Consequently, ciprofloxacin should be administered either 1 to 2 hours before or at least 4 hours after these preparations.

The restriction does not apply to antacids belonging to the class of H2 receptor blockers.

Food and Dairy Products

Dietary calcium as part of a meal does not significantly affect absorption. However, the concurrent administration of dairy products or mineral-fortified drinks alone (e.g., milk, yoghurt, calcium-fortified orange juice) with ciprofloxacin should be avoided because absorption of ciprofloxacin may be reduced

Effects of Ciprofloxacin on Other Medicinal Products

Phenytoin

Simultaneous administration of ciprofloxacin and phenytoin may result in increased or reduced serum levels of phenytoin; hence, monitoring of drug levels is recommended.

Vitamin K Antagonists

Simultaneous administration of ciprofloxacin with vitamin K antagonists may augment its anti-coagulant effects. 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 the International Normalised Ratio (INR) is difficult to assess. It is recommended that the INR should be monitored frequently during and shortly after co-administration of ciprofloxacin with a vitamin K antagonist (e.g., warfarin, acenomoumarol, phenprocoumon or fluindione).

Agomelatine

In clinical studies, it was demonstrated that fluvoxamine, as a strong inhibitor of the CYP450 1A2 isoenzyme, markedly inhibits the metabolism of agomelatine resulting in a 60-fold increase of agomelatine exposure. Although no clinical data are available for a possible interaction with ciprofloxacin, a moderate inhibitor of CYP450 1A2, similar effects can be expected upon concomitant administration (see **Special Warnings and Precautions for Use, Potential Risks with Concomitant Use of Drugs Metabolized by Cytochrome (CY) P450 1A2 Enzymes**).

Table 1: Drugs That Are Affected by and Affecting Ciprofloxacin

Drugs That Are Affected by Ciprofloxacin		
Drug(s)	**Recommendation**	**Comments**

Tizanidine	Contraindicated	Concomitant administration of tizanidine and ciprofloxacin is contraindicated due to the potentiation of hypotensive and sedative effects of tizanidine
Theophylline	Avoid use (plasma exposure likely to be increased and prolonged)	Concurrent administration of ciprofloxacin with theophylline may result in increased risk of a patient developing CNS or other adverse reactions. If concomitant use cannot be avoided, monitor serum levels of theophylline and adjust dosage as appropriate.
Drugs known to prolong QT interval	Avoid use	Ciprofloxacin may further prolong the QT interval in patients receiving drugs known to prolong the QT interval (e.g., class IA or III antiarrhythmics, tricyclic antidepressants, macrolides, antipsychotics)
Oral antidiabetic drugs	Use with caution Glucose-lowering effect potentiated	Hypoglycemia, sometimes severe, has been reported when ciprofloxacin and oral antidiabetic agents, mainly sulfonylureas (e.g., glyburide, glimepiride), were co-administered, presumably by intensifying the action of the oral antidiabetic agent. Fatalities have been reported. Monitor blood glucose when ciprofloxacin is co-administered with oral antidiabetic drugs.
Phenytoin	Use with caution Altered serum levels of phenytoin (increased and decreased)	To avoid the loss of seizure control associated with decreased phenytoin levels and to prevent phenytoin overdose-related adverse reactions upon ciprofloxacin discontinuation in patients receiving both agents, monitor phenytoin therapy, including phenytoin serum concentration during and shortly after co-administration of ciprofloxacin with phenytoin.
Cyclosporine	Use with caution (transient elevations in serum creatinine)	Monitor renal function (in particular, serum creatinine) when ciprofloxacin is co-administered with cyclosporine.
Anticoagulant drugs	Use with caution (increase in anticoagulant effect)	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 is difficult to assess. Monitor prothrombin time and INR frequently during and shortly after co-administration of ciprofloxacin with an oral anticoagulant (e.g., warfarin).
Methotrexate	Use with caution (inhibition of methotrexate renal tubular transport, potentially leading to increased methotrexate plasma levels)	Potential increase in the risk of methotrexate associated toxic reactions. Therefore, carefully monitor patients under methotrexate therapy when concomitant ciprofloxacin therapy is indicated.

Ropinirole	Use with caution	Monitoring for ropinirole-related adverse reactions and appropriate dose adjustment of ropinirole is recommended during and shortly after co-administration with ciprofloxacin
Clozapine	Use with caution	Careful monitoring of clozapine-associated adverse reactions and appropriate adjustment of clozapine dosage during and shortly after co-administration with ciprofloxacin are advised.
Non-steroidal anti-inflammatory drugs (NSAIDs)	Use with caution	NSAIDs (but not acetyl salicylic acid) in combination with very high doses of quinolones have been shown to provoke convulsions in pre-clinical studies and in postmarketing.
Sildenafil	Use with caution (two-fold increase in exposure)	Monitor for sildenafil toxicity.
Duloxetine	Avoid use (five-fold increase in duloxetine exposure)	If unavoidable, monitor for duloxetine toxicity.
Caffeine/Xanthine Derivatives	Use with caution (reduced clearance resulting in elevated levels and prolongation of serum half-life)	Ciprofloxacin inhibits the formation of paraxanthine after caffeine administration (or pentoxifylline-containing products). Monitor for xanthine toxicity and adjust dose as necessary.
Zolpidem	Avoid USE	Co-administration with ciprofloxacin may increase blood levels of zolpidem—concurrent use is not recommended.
Drug(s) Affecting Pharmacokinetics of Ciprofloxacin		
Antacids, sucralfate, multivitamins and other products containing multivalent cations (magnesium/aluminum antacids; polymeric phosphate binders (for example, sevelamer, lanthanum carbonate); sucralfate; didanosine chewable/buffered tablets or pediatric powder; other highly buffered drugs; or products containing calcium, iron, or zinc and dairy products)	Ciprofloxacin should be taken at least 2 hours before or 6 hours after administration of multivalent cation-containing products	Cause decrease in ciprofloxacin absorption, resulting in lower serum and urine levels considerably lower than desired for concurrent administration of these agents with ciprofloxacin.
Probenecid	Use with caution (interferes with renal tubular secretion of ciprofloxacin and increases ciprofloxacin serum levels)	Potentiation of ciprofloxacin toxicity may occur.

Use in Special Populations

Pregnant Women

Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. Ciprofloxacin should not be used during pregnancy unless the potential benefit justifies the potential risk to both the fetus and the mother. An expert review of published data on experiences with ciprofloxacin use during pregnancy by TERIS—the Teratogen Information System—concluded that therapeutic doses during pregnancy are unlikely to pose a substantial teratogenic risk (quantity and quality of data = fair), but the data are insufficient to state that there is no risk.

A controlled prospective observational study followed 200 women exposed to fluoroquinolones (52.5% exposed to ciprofloxacin and 68% first-trimester exposures) during gestation. *In utero* exposure to fluoroquinolones during embryogenesis was not associated with increased risk of major malformations. The reported rates of major congenital malformations were 2.2% for the fluoroquinolone group and 2.6% for the control group (background incidence of major malformations is 1 to 5%). Rates of spontaneous abortions, prematurity and low-birth-weight did not differ between the groups and there were no clinically significant musculoskeletal dysfunctions up to 1 year of age in the ciprofloxacin exposed children.

Another prospective follow-up study reported on 549 pregnancies with fluoroquinolone exposure (93% first-trimester exposures). There were 70 ciprofloxacin exposures, all within the first trimester. The malformation rates among live-born babies exposed to ciprofloxacin and to fluoroquinolones overall were both within background incidence ranges. No specific patterns of congenital abnormalities were found. The study did not reveal any clear adverse reactions due to in utero exposure to ciprofloxacin.

No differences in the rates of prematurity, spontaneous abortions, or birth weight were seen in women exposed to ciprofloxacin during pregnancy. However, these small postmarketing epidemiology studies, of which most experience is from short-term first-trimester exposure, are insufficient to evaluate the risk for less common defects or to permit reliable and definitive conclusions regarding the safety of ciprofloxacin in pregnant women and their developing fetuses.

Reproduction studies have been performed in rats and mice using oral doses up to 100 mg/kg (0.6 and 0.3 times the maximum daily human dose based upon body surface area, respectively) and have revealed no evidence of harm to the fetus due to ciprofloxacin. In rabbits, oral ciprofloxacin dose levels of 30 and 100 mg/kg (approximately 0.4- and 1.3-times the highest recommended therapeutic dose based upon body surface area) produced gastrointestinal toxicity, resulting in maternal weight loss and an increased incidence of abortion, but no teratogenicity was observed at either dose level. After I.V. administration of doses up to 20 mg/kg (approximately 0.3-times the highest recommended therapeutic dose based upon body surface area), no maternal toxicity was produced and no embryotoxicity or teratogenicity was observed.

Lactating Women

Ciprofloxacin is excreted in human milk. The amount of ciprofloxacin absorbed by the nursing infant is unknown. Because of the potential risk of serious adverse reactions (including articular damage) in infants nursing from mothers taking ciprofloxacin, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Patients

Although effective in clinical trials, ciprofloxacin is not a drug of first choice in the pediatric population due to an increased incidence of adverse reactions compared with controls. Quinolones, including ciprofloxacin, cause arthropathy (arthralgia, arthritis), in juvenile animals.

Geriatric Patients

Geriatric patients are at increased risk for developing severe tendon disorders including tendon rupture when being treated with a fluoroquinolone such as ciprofloxacin. This risk is further increased in patients receiving concomitant corticosteroid therapy. Tendinitis or tendon rupture can involve the Achilles tendon, hand, shoulder, or other tendon sites and can occur during or after completion of therapy; cases occurring up to several months after fluoroquinolone treatment have been reported. Caution should be used when prescribing ciprofloxacin to elderly patients especially those on corticosteroids. Patients should be informed of this potential adverse reaction and advised to discontinue ciprofloxacin and contact their healthcare provider if any symptoms of tendinitis or tendon rupture occur.

Epidemiologic studies report an increased rate of aortic aneurysm and dissection within 2 months following use of fluoroquinolones, particularly in elderly patients

In a retrospective analysis of 23 multiple-dose controlled clinical trials of ciprofloxacin encompassing over 3,500 ciprofloxacin-treated patients, 25% of patients were greater than or equal to 65 years of age and 10% were greater than or equal to 75 years of age. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals on any drug therapy cannot be ruled out. Ciprofloxacin is known to be substantially excreted by the kidneys, and the risk of adverse reactions may be greater in patients with impaired renal function. No alteration of dosage is necessary for patients greater than 65 years of age with normal renal function. However, since some older individuals experience reduced renal function by virtue of their advanced age, care should be taken in dose selection for elderly patients, and renal function monitoring may be useful in these patients

In general, elderly patients may be more susceptible to drug-associated effects on the QT interval. Therefore, precaution should be taken when using ciprofloxacin with concomitant drugs that can result in prolongation of the QT interval (e.g., class IA or class III antiarrhythmics) or in patients with risk factors for *torsades de pointes* (e.g., known QT prolongation, uncorrected hypokalemia)

Patients with 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 alternative pathways of drug elimination appear to compensate for the reduced renal excretion in patients with renal impairment. Nonetheless, some modification of dosage is recommended, particularly for patients with severe renal dysfunction.

Patients with Hepatic Impairment

In preliminary studies in patients with stable chronic liver cirrhosis, no significant changes in ciprofloxacin pharmacokinetics have been observed. The pharmacokinetics of ciprofloxacin in patients with acute hepatic insufficiency, have not been studied.

Effects on the Ability to Drive and Use Machines

Due to its neurological effects, ciprofloxacin may affect reaction time. Thus, the ability to drive or to operate machinery may be impaired.

Undesirable Effects

The following serious and otherwise important adverse drug reactions are discussed in greater detail in other sections of the labeling (see **Special Warnings and Precautions for Use**):

- Disabling and Potentially Irreversible Serious Adverse Reactions
- Tendinitis and Tendon Rupture
- Peripheral Neuropathy
- CNS Effects
- Exacerbation of Myasthenia Gravis
- Other Serious, and Sometimes Fatal, Adverse Reactions
- Hypersensitivity Reactions
- Hepatotoxicity
- Serious Adverse Reactions with Concomitant Theophylline
- *Clostridium difficile*-associated Diarrhea
- Prolongation of the QT Interval
- Musculoskeletal Disorders in Pediatric Patients
- Photosensitivity/Phototoxicity
- Development of Drug-resistant Bacteria

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adult Patients

During clinical investigations with oral and parenteral ciprofloxacin, 49,038 patients received courses of the drug. The most frequently reported adverse reactions, from clinical trials of all formulations, all dosages, all drug-therapy durations, and for all indications of ciprofloxacin therapy were nausea (2.5%), diarrhea (1.6%), liver function tests abnormal (1.3%), vomiting (1%), and rash (1%).

Medically Important Adverse Reactions That Occurred In Less Than 1% of Ciprofloxacin Patients

System Organ Class	Adverse Reactions
Body as a Whole	Headache Abdominal pain/discomfort Pain
Cardiovascular	Syncope Angina pectoris Myocardial infarction Cardiopulmonary arrest Tachycardia Hypotension

CNS	Restlessness Dizziness Insomnia Nightmares Hallucinations Paranoia Psychosis (toxic) Manic reaction Irritability Tremor Ataxia Seizures (including status epilepticus) Malaise Anorexia Phobia Depersonalization Depression (potentially culminating in self-injurious behavior (such as suicidal ideations/thoughts and attempted or completed suicide) Paresthesia Abnormal gait Migraine
Gastrointestinal	Intestinal perforation Gastrointestinal bleeding Cholestatic jaundice Hepatitis Pancreatitis
Hemic/Lymphatic	Petechia
Metabolic/Nutritional	Hyperglycemia Hypoglycemia
Musculoskeletal	Arthralgia Joint stiffness Muscle weakness
Renal/Urogenital	Interstitial nephritis Renal failure
Respiratory	Dyspnea Laryngeal edema Hemoptysis Bronchospasm
Skin/Hypersensitivity	Anaphylactic reactions, including life-threatening anaphylactic shock Erythema multiforme/Stevens-Johnson syndrome Exfoliative dermatitis Toxic epidermal necrolysis Pruritus Urticaria Photosensitivity/phototoxicity reaction Flushing Fever Angioedema Erythema nodosum Sweating

Special Senses	Blurred vision Disturbed vision (chromatopsia and photopsia) Decreased visual acuity Diplopia Tinnitus Hearing loss Bad taste

In randomized, double-blind controlled clinical trials comparing ciprofloxacin tablets [500 mg two times daily (BID)] to cefuroxime axetil (250 to 500 mg BID) and to clarithromycin (500 mg BID) in patients with respiratory tract infections, ciprofloxacin demonstrated a CNS adverse reaction profile comparable to the control drugs.

The most commonly reported adverse drug reactions are nausea and diarrhoea.

Adverse drug reactions derived from clinical studies and postmarketing surveillance with ciprofloxacin (oral, I.V., and sequential therapy) sorted by categories of frequency are listed below. The frequency analysis takes into account data from both oral and I.V. administration of ciprofloxacin.

System Organ Class	**Common** ≥1/100 to <1/10	**Uncommon** ≥1/1,000 to <1/100	**Rare** ≥1/10,000 to <1/1,000	**Very Rare** < 1/10,000	**Frequency Not Known** (cannot be estimated from available data)
Infections and Infestations		Mycotic superinfections			
Blood and Lymphatic System Disorders		Eosinophilia	Leukopenia Anemia Neutropenia Leukocytosis Thrombocytopenia Thrombocytemia	Hemolytic anemia Agranulocytosis Pancytopenia (life-threatening) Bone marrow depression (life-threatening)	
Immune System Disorders			Allergic reaction Allergic edema/ angioedema	Anaphylactic reaction Anaphylactic shock (life-threatening) Serum sickness-like reaction	
Endocrine disorders					Syndrome of inappropriate secretion of antidiuretic hormone (SIADH)
Metabolism and Nutrition Disorders		Decreased appetite	Hyperglycemia Hypoglycemia		Hypogly-cemic coma

Psychiatric Disorders*		Psychomotor hyperactivity/agitation	Confusion and disorientation Anxiety reaction Abnormal dreams Depression (potentially culminating in suicidal ideations/ thoughts or suicide attempts and completed suicide) Hallucinations	Psychotic reactions (potentially culminating in suicidal ideations/ thoughts or suicide attempts and completed suicide)	Mania Hypomania
Nervous System Disorders*		Headache Dizziness Sleep disorders Taste disorders	Paresthesia Dysesthesia Hypesthesia Tremor Seizures (including status epilepticus) Vertigo	Migraine Disturbed coordination Gait disturbance Olfactory nerve disorders Intracranial hypertension and pseudotumor cerebri	Peripheral neuropathy and polyneuro-pathy
Eye Disorders*			Visual disturbances (e.g., diploia)	Visual color distortions	
Ear and Labyrinth Disorders*			Tinnitus Hearing loss/hearing impaired		
Cardiac Disorders			Tachycardia		Ventricular arrhythmia and *torsades de pointes* (reported predominantly in patients with risk factors for QT prolongation), ECG QT prolonged
Vascular Disorders			Vasodilatation Hypotension Syncope	Vasculitis	

Respiratory, Thoracic and Mediastinal Disorders			Dyspnea (including asthmatic condition)		
Gastrointestinal Disorders	Nausea Diarrhoea	Vomiting Gastrointestinal and abdominal pains Dyspepsia Flatulence	Antibiotic-associated diarrhea (including pseudo-membraneous colitis)	Pancreatitis	
Hepatobiliary Disorders		Increase in transaminases	Hepatic impairment Cholestatic icterus		
		Increased bilirubin	Hepatitis	Liver necrosis (very rarely progressing to life-threatening hepatic failure)	
Skin and Subcutaneous Tissue Disorders		Rash Pruritus Urticaria	Photosensitivity reactions	Petechiae Erythema multiforme Erythema nodosum Stevens- Johnson syndrome (potentially life-threatening) Toxic epidermal necrolysis (potentially life-threatening)	Acute generalised exanthe-matous pustulosis (AGEP) DRESS
Musculo-skeletal, Connective Tissue and Bone Disorders*		Musculo-skeletal pain (e.g., extremity pain, back pain, chest pain) Arthralgia	Myalgia Arthritis Increased muscle tone and cramping	Muscular weakness Tendinitis Tendon rupture (predominantly Achilles tendon) Exacerbation of symptoms of myasthenia gravis	
Renal and Urinary Disorders		Renal impairment	Renal failure Haematuria Crystalluria Tubulointerstitial nephritis		
General Disorders and Administration Site Conditions*		Asthenia Fever	Edema Sweating (hyperhidrosis)		
Investigations		Increase in blood alkaline phosphatase	Increased amylase		INR increased (in patients treated with vitamin K antagonists)

* Very rare cases of prolonged (up to months or years), disabling and potentially irreversible serious drug reactions affecting several, sometimes multiple, system organ classes and senses (including reactions such as tendonitis, tendon rupture, arthralgia, pain in extremities, gait disturbance, neuropathies associated with paresthesia, depression, fatigue, memory impairment, sleep disorders, and impairment of hearing, vision, taste and smell) have been reported in association with the use of quinolones and fluoroquinolones in some cases irrespective of pre-existing risk factors.

Paediatric Patients

The incidence of arthropathy, mentioned above, is referring to data collected in studies with adults. In children, arthropathy is reported to occur commonly.

Postmarketing Experience

The following adverse reactions have been reported from worldwide marketing experience with fluoroquinolones, including ciprofloxacin. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure:

Postmarketing Reports of Adverse Drug Reactions

System Organ Class	Adverse Reactions
Cardiovascular	QT prolongation *Torsades de pointes* Vasculitis and ventricular arrhythmia
CNS	Hypertonia Myasthenia Exacerbation of myasthenia gravis Peripheral neuropathy Polyneuropathy Twitching
Eye Disorders	Nystagmus
Gastrointestinal	Pseudomembranous colitis
Hemic/Lymphatic	Pancytopenia (life-threatening or fatal outcome) Methemoglobinemia
Hepatobiliary	Hepatic failure (including fatal cases)
Infections and Infestations	Candidiasis (oral, gastrointestinal, vaginal)
Investigations	Prothrombin time prolongation or decrease Cholesterol elevation (serum) Potassium elevation (serum)
Musculoskeletal	Myalgia Myoclonus Tendinitis Tendon rupture
Psychiatric Disorders	Agitation Confusion Delirium Psychosis (toxic)

Skin/Hypersensitivity	AGEP Fixed eruption Serum sickness-like reaction
Special Senses	Anosmia Hyperesthesia Hypesthesia Taste loss

Adverse Laboratory Changes

Changes in laboratory parameters while on ciprofloxacin are listed below:

Hepatic: Elevations of ALT (SGPT), AST (SGOT), alkaline phosphatase, LDH, serum bilirubin.

Hematologic: Eosinophilia, leukopenia, decreased blood platelets, elevated blood platelets, pancytopenia.

Renal: Elevations of serum creatinine, BUN, crystalluria, cylindruria, and hematuria have been reported.

Other changes occurring were as follows: elevation of serum gamma-glutamyl transferase, elevation of serum amylase, reduction in blood glucose, elevated uric acid, decrease in hemoglobin, anemia, bleeding diathesis, increase in blood monocytes, and leukocytosis.

The drug may cause low blood sugar and mental health-related side effects. Low blood sugar levels, also called hypoglycemia, can lead to coma. The mental health-related side effects more prominent and more consistent across the systemic fluoroquinolone drug class are as mentioned below;

- Disturbances in attention
- Disorientation
- Agitation
- Nervousness
- Memory impairment

Serious disturbances in mental abilities (delirium) have also been reported.

Reporting of Suspected Adverse Reactions

*If you experience any side effects, talk to your doctor or pharmacist or write to drugsafety@cipla.com. You can also report side effects directly to the National Pharmacovigilance Programme of India by calling on **1800 180 3024** or you can report to Cipla Ltd. on 1800 267 7779. By reporting side effects, you can help provide more information on the safety of this product.*

Overdose

In the event of acute overdosage, reversible renal toxicity has been reported in some cases. Empty the stomach by inducing vomiting or by gastric lavage. Observe the patient carefully and give supportive treatment, including monitoring of renal function, urinary pH and acidify, if required, to prevent crystalluria and administration of magnesium, aluminium, or calcium-containing antacids, which can reduce the absorption of ciprofloxacin. Adequate hydration must be maintained. Only a small amount of ciprofloxacin (less than 10%) is removed from the body after hemodialysis or peritoneal dialysis.

Pharmacological Properties

Mechanism of Action

Ciprofloxacin is a member of the fluoroquinolone class of antibacterial agents. As a fluoroquinolone, antibacterial agent, the bactericidal action of ciprofloxacin results from the inhibition of both type II topoisomerase (DNA-gyrase) and topoisomerase IV, required for bacterial DNA replication, transcription, repair and recombination.

Pharmacodynamic Properties

Pharmacokinetic/Pharmacodynamic Relationship

Efficacy mainly depends on the relation between the maximum concentration in serum (C_{max}) and the minimum inhibitory concentration (MIC) of ciprofloxacin for a bacterial pathogen and the relation between the area under the curve (AUC) and the MIC.

Mechanism of Resistance

In vitro resistance to ciprofloxacin can be acquired through a stepwise process by target site mutations in both DNA gyrase and topoisomerase IV. The degree of cross-resistance between ciprofloxacin and other fluoroquinolones that results is variable. Single mutations may not result in clinical resistance, but multiple mutations generally result in clinical resistance to many or all active substances within the class.

Impermeability and/or active substance efflux-pump mechanisms of resistance may have a variable effect on susceptibility to fluoroquinolones, which depends on the physiochemical properties of the various active substances within the class and the affinity of transport systems for each active substance. All *in vitro* mechanisms of resistance are commonly observed in clinical isolates.

Resistance mechanisms that inactivate other antibiotics such as permeation barriers (common in *Pseudomonas aeruginosa*) and efflux-pump mechanisms may affect susceptibility to ciprofloxacin. Plasmid-mediated resistance encoded by qnr-genes has been reported. Spectrum of antibacterial activity breakpoints separated susceptible strains from strains with intermediate susceptibility and the latter from resistant strain: EUCAST Recommendations

Microorganisms	**Susceptible**	**Resistant**
Enterobacteriae	S ≤0,5 mg/l	R >1 mg/l
Pseudomonas spp.	S ≤0,5 mg/l	R >1 mg/l
Acinetobacter spp.	S ≤1 mg/l	R >1 mg/l
Staphylococcus spp.[1]	S ≤1 mg/l	R >1 mg/l
Haemophilus influenzae und *Moraxella catarrhalis*	S ≤0,5 mg/l	R >0,5 mg/l
Neisseria gonorrhoeae	S ≤0,03 mg/l	R >0,06 mg/l
Neisseria meningitidis	S ≤0,03 mg/l	R >0,06 mg/l
*Non-species-related breakpoints**	S ≤0,5 mg/l	R >1 mg/l

[1] *Staphylococcus* spp.: Breakpoints for ciprofloxacin relate to high-dose therapy.
* Non-species-related breakpoints have been determined mainly on the basis of pharmacokinetic/pharmacodynamic data and are independent of minimum inhibitory concentration (MIC) distributions of specific species. They are for use only for species that have not been given a species-specific breakpoint and not for those species where susceptibility testing is not recommended.

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. Expert advice should be sought, as needed, when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Groupings of relevant species according to ciprofloxacin susceptibility:

COMMONLY SUSCEPTIBLE SPECIES
Aerobic Gram-Positive MicroOrganisms *Bacillus anthracis*(1)
Aerobic Gram-Negative MicroOrganisms *Aeromonas* spp. *Brucella* spp. *Citrobacter koseri* *Francisella tularensis* *Haemophilus ducreyi* *Haemophilus influenzae** *Legionella* spp. *Moraxella catarrhalis** *Neisseria meningitidis* *Pasteurella* spp. *Salmonella* spp.* *Shigella* spp.* *Vibrio* spp. *Yersinia pestis*
Anaerobic Microorganisms *Mobiluncus*
Other Microorganisms *Chlamydia trachomatis*($) *Chlamydia pneumoniae*($) *Mycoplasma hominis*($) *Mycoplasma pneumoniae*($)
SPECIES FOR WHICH ACQUIRED RESISTANCE MAY BE A PROBLEM
Aerobic Gram-Positive Microorganisms *Enterococcus faecalis*($) *Staphylococcus* spp.*(2)

Aerobic Gram-Negative Microorganisms
Acinetobacter baumannii[+]
Burkholderia cepacia[+]*
Campylobacter spp.[+]*
*Citrobacter freundii**
Enterobacter aerogenes
*Enterobacter cloacae**
*Escherichia coli**
Klebsiella oxytoca
*Klebsiella pneumoniae**
*Morganella morganii**
*Neisseria gonorrhoeae**
*Proteus mirabilis**
*Proteus vulgaris**
Providencia spp.
*Pseudomonas aeruginosa**
Pseudomonas fluorescens
*Serratia marcescens**

Anaerobic Microorganisms
Peptostreptococcus spp.
Propionibacterium acnes

INHERENTLY RESISTANT ORGANISMS

Aerobic Gram-Positive Microorganisms
Actinomyces
Enterococcus faecium
Listeria monocytogenes

Aerobic Gram-Negative MicroOrganisms
Stenotrophomonas maltophilia

Anaerobic Microorganisms
Excepted as listed above

Other Microorganisms
Mycoplasma genitalium
Ureaplasma urealitycum

* Clinical efficacy has been demonstrated for susceptible isolates in approved clinical indications
+ Resistance rate ≥ 50% in one or more EU countries
($) Natural intermediate susceptibility in the absence of acquired mechanism of resistance
(1) Studies have been conducted in experimental animal infections due to inhalations of *Bacillus anthracis* spores; these studies reveal that antibiotics starting early after exposition avoid the occurrence of the disease if the treatment is made up to the decrease of the number of spores in the organism under the infective dose. The recommended use in human subjects is based primarily on *in vitro* susceptibility and on animal experimental data together with limited human data. A 2-month treatment regimen in adults with oral ciprofloxacin given at the following dose, 500 mg BID, is considered as effective to prevent anthrax infection in humans. The treating physician should refer to national and/or international consensus documents regarding treatment of anthrax.
(2) Methicillin-resistant *Staphylococcus aureus* very commonly express co-resistance to fluoroquinolones. The rate of resistance to methicillin is around 20 to 50% among all staphylococcal species and is usually higher in nosocomial isolates.

Pharmacokinetic Properties

Absorption

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

Single doses of 100 to 750 mg produced dose-dependent maximum serum concentrations (C_{max}) between 0.56 and 3.7 mg/L. Serum concentrations increase proportionately with doses up to 1,000 mg.

The absolute bioavailability is approximately 70 to 80% with no substantial loss by first-pass metabolism.

A 500mg oral dose given every 12 hours has been shown to produce an area under the serum concentration-time curve (AUC) equivalent to that produced by an I.V. infusion of 400 mg ciprofloxacin given over 60 minutes every 12 hours.

When ciprofloxacin tablet is given concomitantly with food, there is a delay in the absorption of the drug, resulting in peak concentrations that occur closer to 2 hours after dosing rather than 1 hour given with food. The overall absorption of ciprofloxacin tablet, however, is not substantially affected. Avoid concomitant administration of ciprofloxacin with dairy products (such as milk or yogurt) or calcium-fortified juices alone since decreased absorption is possible; however, ciprofloxacin may be taken with a meal that contains these products.

Distribution

Protein-binding of ciprofloxacin is low (20 to 30%). Ciprofloxacin is present in plasma largely in a non-ionised form and has a large steady state distribution volume of 2 to 3 L/kg body weight. Ciprofloxacin reaches high concentrations in a variety of tissues such as lung (epithelial fluid, alveolar macrophages, biopsy tissue), sinuses, inflamed lesions (cantharides blister fluid), and the urogenital tract (urine, prostate, endometrium) where total concentrations exceeding those of plasma concentrations are reached.

Biotransformation

Low concentrations of four metabolites have been reported, which were identified as desethyleneciprofloxacin (M1), sulphociprofloxacin (M2), oxociprofloxacin (M3) and formylciprofloxacin (M4). The metabolites display *in vitro* antimicrobial activity but to a lower degree than the parent compound. Ciprofloxacin is known to be a moderate inhibitor of the CYP 450 1A2 iso-enzymes.

Elimination

Ciprofloxacin is largely excreted unchanged both renally and, to a smaller extent, fecally. The serum elimination half-life in subjects with normal renal function is approximately 4 to 7 hours. Approximately 40 to 50% of an orally administered dose is excreted in the urine as unchanged drug.

Excretion of Ciprofloxacin (% of Dose)		
	Oral Administration	
	Urine	**Feces**
Ciprofloxacin	44.7	25.0
Metabolites	11.3	7.5

Renal clearance is between 180 to 300 mL/kg/h and the total body clearance is between 480 and 600 mL/kg/h. Ciprofloxacin undergoes both glomerular filtration and tubular secretion. Severely impaired renal function leads to increased half-lives of ciprofloxacin of up to 12 hours.

Non-renal clearance of ciprofloxacin is mainly due to active trans-intestinal secretion and metabolism. Up to 1% of the dose is excreted via the biliary route. Ciprofloxacin is present in the bile in high concentrations.

Special Populations

Geriatric Patients

Pharmacokinetic studies of the oral (single dose) and I.V. (single and multiple dose) forms of ciprofloxacin indicate that plasma concentrations of ciprofloxacin are higher in elderly subjects (older than 65 years) as compared with young adults. Although the C_{max} is increased 16% to 40%, the increase in mean AUC is approximately 30%, and can be at least partially attributed to decreased renal clearance in the elderly. Elimination half-life is only slightly (~20%) prolonged in the elderly. These differences are not considered clinically significant.

Patients with Renal Impairment

In patients with reduced renal function, the half-life of ciprofloxacin is slightly prolonged. Dosage adjustments may be required.

Patients with Hepatic Impairment

In preliminary studies in patients with stable chronic liver cirrhosis, no significant changes in ciprofloxacin pharmacokinetics have been observed. The kinetics of ciprofloxacin in patients with acute hepatic insufficiency, have not been fully studied.

Drug–Drug Interactions

Antacids

Concurrent administration of antacids containing magnesium hydroxide or aluminum hydroxide may reduce the bioavailability of ciprofloxacin by as much as 90%.

Histamine H2-Receptor Antagonists

Histamine H2-receptor antagonists appear to have no significant effect on the bioavailability of ciprofloxacin.

Metronidazole

The serum concentrations of ciprofloxacin and metronidazole were not altered when these two drugs were given concomitantly.

Tizanidine

In a pharmacokinetic study, systemic exposure of tizanidine (4 mg single dose) was significantly increased (C_{max} 7-fold, AUC 10-fold) when the drug was given concomitantly with ciprofloxacin (500 mg twice a day for 3 days). Concomitant administration of tizanidine and ciprofloxacin is contraindicated due to the potentiation of hypotensive and sedative effects of tizanidine.

Ropinirole

In a study conducted in 12 patients with Parkinson's disease who were administered 6 mg ropinirole once daily with 500 mg ciprofloxacin twice daily, the mean C_{max} and mean AUC of ropinirole were increased by 60% and 84%, respectively. Monitoring for ropinirole-related adverse reactions and appropriate dose adjustment of ropinirole is recommended during and shortly after co-administration with ciprofloxacin.

Clozapine

Following concomitant administration of 250 mg ciprofloxacin with 304 mg clozapine for 7 days, serum concentrations of clozapine and N-desmethylclozapine were increased by 29% and 31%, respectively. Careful monitoring of clozapine-associated adverse reactions and appropriate adjustment of clozapine dosage during and shortly after co-administration with ciprofloxacin are advised.

Sildenafil

Following concomitant administration of a single oral dose of 50 mg sildenafil with 500 mg ciprofloxacin to healthy subjects, the mean C_{max} and mean AUC of sildenafil were both increased approximately 2-fold. Use sildenafil with caution when co-administered with ciprofloxacin due to the expected 2-fold increase in the exposure of sildenafil upon co-administration of ciprofloxacin.

Duloxetine

In clinical studies, it was demonstrated that concomitant use of duloxetine with strong inhibitors of the CYP450 1A2 isozyme such as fluvoxamine, may result in a 5-fold increase in mean AUC and a 2.5-fold increase in mean C_{max} of duloxetine.

Lidocaine

In a study conducted in 9 healthy volunteers, concomitant use of 1.5 mg/kg I.V. lidocaine with ciprofloxacin 500 mg twice daily resulted in an increase of lidocaine Cmax and AUC by 12% and 26%, respectively. Although lidocaine treatment was well tolerated at this elevated exposure, a possible interaction with ciprofloxacin and an increase in adverse reactions related to lidocaine may occur upon concomitant administration.

Metoclopramide

Metoclopramide significantly accelerates the absorption of oral ciprofloxacin, resulting in a shorter time to reach maximum plasma concentrations. No significant effect was observed on the bioavailability of ciprofloxacin.

Omeprazole

When ciprofloxacin was administered as a single 1,000 mg dose concomitantly with omeprazole (40 mg once daily for 3 days) to 18 healthy volunteers, the mean AUC and C_{max} of ciprofloxacin were reduced by 20% and 23%, respectively. The clinical significance of this interaction has not been determined.

Nonclinical Properties

Non-clinical data reveal no special hazards for humans based on conventional studies of single-dose

toxicity, repeated-dose toxicity, carcinogenic potential, or toxicity to reproduction.

Like a number of other quinolones, ciprofloxacin is phototoxic in animals at clinically relevant exposure levels. Data on photomutagenicity/photocarcinogenicity show a weak photomutagenic or phototumorigenic effect of ciprofloxacin *in vitro* and in animal experiments. This effect was comparable with that of other gyrase inhibitors**.**

Articular Tolerability

As reported 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. In a study in young beagle dogs, ciprofloxacin caused severe articular changes at therapeutic doses after 2 weeks of treatment, which were still observed after 5 months.

Animal Toxicology or Pharmacology

Ciprofloxacin and other quinolones have been shown to cause arthropathy in immature animals of most species tested. Damage of weight-bearing joints was observed in juvenile dogs and rats. In young beagles, 100 mg/kg ciprofloxacin, given daily for 4 weeks, caused degenerative articular changes of the knee joint. At 30 mg/kg, the effect on the joint was minimal. In a subsequent study in young beagle dogs, oral ciprofloxacin doses of 30 mg/kg and 90 mg/kg ciprofloxacin (approximately 1.3-times and 3.5-times the pediatric dose based upon comparative plasma AUCs) given daily for 2 weeks caused articular changes that were still observable by histopathology after a treatment-free period of 5 months. At 10 mg/kg (approximately 0.6-times the pediatric dose based upon comparative plasma AUCs), no effects on joints were observed. This dose was also not associated with arthrotoxicity after an additional treatment-free period of 5 months. In another study, removal of weight-bearing from the joint reduced the lesions but did not totally prevent them.

Crystalluria, sometimes associated with secondary nephropathy, occurs in laboratory animals dosed with ciprofloxacin. This is primarily related to the reduced solubility of ciprofloxacin under alkaline conditions, which predominate in the urine of test animals; in humans, crystalluria is rare since human urine is typically acidic. In rhesus monkeys, crystalluria without nephropathy was noted after single oral doses as low as 5 mg/kg. (approximately 0.07-times the highest recommended therapeutic dose based upon body surface area). After 6 months of I.V. dosing at 10 mg/kg/day, no nephropathological changes were noted; however, nephropathy was observed after dosing at 20 mg/kg/day for the same duration (approximately 0.2-times the highest recommended therapeutic dose based upon body surface area).

In dogs, ciprofloxacin at 3 mg/kg and 10 mg/kg by rapid I.V. injection (15 seconds) produces pronounced hypotensive effects. These effects are considered to be related to histamine release, since they are partially antagonized by pyrilamine, an antihistamine. In rhesus monkeys, rapid I.V. injection also produces hypotension but the effect in this species is inconsistent and less pronounced.

In mice, concomitant administration of NSAIDs such as phenylbutazone and indomethacin with quinolones has been reported to enhance the CNS stimulatory effect of quinolones.

Ocular toxicity seen with some related drugs has not been observed in ciprofloxacin-treated animals.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Eight *in vitro* mutagenicity tests have been conducted with ciprofloxacin, and the test results are listed below:

- Salmonella/Microsome Test (Negative)
- E. coli DNA Repair Assay (Negative)
- Mouse Lymphoma Cell Forward Mutation Assay (Positive)
- Chinese Hamster V79 Cell HGPRT Test (Negative)
- Syrian Hamster Embryo Cell Transformation Assay (Negative)
- Saccharomyces cerevisiae Point Mutation Assay (Negative)
- Saccharomyces cerevisiae Mitotic Crossover and Gene Conversion Assay (Negative)
- Rat Hepatocyte DNA Repair Assay (Positive)

Thus, two of the eight tests were positive, but results of the following three *in vivo* test systems gave negative results:

- Rat Hepatocyte DNA Repair Assay
- Micronucleus Test (Mice)
- Dominant Lethal Test (Mice)

Long-term carcinogenicity studies in rats and mice resulted in no carcinogenic or tumorigenic effects due to Ciprofloxacin at daily oral dose levels up to 250 mg/kg and 750 mg/kg to rats and mice, respectively (approximately 1.7- and 2.5- times the highest recommended therapeutic dose based upon body surface area, respectively).

Results from photo co-carcinogenicity testing indicate that ciprofloxacin does not reduce the time to appearance of UV-induced skin tumors as compared to vehicle control. Hairless (Skh-1) mice were exposed to UVA light for 3.5 hours five times every 2 weeks for up to 78 weeks while concurrently being administered ciprofloxacin. The time to development of the first skin tumors was 50 weeks in mice treated concomitantly with UVA and ciprofloxacin (mouse dose approximately equal to maximum recommended human dose based upon body surface area), as opposed to 34 weeks when animals were treated with both UVA and vehicle.

The times to development of skin tumors ranged from 16 weeks to 32 weeks in mice treated concomitantly with UVA and other quinolones.

In this model, mice treated with ciprofloxacin alone did not develop skin or systemic tumors. There are no data from similar models using pigmented mice and/or fully haired mice. The clinical significance of these findings to humans is unknown.

Fertility studies performed in rats at oral doses of ciprofloxacin up to 100 mg/kg (approximately 0.7-times the highest recommended therapeutic dose based upon body surface area) revealed no evidence of impairment.

Description

Ciprofloxacin tablets are synthetic antimicrobial agents for oral administration. Ciprofloxacin hydrochloride, USP, a fluoroquinolone, is the monohydrochloride monohydrate salt of 1-cyclopropy--6-fluoro-1, 4-dihydro-4-oxo-7-(1-piperazinyl)-3 quinolinecarboxylic acid. It is a faintly yellowish to light yellow crystalline substance with a molecular weight of 385.8. Its empirical formula is $C_{17}H_{18}FN_3O_3 \bullet HCl \bullet H_2O$.

Pharmaceutical Particulars

Incompatibilities

Not applicable.

Shelf-Life

As on the pack.

Packaging Information

CIPLOX-250 Tablets: Blister pack of 10 tablets

CIPLOX-500 Tablets: Blister pack of 10 tablets

Storage and Handling Instructions

Store at room temperature between 20° and 25°C (68° and 77°F). Protect from light.

Keep **CIPLOX Tablets** and all medicines out of the reach of children.

Patient Counselling Information

Read this patient information guide before you start taking **CIPLOX Tablets** and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

IMPORTANT:

CIPLOX Tablets contain ciprofloxacin, which is a fluoroquinolone antibacterial medicine and can cause serious side effects. Some of these serious side effects can happen at the same time and could result in death.

If you get any of the following serious side effects while you take **CIPLOX Tablets**, you should stop taking **them** immediately and get medical help right away.

1. **Tendon rupture or swelling of the tendon (tendinitis).**

- Tendon problems can happen in people of all ages who take **CIPLOX Tablets**. Tendons are tough cords of tissue that connect muscles to bones. Symptoms of tendon problems may include the following:

◦ Pain, swelling, tears and swelling of the tendons including the back of the ankle (Achilles tendon), shoulder, hand, or other tendon sites.

- The risk of getting tendon problems while you take **CIPLOX Tablets** is higher if you

◦ are over 60 years of age;
◦ are taking steroids (corticosteroids);
◦ have had a kidney, heart or lung transplant

- Tendon problems can happen in people who do not have the above risk factors when they take **CIPLOX Tablets**.

- Other reasons that can increase your risk of tendon problems can include

  - physical activity or exercise;
  - kidney failure;
  - tendon problems in the past, such as in people with rheumatoid arthritis (RA)

- Stop taking **CIPLOX Tablets** immediately and get medical help right away at the first sign of tendon pain, swelling or inflammation. The most common area of pain and swelling is the Achilles tendon at the back of your ankle. This can also happen with other tendons.
- Tendon rupture can happen while you are taking or after you have finished taking **CIPLOX Tablets**. Tendon ruptures can happen within hours or days of taking **CIPLOX Tablets** and have happened up to several months after people have finished taking their fluoroquinolone.
- Stop taking **CIPLOX Tablets** immediately and get medical help right away if you get any of the following signs or symptoms of a tendon rupture:

  - Hear or feel a snap or pop in a tendon area
  - Bruising right after an injury in a tendon area
  - Unable to move the affected area or bear weight

1. **Changes in sensation and possible nerve damage (peripheral neuropathy).** Damage to the nerves in arms, hands, legs, or feet can happen in people who take fluoroquinolones, including **CIPLOX Tablets**. Stop taking **CIPLOX Tablets** immediately and talk to your healthcare provider right away if you get any of the following symptoms of peripheral neuropathy in your arms, hands, legs, or feet:
   - Pain
   - Numbness
   - Burning
   - Weakness
   - Tingling

CIPLOX Tablets may need to be stopped to prevent permanent nerve damage.

1. **Central nervous system (CNS) effects.** Seizures have been reported in people who take fluoroquinolone antibacterial medicines, including **CIPLOX Tablets**. Tell your healthcare provider if you have a history of seizures before you start taking CIPLOX tablet. CNS side effects may happen as soon as after taking the first dose of **CIPLOX Tablets**. Stop taking **CIPLOX Tablets** immediately and talk to your healthcare provider right away if you get any of these side effects, or other changes in mood or behavior:
   - Seizures
   - Trouble sleeping
   - Hear voices, see things, or sense things that are not there (hallucinations)
   - Nightmares
   - Feel lightheaded or dizzy
   - Feel more suspicious (paranoia)
   - Feel restless
   - Suicidal thoughts or acts
   - Tremors
   - Headaches that will not go away, with or without blurred vision
   - Feel anxious or nervous
   - Confusion
   - Depression
2. **Worsening of myasthenia gravis (a problem that causes muscle weakness).** Fluoroquinolones like **CIPLOX Tablets** may cause worsening of myasthenia gravis symptoms,

including muscle weakness and breathing problems. Tell your healthcare provider if you have a history of myasthenia gravis before you start taking **CIPLOX Tablets**. Call your healthcare provider right away if you have any worsening muscle weakness or breathing problems.

l What is CIPLOX Tablets?

CIPLOX Tablets contain ciprofloxacin, which is a fluoroquinolone antibacterial medicine used in adults age 18 years and older to treat certain infections caused by certain germs called bacteria. These bacterial infections include the following:

- Urinary tract infection
- Chronic prostate infection
- Respiratory tract infection
- Surgical infections
- Skin and soft tissue infection
- Bone and joint infection
- Gastrointestinal infections such as intra-abdominal infection, typhoid (enteric) fever
- Gynecological infections
- Sexually transmitted diseases

l Who should not take CIPLOX Tablets?

Do not take CIPLOX Tablets in case of the following:

- If you have ever had a severe allergic reaction to an antibacterial medicine known as a fluoroquinolone, or are allergic to ciprofloxacin hydrochloride or any of the ingredients in **CIPLOX Tablets**. See the end of this patient information guide for a complete list of ingredients in **CIPLOX Tablets**.
- If you also take a medicine called tizanidine.
- If you are below 18 years of age.

Ask your healthcare provider if you are not sure.

l What should I tell my healthcare provider before taking CIPLOX Tablets?

Before you take CIPLOX Tablets, tell your healthcare provider if you

- have tendon problems; **CIPLOX Tablets** should not be used in patients who have a history of tendon problems;
- have a disease that causes muscle weakness (myasthenia gravis); **CIPLOX Tablets** should not be used in patients who have a known history of myasthenia gravis;
- have liver problems;
- have CNS problems (such as epilepsy);
- have nerve problems; **CIPLOX Tablets** should not be used in patients who have a history of a nerve problem called peripheral neuropathy;
- have or anyone in your family has an irregular heartbeat, especially a condition called “QT prolongation”;
- have or have had seizures;
- have kidney problems—you may need a lower dose of **CIPLOX Tablets** if your kidneys do not work well;
- have joint problems, including rheumatoid arthritis (RA);
- have trouble swallowing pills;

- have any other medical conditions;
- are pregnant or plan to become pregnant—it is not known if **CIPLOX Tablets** will harm your unborn baby;
- are breastfeeding or plan to breastfeed—**CIPLOX Tablets** medicine passes into breast milk.

You and your healthcare provider should decide whether you will take **CIPLOX Tablets** or breastfeed. You should not do both.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

- **CIPLOX Tablets** and other medicines can affect each other, causing side effects.
- Especially tell your healthcare provider if you take the following:

- A steroid medicine
- An anti-psychotic medicine
- A tricyclic antidepressant
- A water pill (diuretic)
- Theophylline
- A medicine to control your heart rate or rhythm (antiarrhythmics)
- An oral anti-diabetes medicine
- Phenytoin
- Cyclosporine
- A blood thinner
- Methotrexate
- Ropinirole
- Clozapine
- A non-steroidal anti-inflammatory drug (NSAID). Many common medicines for pain relief are NSAIDs. Taking an NSAID while you take **CIPLOX Tablets** or other fluoroquinolones may increase your risk of CNS effects and seizures.
- Sildenafil
- Duloxetine
- Products that contain caffeine
- Probenecid

- Certain medicines may keep **CIPLOX Tablets** from working correctly. Take **CIPLOX Tablets** either 2 hours before or 6 hours after taking these medicines, vitamins, or supplements:

- An antacid, multivitamin, or other medicine or supplements that has magnesium, calcium, aluminum, iron, or zinc
- Sucralfate
- Didanosine

Ask your healthcare provider for a list of these medicines if you are not sure.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

l How should I take CIPLOX Tablets?

- Take **CIPLOX Tablets** exactly as your healthcare provider tells you to take it.
- Your healthcare provider will tell you how much **CIPLOX Tablets** to take and when to take it.
- Swallow the tablet whole. Do not split, crush or chew the tablet. Tell your healthcare provider if

you cannot swallow the tablet whole.
- **CIPLOX Tablets** can be taken with or without food.
- **CIPLOX Tablets** should not be taken with dairy products (such as milk or yogurt) or calcium-fortified juices alone, but may be taken with a meal that contains these products.
- Drink plenty of fluids while taking **CIPLOX Tablets**.
- Do not skip any doses of **CIPLOX Tablets**, or stop taking it, even if you begin to feel better, until you finish your prescribed treatment unless:

Taking all of your doses of **CIPLOX Tablets** will help make sure that all of the bacteria are killed and will help lower the chance that the bacteria will become resistant to **CIPLOX Tablets**. If you become resistant to **CIPLOX Tablets**, then **CIPLOX Tablets** and other antibacterial medicines may not work for you in the future.

If you take too many **CIPLOX Tablets**, call your healthcare provider or get medical help right away.

lWhat should I avoid while taking CIPLOX Tablets?

- **CIPLOX Tablets** can make you feel dizzy and lightheaded. **Do not** drive, operate machinery, or do other activities that require mental alertness or coordination until you know how **CIPLOX Tablets** affects you.
- Avoid sunlamps, tanning beds, and try to limit your time in the sun. **CIPLOX Tablets** can make your skin sensitive to the sun (photosensitivity) and the light from sunlamps and tanning beds. You could get a severe sunburn, blisters or swelling of your skin. If you get any of these symptoms while you take **CIPLOX Tablets**, call your healthcare provider right away. You should use a sunscreen and wear a hat and clothes that cover your skin if you have to be in sunlight.

l What are the possible side effects of CIPLOX Tablets?

CIPLOX Tablets may cause serious side effects, including the following:

- **Serious allergic reactions.** Serious allergic reactions, including death, can happen in people taking fluoroquinolones, including **CIPLOX Tablets**, even after only one dose. Stop taking **CIPLOX Tablets** and get emergency medical help right away if you get any of the following symptoms of a severe allergic reactions:

◦ Hives
◦ Trouble breathing or swallowing
◦ Swelling of the lips, tongue, face
◦ Throat tightness, hoarseness
◦ Rapid heartbeat
◦ Feeling faint
◦ Skin rash

Skin rash may happen in people taking **CIPLOX Tablets** even after only one dose. Stop taking **CIPLOX Tablets** at the first sign of a skin rash and call your healthcare provider. Skin rash may be a sign of a more serious reaction to **CIPLOX Tablets**.

- **Liver damage (hepatotoxicity).** Hepatotoxicity can happen in people who take **CIPLOX Tablets**. Call your healthcare provider right away if you have unexplained symptoms such as the following:

◦ Nausea or vomiting
◦ Stomach pain
◦ Fever

- Weakness
- Abdominal pain or tenderness
- Itching
- Unusual tiredness
- Loss of appetite
- Light-colored stools
- Dark-colored urine
- Yellowing of your skin or the whites of your eyes

Stop taking **CIPLOX Tablets** and tell your healthcare provider right away if you have yellowing of your skin or white part of your eyes, or if you have dark urine. These can be signs of a serious reaction to **CIPLOX Tablets** (a liver problem).

- **Aortic aneurysm and dissection.** Tell your healthcare provider if you have ever been told that you have an aortic aneurysm, a swelling of the large artery that carries blood from the heart to the body. Get emergency medical help right away if you have sudden chest, stomach, or back pain.
- **Intestine infection (pseudomembranous colitis).** Pseudomembranous colitis can happen with many antibacterial medicines, including **CIPLOX Tablets**. Call your healthcare provider right away if you get watery diarrhea, diarrhea that does not go away, or bloody stools. You may have stomach cramps and a fever. Pseudomembranous colitis can happen 2 or more months after you have finished your antibacterial medicine.
- **Serious heart rhythm changes (QT prolongation and *torsades de pointes*).** Tell your healthcare provider right away if you have a change in your heart beat (a fast or irregular heartbeat), or if you faint. **CIPLOX Tablets** may cause a rare heart problem known as prolongation of the QT interval. This condition can cause an abnormal heartbeat and can be very dangerous. The chances of this event are higher in people

- who are elderly;
- with a family history of prolonged QT interval;
- with low blood potassium (hypokalemia);
- who take certain medicines to control heart rhythm (antiarrhythmics)

- **Joint problems.** Increased chance of problems with joints and tissues around joints in children under 18 years of age can happen. Tell your child’s healthcare provider if your child has any joint problems during or after treatment with **CIPLOX Tablets**.
- Sensitivity to sunlight (photosensitivity)

Changes in blood sugar

- People who take **CIPLOX Tablets** and other fluoroquinolone medicines with oral anti-diabetes medicines or with insulin can get low blood sugar (hypoglycemia) and high blood sugar (hyperglycemia). Follow your healthcare provider's instructions for how often to check your blood sugar. If you have diabetes and you get low blood sugar while taking **CIPLOX Tablets**, stop taking them and call your healthcare provider right away. Your antibiotic medicine may need to be changed.

The most common side effects of **CIPLOX Tablets** include the following:

- Nausea
- Diarrhea
- Changes in liver function tests
- Vomiting
- Rash

Tell your healthcare provider about any side effect that bothers you, or that does not go away.

These are not all the possible side effects of **CIPLOX Tablets**. For more information and advice, ask your healthcare provider or pharmacist.

Reporting of side effects

*If you experience any side effects, talk to your doctor or pharmacist or write to drugsafety@cipla.com. You can also report side effects directly to the National Pharmacovigilance Programme of India by calling on **1800 180 3024** or you can report to Cipla Ltd. on 1800 267 7779. By reporting side effects, you can help provide more information on the safety of this product.*

l How should I store CIPLOX Tablets?

- Store at room temperature between 20° and 25°C (68° and 77°F).
- Keep **CIPLOX Tablets** and all medicines out of the reach of children.

l General Information about the safe and effective use of CIPLOX Tablets

Medicines are sometimes prescribed for purposes other than those listed in a patient information guide.

Do not use **CIPLOX Tablets** for a condition for which it is not prescribed.

Do not give **CIPLOX Tablets** to other people, even if they have the same symptoms that you have. It may harm them.

This patient information guide summarizes the most important information about **CIPLOX Tablets**. If you would like more information about **CIPLOX Tablets**, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about **CIPLOX Tablets** that is written for healthcare professionals.

l What are the ingredients in CIPLOX Tablets?

Active ingredient: Ciprofloxacin hydrochloride

Details of The Manufacturer

M/S Golden Cross Pharma Pvt. Ltd,

Tarpin Block, Rorathang,

Sikkim - 737133

Cipla Ltd. Registered Office:

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Details of Permission or Licence Number with Date

For Ciplox 250mg and 500mg tablet - M/485/08

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