CIPLOX-TZ Tablets (Ciprofloxacin + Tinidazole)

Black Box Warning

Serious Adverse Reactions Including Tendinitis, Tendon Rupture, Peripheral Neuropathy, Central Nervous System (CNS) Effects and Exacerbation of Myasthenia Gravis

See the full prescribing information for complete boxed warning
Fluoroquinolones, including ciprofloxacin, have been associated with disabling and potentially irreversible serious adverse reactions that have occurred together, including

- tendinitis and tendon rupture;
- peripheral neuropathy; and,
- 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 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.

Warning: Potential Risk for Carcinogenicity
Carcinogenicity has been seen in mice and rats treated chronically with metronidazole, another nitroimidazole agent. Although such data have not been reported for tinidazole, the two drugs are structurally related and have similar biologic effects.

Qualitative and Quantitative Composition

CIPLOX-TZ Tablets
Each film-coated tablet contains:
Ciprofloxacin Hydrochloride, IP, equivalent to Ciprofloxacin..... 500 mg

Tinidazole, IP ..... 600 mg

Dosage Form(S) and Strength(S)

Ciprofloxacin 500 mg and Tinidazole 600 mg Film Coated Tablets

Clinical Particulars

Therapeutic Indications

CIPLOX-TZ Tablets are indicated for the treatment of a wide variety of infections caused by susceptible Gram-positive and Gram-negative organisms along with anaerobes and protozoa.

Posology and Method of Administration

CIPLOX-TZ Tablets should be taken 1 hour before or 2 hours after meals with a glass of water.

Adults
One tablet twice daily for 5–10 days, depending on severity and response.

Children
Not recommended for children.

Contraindications

· Ciprofloxacin is contraindicated in persons with a history of hypersensitivity to ciprofloxacin, any member of the quinolone class of antibacterial, or any of the product components

· Concomitant administration with tizanidine is contraindicated

· In patients with a previous history of hypersensitivity to tinidazole or other nitroimidazole derivatives. Reported reactions have ranged in severity from urticaria to Stevens-Johnson syndrome

· During first trimester of pregnancy

· In nursing mothers: Interruption of breastfeeding is recommended during tinidazole therapy and for 3 days following the last dose

Special Warnings and Precautions for Use

Ciprofloxacin

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. 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.

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 paraesthesia, hypoesthesia, dysaesthesia 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 minimise the development of an irreversible condition. Avoid fluoroquinolones, including ciprofloxacin, in patients who have previously experienced peripheral neuropathy.

CNS Effects

Fluoroquinolones, including ciprofloxacin, have been associated with an increased risk of CNS effects, including convulsions, increased intracranial pressure (including pseudotumour cerebri), and toxic psychosis. Ciprofloxacin may also cause CNS events, including nervousness, agitation, insomnia, anxiety, nightmares, paranoia, dizziness, confusion, tremors, hallucinations, depression, and psychotic reactions progressing to suicidal ideations/thoughts and self-injurious behaviour such as attempted or completed suicide. 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. Ciprofloxacin, like other fluoroquinolones, is known to trigger seizures or lower the seizure threshold. 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). Use ciprofloxacin when the benefits of treatment exceed the risks, since these patients are endangered because of possible undesirable CNS side effects. Cases of status epilepticus have been reported. If seizures occur, discontinue ciprofloxacin.

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 aetiology, 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

· Anaemia, including haemolytic and aplastic; thrombocytopaenia, including thrombotic thrombocytopaenic purpura; leucopaenia; agranulocytosis; pancytopaenia; and/or other haematologic abnormalities

Discontinue ciprofloxacin immediately at the first appearance of a skin rash, jaundice, or any other sign of hypersensitivity and ensure that supportive measures are 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 oedema, dyspnoea, 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, IV fluids, IV antihistamines, corticosteroids, pressor amines, and airway management, including intubation.

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, 1–39 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.

Serious Adverse Reactions with Concomitant Theophylline

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 Diarrhoea

Clostridium difficile (*C. difficile*)-associated diarrhoea (CDAD) has been reported with the use of nearly all antibacterial agents, including ciprofloxacin, and may range in severity from mild diarrhoea 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 diarrhoea 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.

Prolongation of the QT Interval

Some fluoroquinolones, including ciprofloxacin, have been associated with prolongation of the QT interval on the electrocardiogram (ECG) 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 hypokalaemia or hypomagnesaemia and cardiac disease, such as heart failure, myocardial infarction, or bradycardia), and patients receiving Class IA anti-arrhythmic agents (quinidine, procainamide), or Class III anti-arrhythmic 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 Paediatric Patients and Arthropathic Effects in Animals

Ciprofloxacin is indicated in paediatric patients (<18 years of age) only for cUTI, prevention of inhalational anthrax (post-exposure), and plague. An increased incidence of adverse reactions compared with 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, oedema) 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 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.

Potential Risks with Concomitant Use of Drugs Metabolised by CYP450 1A2 Enzymes

Ciprofloxacin is an inhibitor of the hepatic CYP1A2 enzyme pathway. Co-administration of ciprofloxacin and other drugs primarily metabolised 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 gonorrhoea may mask or delay the symptoms of incubating syphilis. Perform a serologic test for syphilis in all patients with gonorrhoea at the time of diagnosis. Perform follow-up serologic test for syphilis 3 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 hyperglycaemia and hypoglycaemia, usually in diabetic patients receiving concomitant treatment with an oral hypoglycaemic agent (e.g. glyburide) or with insulin. In these patients, careful monitoring of blood glucose is recommended. Severe cases of hypoglycaemia resulting in coma or death have been reported. If a hypoglycaemic reaction occurs in a patient being treated with ciprofloxacin, discontinue ciprofloxacin tablets and initiate appropriate therapy immediately.

Tinidazole

Neurological Adverse Reactions

Convulsive seizures and peripheral neuropathy, the latter characterised mainly by numbness or

paraesthesia of an extremity, have been reported in patients treated with tinidazole. The appearance of abnormal neurologic signs demands the prompt discontinuation of tinidazole therapy.

Vaginal Candidiasis

The use of tinidazole may result in Candida vaginitis. In a clinical study of 235 women who received tinidazole for bacterial vaginosis, a vaginal fungal infection developed in 11 (4.7%) of all study subjects.

Blood Dyscrasia

Tinidazole should be used with caution in patients with evidence of or a history of blood dyscrasia.

Drug Resistance

Prescribing tinidazole 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.

Drugs Interactions

Ciprofloxacin

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

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 anti-arrhythmics, tricyclic antidepressants, macrolides, antipsychotics).

Oral antidiabetic drugs	Use with caution Glucose-lowering effect potentiated	Hypoglycaemia, sometimes severe, has been reported when ciprofloxacin and oral antidiabetic agents, mainly sulphonylureas (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 the International Normalised Ratio (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.
Nonsteroidal anti-inflammatory drugs	Use with caution	Non-steroidal anti-inflammatory drugs (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/aluminium antacids; polymeric phosphate binders (e.g. sevelamer, lanthanum carbonate); sucralfate; Videx® (didanosine) chewable/buffered tablets or paediatric 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	Decrease in ciprofloxacin absorption, resulting in lower serum and urine levels.
Probenecid	Use with caution (interferes with renal tubular secretion of ciprofloxacin and increases ciprofloxacin serum levels)	Potentiation of ciprofloxacin toxicity may occur.

Tinidazole

Although not specifically identified in studies with tinidazole, the following drug interactions were reported for metronidazole, a chemically-related nitroimidazole. Therefore, these drug interactions may occur with tinidazole.

Potential Effects of Tinidazole on Other Drugs

Warfarin and Other Oral Coumarin Anticoagulants: As with metronidazole, tinidazole may enhance the effect of warfarin and other coumarin anticoagulants, resulting in a prolongation of prothrombin time. The dosage of oral anticoagulants may need to be adjusted during tinidazole co-administration and up to 8 days after discontinuation.

Alcohols, Disulfiram: Alcoholic beverages and preparations containing ethanol or propylene glycol should be avoided during tinidazole therapy and for 3 days afterward because abdominal cramps, nausea, vomiting, headaches and flushing may occur. Psychotic reactions have been reported in alcoholic patients using metronidazole and disulfiram concurrently. Though no similar reactions have been reported with tinidazole, tinidazole should not be given to patients who have taken disulfiram within the last 2 weeks.

Lithium: Metronidazole has been reported to elevate serum lithium levels. It is not known if tinidazole shares this property with metronidazole, but consideration should be given to measuring serum lithium and creatinine levels after several days of simultaneous lithium and tinidazole treatment to detect potential lithium intoxication.

Phenytoin, Fosphenytoin: Concomitant administration of oral metronidazole and intravenous phenytoin was reported to result in prolongation of the half-life and reduction in the clearance of phenytoin. Metronidazole did not significantly affect the pharmacokinetics of orally-administered phenytoin.

Cyclosporine, Tacrolimus: There are several case reports suggesting that metronidazole has the potential to increase the levels of cyclosporine and tacrolimus. During tinidazole co-administration with either of these drugs, the patient should be monitored for signs of calcineurin-inhibitor associated toxicities.

Fluorouracil: Metronidazole was shown to decrease the clearance of fluorouracil, resulting in an increase in side effects without an increase in therapeutic benefits. If the concomitant use of tinidazole and fluorouracil cannot be avoided, the patient should be monitored for fluorouracil-associated toxicities.

Potential Effects of Other Drugs on Tinidazole

CYP3A4 Inducers and Inhibitors: Simultaneous administration of tinidazole with drugs that induce liver microsomal enzymes, i.e. CYP3A4 inducers such as phenobarbital, rifampin, phenytoin *and fosphenytoin* (a pro-drug of phenytoin), may accelerate the elimination of tinidazole, decreasing the plasma level of tinidazole. Simultaneous administration of drugs that inhibit the activity of liver microsomal enzymes, i.e. CYP3A4 inhibitors such as cimetidine and ketoconazole, may prolong the half-life and decrease the plasma clearance of tinidazole, increasing the plasma concentrations of tinidazole.

Cholestyramine: Cholestyramine was shown to decrease the oral bioavailability of metronidazole by 21%. Thus, it is advisable to separate the dosing of cholestyramine and tinidazole to minimise any potential effect on the oral bioavailability of tinidazole.

Oxytetracycline: Oxytetracycline was reported to antagonize the therapeutic effect of metronidazole.

Laboratory Test Interactions

Tinidazole, like metronidazole, may interfere with certain types of determinations of serum chemistry values, such as aspartate aminotransferase (AST, SGOT), alanine aminotransferase (ALT, SGPT), lactate dehydrogenase (LDH), triglycerides, and hexokinase glucose. Values of zero may be observed. All of the assays in which interference has been reported involve enzymatic coupling of the assay to oxidation-reduction of nicotinamide adenine dinucleotide (NAD + NADH). Potential interference is due to the similarity of absorbance peaks of NADH and tinidazole.

Tinidazole, like metronidazole, may produce transient leucopaenia and neutropaenia; however, no persistent haematological abnormalities attributable to tinidazole have been observed in clinical studies. Total and differential leucocyte counts are recommended if re-treatment is necessary.

Use in Special Populations

Pregnant Women

Ciprofloxacin- 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 foetus and 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 1–5%). 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 foetuses.

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 foetus due to ciprofloxacin. In rabbits, oral ciprofloxacin dose levels of 30 and 100 mg/kg (approximately 0.4 times 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 IV 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.

Tinidazole -Teratogenic Effects: Pregnancy Category C

The use of tinidazole in pregnant patients has not been studied. Since tinidazole crosses the placental barrier and enters foetal circulation, it should not be administered to pregnant patients in the first trimester.

Embryo-foetal developmental toxicity studies in pregnant mice indicated no embryo-foetal toxicity or malformations at the highest dose level of 2,500 mg/kg (approximately 6.3-fold the highest human therapeutic dose based upon body surface area conversions). In a study with pregnant rats a slightly higher incidence of fetal mortality was observed at a maternal dose of 500 mg/kg (2.5-fold the highest human therapeutic dose based upon body surface area conversions). No biologically relevant neonatal developmental effects were observed in rat neonates following maternal doses as high as 600 mg/kg (3-fold the highest human therapeutic dose based upon body surface area conversions). Although there is some evidence of mutagenic potential and animal reproduction studies are not always predictive of human response, the use of tinidazole after the first trimester of pregnancy requires that the potential benefits of the drug be weighed against the possible risks to both the mother and the foetus.

Lactating Women

Ciprofloxacin

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.

Tinidazole

Tinidazole is excreted in breast milk. Tinidazole may continue to appear in breast milk for more than 72 hours after administration. Interruption of breastfeeding is recommended during tinidazole therapy and for 3 days following the last dose.

Paediatric Use

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

Other than for use in the treatment of giardiasis and amoebiasis in paediatric patients >3 years of age, safety and effectiveness of tinidazole in paediatric patients have not been established.

Geriatric Use

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 Achillestendon, 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.

In a retrospective analysis of 23 multiple-dose controlled clinical trials of ciprofloxacin encompassing over 3,500 ciprofloxacin-treated patients, 25% of patients were ≥65 years of age and 10% were ≥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 ≥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 anti-arrhythmics) or in patients with risk factors for *torsades de pointes* (e.g. known QT prolongation, uncorrected hypokalaemia).

Clinical studies of tinidazole did not include sufficient numbers of subjects aged ≥65 years to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Renal Impairment

Ciprofloxacin

Ciprofloxacin is eliminated primarily by renal excretion; however, the drug is also metabolised 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.

Tinidazole

Because the pharmacokinetics of tinidazole in patients with severe renal impairment (CrCL <22 mL/min) are not significantly different from those in healthy subjects, no dose adjustments are necessary in these patients.

Patients Undergoing Haemodialysis: If tinidazole is administered on the same day as and prior to haemodialysis, it is recommended that an additional dose of tinidazole equivalent to one-half of the recommended dose be administered after the end of the haemodialysis.

Hepatic Impairment

Ciprofloxacin

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 has not been studied.

Tinidazole

There are no data on tinidazole pharmacokinetics in patients with impaired hepatic function. Reduced elimination of metronidazole, a chemically-related nitroimidazole, has been reported in this population. Usual recommended doses of tinidazole should be administered cautiously in patients with hepatic dysfunction

Effects on 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.

Drugs of similar chemical structure, including tinidazole, have been associated with various neurological disturbances such as dizziness, vertigo, ataxia, peripheral neuropathy (paraesthesia, sensory disturbances, hypoesthesia) and rarely convulsions. If any abnormal neurological signs develop during tinidazole therapy, the drug should be discontinued.

Undesirable Effects

Ciprofloxacin

The following serious and otherwise important adverse drug reactions are discussed in greater detail in other sections of the labelling:

- 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 Diarrhoea
- Prolongation of the QT Interval
- Musculoskeletal Disorders in Paediatric Patients and Arthropathic Effects in Animals
- 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 to 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%), diarrhoea (1.6%), liver function tests abnormal (1.3%), vomiting (1%), and rash (1%).

Medically Important Adverse Reactions That Occurred In <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 Depersonalisation Depression (potentially culminating in self-injurious behaviour (such as suicidal ideations/thoughts and attempted or completed suicide) Paraesthesia Abnormal gait Migraine
Gastrointestinal	Intestinal perforation Gastrointestinal bleeding Cholestatic jaundice Hepatitis Pancreatitis
Haemic/Lymphatic	Petechia
Metabolic/Nutritional	Hyperglycaemia Hypoglycaemia

Musculoskeletal	Arthralgia Joint stiffness Muscle weakness
Renal/Urogenital	Interstitial nephritis Renal failure
Respiratory	Dyspnoea Laryngeal oedema Haemoptysis 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 Angio-oedema Erythema nodosum Sweating
Special Senses	Blurred vision Disturbed vision (chromatopsia and photopsia) Decreased visual acuity Diplopia Tinnitus Hearing loss Bad taste

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

Paediatric Patients

Short- (6 weeks) and long-term (1 year) musculoskeletal and neurological safety of oral/IV ciprofloxacin, was compared with a cephalosporin for treatment of cUTI or pyelonephritis in paediatric patients, 1 to 17 years of age (mean age of 6 ± 4 years), in an international multicentre trial. The duration of therapy was 10–21 days (mean duration of treatment was 11 days, with a range of 1–88 days). A total of 335 ciprofloxacin- and 349 comparator-treated patients were enrolled.

An Independent Paediatric Safety Committee (IPSC) reviewed all cases of musculoskeletal adverse reactions, including abnormal gait or abnormal joint exam (baseline or treatment-emergent). Within 6 weeks of treatment initiation, the rates of musculoskeletal adverse reactions were 9.3% (31/335) in the ciprofloxacin-treated group versus 6% (21/349) in comparator-treated patients. All musculoskeletal adverse reactions occurring by 6 weeks resolved (clinical resolution of signs and symptoms), usually within 30 days of end of treatment. Radiological evaluations were not routinely used to confirm resolution of the adverse reactions. Ciprofloxacin-treated patients were more likely to report more than one adverse reaction and on more than one occasion compared with control patients. The rate of musculoskeletal adverse reactions was consistently higher in the ciprofloxacin

group compared with the control group across all age subgroups. At the end of 1 year, the rate of these adverse reactions reported at any time during that period was 13.7% (46/335) in the ciprofloxacin-treated group versus 9.5% (33/349) in the comparator-treated patients.

Musculoskeletal Adverse Reactions[1] as Assessed by the IPSC

	Ciprofloxacin	Comparator
All Patients (within 6 weeks)	31/335 (9.3%)	21/349 (6%)
95% Confidence Interval[2]	(–0.8%, +7.2%)	
Age Group		
12 months to <24 months	1/36 (2.8%)	0/41
2 years to <6 years	5/124 (4%)	3/118 (2.5%)
6 years to <12 years	18/143 (12.6%)	12/153 (7.8%)
12 years to 17 years	7/32 (21.9%)	6/37 (16.2 %)
All Patients (within 1 year)	46/335 (13.7%)	33/349 (9.5%)
95% Confidence Interval[1]	(–0.6%, + 9.1%)	

[1]Included: arthralgia, abnormal gait, abnormal joint exam, joint sprains, leg pain, back pain, arthrosis, bone pain, pain, myalgia, arm pain, and decreased range of motion in a joint (knee, elbow, ankle, hip, wrist, and shoulder)
[2]The study was designed to demonstrate that the arthropathy rate for the ciprofloxacin group did not exceed that of the control group by more than +6%. At both the 6-week and 1-year evaluations, the 95% confidence interval indicated that it could not be concluded that the ciprofloxacin group had findings comparable to the control group.

The incidence rates of neurological adverse reactions within 6 weeks of treatment initiation were 3% (9/335) in the ciprofloxacin group versus 2% (7/349) in the comparator group and included dizziness, nervousness, insomnia, and somnolence.

In this trial, the overall incidence rates of adverse reactions within 6 weeks of treatment initiation were 41% (138/335) in the ciprofloxacin group versus 31% (109/349) in the comparator group. The most frequent adverse reactions were gastrointestinal in 15% (50/335) of ciprofloxacin patients compared with 9% (31/349) of comparator patients. Serious adverse reactions were seen in 7.5% (25/335) of ciprofloxacin-treated patients compared with 5.7% (20/349) of control patients. Discontinuation of drug due to an adverse reaction was observed in 3% (10/335) of ciprofloxacin-treated patients versus 1.4% (5/349) of comparator patients. Other adverse reactions that occurred in at least 1% of ciprofloxacin patients were diarrhoea (4.8%), vomiting (4.8%), abdominal pain

(3.3%), dyspepsia (2.7%), nausea (2.7%), fever (2.1%), asthma (1.8%), and rash (1.8%).

Short-term safety data for ciprofloxacin was also collected in a randomised, double-blind, clinical trial for the treatment of acute pulmonary exacerbations in cystic fibrosis patients (aged 5–17 years). A total of 67 patients received ciprofloxacin IV 10 mg/kg/dose every 8 hours for 1 week followed by ciprofloxacin tablets 20 mg/kg/dose every 12 hours to complete 10–21 days of treatment and 62 patients received the combination of ceftazidime IV 50 mg/kg/dose every 8 hours and tobramycin IV 3 mg/kg/dose every 8 hours for a total of 10–21 days. Periodic musculoskeletal assessments were conducted by treatment-blinded examiners. Patients were followed for an average of 23 days after completing treatment (range, 0–93 days). Musculoskeletal adverse reactions were reported in 22% of the patients in the ciprofloxacin group and 21% in the comparison group. Decreased range of motion was reported in 12% of the subjects in the ciprofloxacin group and 16% in the comparison group. Arthralgia was reported in 10% of the patients in the ciprofloxacin group and 11% in the comparison group. Other adverse reactions were similar in nature and frequency between treatment arms. The efficacy of ciprofloxacin for the treatment of acute pulmonary exacerbations in paediatric cystic fibrosis patients has not been established.

In addition to the adverse reactions reported in paediatric patients in clinical trials, it should be expected that adverse reactions reported in adults during clinical trials or postmarketing experience may also occur in paediatric patients.

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
Haemic/Lymphatic	Pancytopenia (life threatening or fatal outcome) Methemoglobinaemia
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
Skin/Hypersensitivity	Acute generalised exanthematous pustulosis (AGEP) Fixed eruption Serum sickness-like reaction
Special Senses	Anosmia Hyperesthesia Hypoesthesia 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.

Haematologic: eosinophilia, leucopaenia, decreased blood platelets, elevated blood platelets, pancytopaenia.

Renal: elevations of serum creatinine, BUN, crystalluria, cylindruria, and haematuria have been reported.

Other changes occurring were as follows: elevation of serum gammaglutamyl transferase, elevation of serum amylase, reduction in blood glucose, elevated uric acid, decrease in haemoglobin, anaemia, bleeding diathesis, increase in blood monocytes, and leucocytosis.

The drug may cause low blood sugar and mental health-related side effects. Low blood sugar levels, also called hypoglycaemia, can lead to coma. The mental health 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 called delirium

Tinidazole

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

Among 3,669 patients treated with a single 2 g dose of tinidazole, in both controlled and uncontrolled trichomoniasis and giardiasis clinical studies, adverse reactions were reported by 11.0% of patients. For multi-day dosing in controlled and uncontrolled amoebiasis studies, adverse reactions were reported by 13.8% of 1,765 patients. Common (≥1% incidence) adverse reactions reported by body system are as follows.

Other Adverse Reactions Reported with Tinidazole

Central Nervous System: Two serious adverse reactions reported included convulsions and transient peripheral neuropathy, including numbness and paraesthesia. Other CNS reports included vertigo, ataxia, giddiness, insomnia, drowsiness.

Gastrointestinal: tongue discolouration, stomatitis, diarrhoea

Hypersensitivity: urticaria, pruritus, rash, flushing, sweating, dryness of mouth, fever, burning sensation, thirst, salivation, angio-oedema

Renal: darkened urine

Cardiovascular: palpitations

Haematopoietic: transient neutropaenia, transient leucopaenia

*Other: Candid*a overgrowth, increased vaginal discharge, oral candidiasis, hepatic abnormalities, including raised transaminase level, arthralgias, myalgias, and arthritis.

Adverse Reactions Summary of Published Reports

	2 g Single Dose	**Multi-Day Dose**
Gastrointestinal: Metallic/bitter taste	3.7%	6.3%
Nausea	3.2%	4.5%
Anorexia	1.5%	2.5%
Dyspepsia/cramps/epigastric discomfort	1.8%	1.4%
Vomiting	1.5%	0.9%
Constipation	0.4%	1.4%
CNS: Weakness/fatigue/malaise	2.1%	1.1%
Dizziness	1.1%	0.5%
Other: Headache	1.3%	0.7%
Total patients with adverse reactions	11.0% (403/3,669)	13.8% (244/1,765)

Rare reported adverse reactions include bronchospasm, dyspnoea, coma, confusion, depression, furry tongue, pharyngitis, and reversible thrombocytopaenia.

Adverse Reactions in Paediatric Patients

In pooled paediatric studies, adverse reactions reported in paediatric patients taking tinidazole were similar in nature and frequency to adult findings, including nausea, vomiting, diarrhoea, taste change, anorexia, and abdominal pain.

Bacterial Vaginosis: The most common adverse reactions in treated patients (incidence >2%), which were not identified in the trichomoniasis, giardiasis and amoebiasis studies, are gastrointestinal: decreased appetite, and flatulence; renal: urinary tract infection, painful urination, and urine abnormality; and other reactions, including pelvic pain, vulvo-vaginal discomfort, vaginal odour, menorrhagia, and upper respiratory tract infection.

Postmarketing Experience

The following adverse reactions have been identified and reported during post-approval use of tinidazole. Because the reports of these reactions are voluntary and the population is of uncertain size, it is not always possible to reliably estimate the frequency of the reaction or establish a causal relationship to drug exposure.

Severe acute hypersensitivity reactions have been reported on initial or subsequent exposure to tinidazole. Hypersensitivity reactions may include urticaria, pruritus, angio-oedema, Stevens-Johnson syndrome and erythema multiforme.

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 via the National Pharmacovigilance Programme of India (PvPI) by calling on 1800 267 7779 (Cipla number) or you can report to PvPI on 1800 180 3024. By reporting side-effects, you can help provide more information on the safety of this product.

Overdose

Ciprofloxacin

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 haemodialysis or peritoneal dialysis.

Tinidazole

There are no reported overdoses with tinidazole in humans. There is no specific antidote for the treatment of overdosage with tinidazole; therefore, treatment should be symptomatic and supportive. Gastric lavage may be helpful. Haemodialysis can be considered because approximately 43% of the amount present in the body is eliminated during a 6-hour haemodialysis session.

Pharmacological Properties

Mechanism of Action

Ciprofloxacin

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.

Tinidazole

The mode of action of tinidazole against anaerobic bacteria and protozoa involves penetration of the drug into the cell of the micro-organism and subsequent damage of DNA strands or inhibition of their synthesis.

Pharmacodynamic Properties

Ciprofloxacin

Pharmacotherapeutic group: Fluoroquinolones, ATC code: J01MA02

The bactericidal action of ciprofloxacin results from inhibition of the enzymes, topoisomerase II (DNA gyrase) and topoisomerase IV, which are required for bacterial DNA replication, transcription, repair and recombination. The mechanism of action of fluoroquinolones, including ciprofloxacin, is different from that of penicillins, cephalosporins, aminoglycosides, macrolides and tetracyclines; therefore, microorganisms resistant to these classes of drugs may be susceptible to ciprofloxacin. There is no known cross-resistance between ciprofloxacin and other classes of antimicrobials. *In vitro* resistance to ciprofloxacin develops slowly by multiple-step mutations.

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

Gram-positive Bacteria

Bacillus anthracis

Enterococcus faecalis

Staphylococcus aureus (methicillin-susceptible isolates only)

Staphylococcus epidermidis (methicillin-susceptible isolates only)

Staphylococcus saprophyticus

Streptococcus pneumoniae

Streptococcus pyogenes

Gram-negative Bacteria

Campylobacter jejuni *Citrobacter koseri* *Citrobacter freundii* *Enterobacter cloacae* *Escherichia coli* *Haemophilus influenzae* *Haemophilus parainfluenzae* *Klebsiella pneumoniae* *Moraxella catarrhalis* *Morganella morganii* *Neisseria gonorrhoeae* *Proteus mirabilis* *Proteus vulgaris*	*Providencia rettgeri* *Providencia stuartii* *Pseudomonas aeruginosa* *Salmonella typhi* *Serratia marcescens* *Shigella boydii* *Shigella dysenteriae* *Shigella flexneri* *Shigella sonnei* *Yersinia pestis*

The following *in vitro* data are available, **but their clinical significance is unknown**. At least 90% of the following bacteria exhibit an in vitro minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for ciprofloxacin (≤1 mcg/mL). However, the efficacy of ciprofloxacin in treating clinical infections due to these bacteria has not been established in adequate and well-controlled clinical trials.

Gram-positive Bacteria

Staphylococcus haemolyticus (methicillin-susceptible isolates only)

Staphylococcus hominis (methicillin-susceptible isolates only)

Gram-negative Bacteria

Acinetobacter *iwoffi*	*Pasteurella multocida*
Aeromonas hydrophila	*Salmonella enteritidis*
Edwardsiella tarda	Vibrio cholerae
Enterobacter aerogenes	Vibrio *parahaemolyticus*
Klebsiella oxytoca	*Vibrio vulnificus*
Legionella *pneumophila*	Yersinia enterocolitica

Tinidazole

Pharmacotherapeutic group: Anti-infective for systemic use

ATC code: J 01XD02

Tinidazole is an antiprotozoal, antibacterial agent. The nitro-group of tinidazole is reduced by cell extracts of Trichomonas. The free nitro-radical generated as a result of this reduction may be responsible for the antiprotozoal activity.

Chemically reduced tinidazole was shown to release nitrites and cause damage to purified bacterial DNA in vitro. Additionally, the drug caused DNA base changes in bacterial cells and DNA strand breakage in mammalian cells. The mechanism by which tinidazole exhibits activity against Giardia and Entamoeba species is not known.

Culture and sensitivity testing of bacteria are not routinely performed to establish the diagnosis of bacterial vaginosis; standard methodology for the susceptibility testing of potential bacterial pathogens, i.e. Gardnerella vaginalis, Mobiluncus spp. or Mycoplasma hominis, has not been defined. The following in vitro data are available, but their clinical significance is unknown. Tinidazole is active in vitro against most strains of the following organisms that have been reported to be associated with bacterial vaginosis:

· Bacteroides spp.

· Gardnerella vaginalis

· Prevotella spp.

Tinidazole does not appear to have activity against most strains of vaginal lactobacilli.

Tinidazole demonstrates activity both in vitro and in clinical infections against the following protozoa: Trichomonas vaginalis; Giardia duodenalis (also termed G. lamblia); and Entamoeba histolytica.

For protozoal parasites, standardised susceptibility tests do not exist for use in clinical microbiology laboratories.

The development of resistance to tinidazole by G. duodenalis, E. histolytica, or bacteria associated with bacterial vaginosis has not been examined.

Approximately 38% of T. vaginalis isolates exhibiting reduced susceptibility to metronidazole also show reduced susceptibility to tinidazole in vitro. The clinical significance of such an effect is not known.

Pharmacokinetic Properties

Ciprofloxacin

Absorption

Ciprofloxacin given as an oral tablet is rapidly and well absorbed from the gastrointestinal tract after oral administration. The absolute bioavailability is approximately 70%, with no substantial loss by first-pass metabolism.

Ciprofloxacin maximum serum concentrations and area under the curve (AUC) are shown in the chart for the 250–1,000 mg dose range.

Dose (mg)	**Maximum Serum Concentration (mcg/mL)**	**AUC (mcg•hr/mL)**
250	1.2	4.8
500	2.4	11.6
750	4.3	20.2
1,000	5.4	30.8

Maximum serum concentrations are attained 1–2 hours after oral dosing. Mean concentrations 12 hours after dosing with 250, 500 or 750 mg are 0.1, 0.2 and 0.4 µg/mL, respectively. The serum elimination half-life in subjects with normal renal function is approximately 4 hours. Serum concentrations increase proportionately with doses up to 1,000 mg.

A 500 mg oral dose given every 12 hours has been shown to produce an AUC equivalent to that produced by an intravenous (IV) infusion of 400 mg ciprofloxacin given over 60 minutes every 12 hours. A 750 mg oral dose given every 12 hours has been shown to produce an AUC at the steady state equivalent to that produced by an IV infusion of 400 mg given over 60 minutes every 8 hours. A 750 mg oral dose results in a C_{max} similar to that observed with a 400 mg IV dose. A 250 mg oral dose given every 12 hours produces an AUC equivalent to that produced by an infusion of 200 mg ciprofloxacin given every 12 hours.

Steady-state Pharmacokinetic Parameters Following Multiple Oral and IV Doses				
Parameters	**500 mg**	**400 mg**	**750 mg**	**400 mg**

	every 12 hours, orally	every 12 hours, IV	every 12 hours, orally.	every 8 hours, IV
AUC (mcg•hr/mL)	13.7	12.7	31.6	32.9
C_{max} (mcg/mL)	2.97	4.56	3.59	4.07

Food

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, whereas there is no delay observed when ciprofloxacin suspension is given with food. The overall absorption of ciprofloxacin tablet or ciprofloxacin suspension, however, is not substantially affected. The pharmacokinetics of ciprofloxacin given as the suspension is also not affected by food. Avoid concomitant administration of ciprofloxacin with dairy products (like milk or yoghurt) or calcium-fortified juices alone since decreased absorption is possible; however, ciprofloxacin may be taken with a meal that contains these products.

With oral administration, a 500 mg dose, given as 10 mL of the 5% ciprofloxacin suspension (containing 250 mg ciprofloxacin/5 mL) is bioequivalent to the 500 mg tablet.

Distribution

The binding of ciprofloxacin to serum proteins is 20–40%, which is not likely to be high enough to cause significant protein-binding interactions with other drugs.

After oral administration, ciprofloxacin is widely distributed throughout the body. Tissue concentrations often exceed serum concentrations in both men and women, particularly in genital tissue, including the prostate. Ciprofloxacin is present in active form in the saliva, nasal and bronchial secretions, mucosa of the sinuses, sputum, skin blister fluid, lymph, peritoneal fluid, bile, and prostatic secretions. Ciprofloxacin has also been detected in the lungs, skin, fat, muscle, cartilage and bone. The drug diffuses into the cerebrospinal fluid (CSF); however, CSF concentrations are generally less than 10% of peak serum concentrations. Low levels of the drug have been detected in the aqueous and vitreous humours of the eye.

Metabolism

Four metabolites have been identified in human urine, which together account for approximately 15% of an oral dose. The metabolites have antimicrobial activity, but are less active than unchanged ciprofloxacin. Ciprofloxacin is an inhibitor of human cytochrome (CY) P450 1A2 (CYP1A2)-mediated metabolism. Co-administration of ciprofloxacin with other drugs primarily metabolised by CYP1A2 results in increased plasma concentrations of these drugs and could lead to clinically significant adverse events of the co-administered drug.

Excretion

The serum elimination half-life in subjects with normal renal function is approximately 4 hours. Approximately 40–50% of an orally administered dose is excreted in the urine as unchanged drug. After a 250 mg oral dose, urine concentrations of ciprofloxacin usually exceed 200 µg/mL during the first 2 hours, and are approximately 30 µg/mL at 8–12 hours after dosing. The urinary excretion of ciprofloxacin is virtually complete within 24 hours after dosing. The renal clearance of ciprofloxacin, which is approximately 300 mL/minute, exceeds the normal glomerular filtration rate of 120 mL/minute. Thus, active tubular secretion would seem to play a significant role in its elimination. Co-administration of probenecid with ciprofloxacin results in about a 50% reduction in the ciprofloxacin

renal clearance and a 50% increase in its concentration in the systemic circulation. Although bile concentrations of ciprofloxacin are several-fold higher than serum concentrations after oral dosing, only a small amount of the dose administered is recovered from the bile as unchanged drug. An additional 1–2% of the dose is recovered from the bile in the form of metabolites. Approximately 20–35% of an oral dose is recovered from the faeces within 5 days after dosing. This may arise from either biliary clearance or transintestinal elimination.

Drug–Drug Interactions

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

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

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

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.

In a study conducted in 12 patients with Parkinson's disease who were administered 6 mg ropinirole once daily with twice-daily 500 mg ciprofloxacin, 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.

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.

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 two-fold. Use sildenafil with caution when co-administered with ciprofloxacin due to the expected two-fold increase in the exposure of sildenafil upon co-administration of ciprofloxacin.

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.

In a study conducted in 9 healthy volunteers, concomitant use of 1.5 mg/kg IV lidocaine with ciprofloxacin 500 mg twice daily resulted in an increase of lidocaine C_{max} 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 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.

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

Special Populations

Elderly

Pharmacokinetic studies of the oral (single dose) and IV (single- and multiple-dose) forms of ciprofloxacin indicate that plasma concentrations of ciprofloxacin are higher in elderly subjects (aged ≥65 years) as compared with young adults. Although the C_{max} is increased by 16–40%, 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.

Renal Impairment

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

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 impairment, however, has not been fully studied.

Tinidazole

Absorption

After oral administration, tinidazole is rapidly and completely absorbed. A bioavailability study of tinidazole tablets was conducted in adult healthy volunteers. All subjects received a single oral dose of 2 g (four 500 mg tablets) of tinidazole following an overnight fast. Oral administration of four 500 mg tablets of tinidazole under fasted conditions produced a mean peak plasma concentration (C_{max}) of 47.7 (±7.5) µg/mL with a mean time to peak concentration (Tmax) of 1.6 (±0.7) hours, and a mean area under the plasma concentration time curve (AUC, 0-infinity) of 901.6 (± 126.5) µg.hr/mL at 72 hours. The elimination half-life (T½) was 13.2 (±1.4) hours. Mean plasma levels decreased to 14.3 µg/mL at 24 hours, 3.8 µg/mL at 48 hours and 0.8 µg/mL at 72 hours following administration. Steady-state conditions are reached in 2½ – 3 days of multi-day dosing.

Administration of tinidazole tablets with food resulted in a delay in Tmax of approximately 2 hours and a decline in C_{max} of approximately 10%, compared with fasted conditions. However, administration of tinidazole with food did not affect AUC or T½ in this study.

In healthy volunteers, administration of crushed tinidazole tablets in artificial cherry syrup after an overnight fast had no effect on any pharmacokinetic parameter as compared with tablets swallowed whole under fasted conditions.

Distribution

Tinidazole is distributed into virtually all tissues and body fluids and also crosses the blood-brain barrier. The apparent volume of distribution is about 50 litres. Plasma protein binding of tinidazole

is 12%. Tinidazole crosses the placental barrier and is secreted in breast milk.

Metabolism

Tinidazole is significantly metabolised in humans prior to excretion. Tinidazole is partly metabolised by oxidation, hydroxylation and conjugation. Tinidazole is the major drug-related constituent in plasma after human treatment, along with a small amount of the 2-hydroxymethyl metabolite.

Tinidazole is biotransformed mainly by CYP3A4. In an in vitro metabolic drug interaction study, tinidazole concentrations of up to 75 µg/mL did not inhibit the enzyme activities of CYP1A2, CYP2B6, CYP2C9, CYP2D6, CYP2E1 and CYP3A4. The potential of tinidazole to induce the metabolism of other drugs has not been evaluated.

Elimination

The plasma half-life of tinidazole is approximately 12–14 hours. Tinidazole is excreted by the liver and the kidneys. Tinidazole is excreted in the urine mainly as unchanged drug (approximately 20–25% of the administered dose). Approximately 12% of the drug is excreted in the faeces.

Special Populations

The pharmacokinetics of tinidazole in patients with severe renal impairment (creatinine clearance [CrCL] <22 mL/min) is not significantly different from the pharmacokinetics seen in healthy subjects. However, during haemodialysis, clearance of tinidazole is significantly increased; the half-life is reduced from 12.0 hours to 4.9 hours. Approximately 43% of the amount present in the body is eliminated during a 6-hour haemodialysis session. The pharmacokinetics of tinidazole in patients undergoing routine continuous peritoneal dialysis has not been investigated.

There are no data on tinidazole pharmacokinetics in patients with impaired hepatic function. Reduction of metabolic elimination of metronidazole, a chemically-related nitroimidazole, in patients with hepatic dysfunction has been reported in several studies.

Non-Clinical Properties

Animal Toxicology or Pharmacology

Ciprofloxacin

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 to 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 two weeks of treatment, which were still

observed after 5 months.

Tinidazole

Tinidazole has been shown to be mutagenic in some bacterial strains tested *in vitro* (with and without metabolic activation). Tinidazole was negative for mutagenicity in a mammalian cell culture system utilising Chinese hamster lung V79 cells (HGPRT test system) and negative for genotoxicity in the Chinese hamster ovary (CHO) sister chromatid exchange assay. Tinidazole was positive for *in vivo* genotoxicity in the mouse micronucleus assay.

Description

CIPLOX-TZ/CIPLOX-TZ H Tablets are a fixed-dose combination of ciprofloxacin hydrochloride and tinidazole.

Ciprofloxacin is a fluoroquinolone antibacterial agent with a broad spectrum of activity.

Tinidazole is a nitroimidazole that has antimicrobial action against microaerophilic Protozoa, *Giardia lamblia*, *Entamoeba histolytica* and *Trichomonas vaginalis*, and against obligate anaerobic bacteria.

The combination of ciprofloxacin and tinidazole provides broad-spectrum coverage of both aerobic and anaerobic organisms in a variety of infections.

Pharmaceutical Particulars

Incompatibilities

Not applicable

Shelf-Life

See on Pack

Packaging Information

CIPLOX TZ: Each strip contains 10 tablets

Storage and Handling Instructions

Store in cool dry place

Patient Counselling Information

1. What is CIPLOX-TZ?

CIPLOX-TZ is a medicine which contains ciprofloxacin hydrochloride and tinidazole.

Ciprofloxacin is an antibiotic belonging to the fluoroquinolone family. The active substance is ciprofloxacin. Ciprofloxacin works by killing bacteria that cause infections. It only works with specific strains of bacteria.

Tinidazole is an antibiotic that is used to treat certain types of vaginal infections (bacterial

vaginosis, trichomoniasis). It is also used to treat certain types of parasite infections (giardiasis, amebiasis). It works by stopping the growth of certain bacteria and parasites.

2. Do not take if you have an allergy to CIPLOX-TZ Tablets

Do not take this medicine

· if you are allergic to ciprofloxacin, to other quinolone drugs or to any of the other ingredients of this medicine

· if you are taking tizanidine

· If you are allergic (hypersensitive) to tinidazole or any similar drugs An allergic reaction could cause itching, a skin rash or wheezing.

3. Before you take CIPLOX-TZ Tablets, tell your doctor about other medication

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Do not take Ciprofloxacin together with tizanidine, because this may cause side effects such as low blood pressure and sleepiness.

The following medicines are known to interact with Ciprofloxacin in your body. Taking Ciprofloxacin together with these medicines can influence the therapeutic effect of those medicines. It can also increase the probability of experiencing side effects.

Tell your doctor if you are taking:

· Vitamin K antagonists (e.g.warfarin, acenocoumarol, phenprocoumon or fluindione) or other oral anti-coagulants (to thin the blood)

· theophylline (for breathing problems)

· phenytoin (for epilepsy) • probenecid (for gout)

· ropinirole (for Parkinson’s disease)

· methotrexate (for certain types of cancer, psoriasis, rheumatoid arthritis)

· tizanidine (for muscle spasticity in multiple sclerosis)

· olanzapine (an antipsychotic)

· clozapine (an antipsychotic) • metoclopramide (for nausea and vomiting)

· cyclosporin (for skin conditions, rheumatoid arthritis and in organ transplantation)

· •other medicines that can alter your heart rhythm: medicines that belong to the group of antiarrhythmics (e.g. quinidine, hydroquinidine, disopyramide, amiodarone, sotalol, dofetilide, ibutilide), tricyclic antidepressants, some antimicrobials (that belong to the group of macrolides), some antipsychotics.

· zolpidem (for sleep disorders)

Ciprofloxacin may increase the levels of the following medicines in your blood:

· pentoxifylline (for circulatory disorders)

· caffeine • duloxetine (for depression, diabetic nerve damage or incontinence)

· lidocaine (for heart conditions or anaesthetic use)

· sildenafil (e.g. for erectile dysfunction)

· agomelatine (for depression)

Some medicines reduce the effect of Ciprofloxacin.

Tell your doctor if you take or wish to take:

· antacids

· omeprazole

· mineral supplements

· sucralfate

· a polymeric phosphate binder (e.g. sevelamer or lanthanum carbonate)

· medicines or supplements containing calcium, magnesium, aluminium or iron If these preparations are essential, take Ciprofloxacin about two hours before or no sooner than four hours after them.

· Ciprofloxacin with food, drink and alcohol

· Unless you take Ciprofloxacin during meals, do not eat or drink any dairy products (such as milk or yoghurt) or drinks with added calcium when you take the tablets, as they may affect the absorption of the active substance.

Tell your doctor if you are taking or have recently taken any other medicines including those obtained without a prescription.

You should tell your doctor if you are currently taking blood thinners such as

warfarin to prevent blood clots as your doctor may wish to monitor you more closely. Tinidazole medicine with food and drink

You should not drink wine, beer or spirits during treatment and for 3 days after stopping treatment with this medicine. The combination may cause flushing, stomach cramps, vomiting (being sick) and palpitations (pounding heart).

4. How should I take CIPLOX-TZ Tablets?

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Tell your doctor if you suffer from kidney problems because your dose may need to be adjusted.

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist

if you are not sure how many tablets to take and how to take

Swallow this medicine with plenty of fluid. Do not chew the tablets because they do not taste nice. Do try to take the tablets at around the same time every day. You can take the tablets at mealtimes or between meals.

Any calcium you take as part of a meal will not seriously affect uptake. However, do not take this medicine with dairy products such as milk or yoghurt or with fortified fruit juices (e.g. calcium-fortified orange juice). Remember to drink plenty of fluids while you are taking this medicine.

If **you take more this medicine than you should**: If you take more than the prescribed dose, get medical help immediately. If possible, take your tablets or the box with you to show the doctor.

If you forget to take this medicine: Take the normal dose as soon as possible and then continue as prescribed. However, if it is almost time for your next dose, do not take the missed dose and continue as usual. Do not take a double dose to make up for a forgotten dose.

Be sure to complete your course of treatment. If you stop taking this medicine, It is important that you finish the course of treatment even if you begin to feel better after a few days. If you stop taking this medicine too soon, your infection may not be completely cured, and the symptoms of the infection may return or get worse. You might also develop resistance to the antibiotic.

If you have any further questions about the use of this medicine, ask your doctor or pharmacist.

5. What are the possible side effects of CIPLOX-TZ Tablets?

Ciprofloxacin

Like all medicines, this medicine can cause side effects, although not everybody gets them. The following section contains the most serious side effects that you can recognize yourself: Stop taking Ciprofloxacin and contact your doctor immediately in order to consider another antibiotic treatment if you notice any of the following serious side effects:

Rare (may affect up to 1 in 1,000 people) - Seizure

Very rare (may affect up to 1 in 10,000 people) - Severe, sudden allergic reaction with symptoms such as tightness in the chest, feeling dizzy, sick or faint, or experience dizziness when standing up (anaphylactic reaction/shock)

- Muscle weakness, inflammation of the tendons which could lead to rupture of the tendon, particularly affecting the large tendon at the back of the ankle (Achilles tendon)

- A serious life-threatening skin rash, usually in the form of blisters or ulcers in the mouth, throat, nose, eyes and other mucous membranes such as genitals which may progress to widespread blistering or peeling of the skin (Stevens-Johnson syndrome, toxic epidermal necrolysis).

Not known (frequency cannot be estimated from the available data)

- Unusual feelings of pain, burning tingling, numbness or muscle weakness in the extremities (neuropathy)

- A drug reaction that causes rash, fever, inflammation of internal organs, hematologic

abnormalities and systemic illness (DRESS Drug Reaction with Eosinophilia and Systemic Symptoms, AGEP Acute Generalised Exanthematous Pustulosis). Other side effects which have been observed during treatment with **Ciprofloxacin are listed below by how likely they are:**
Common (may affect up to 1 in 10 people):

· nausea, diarrhoea - joint pain and joint inflammation in children Uncommon (may affect up to 1 in 100 people):

· fungal superinfections

· a high concentration of eosinophils, a type of white blood cell

· decreased appetite (anorexia)

· hyperactivity or agitation

· headache, dizziness, sleeping problems, or taste disorders

· vomiting, abdominal pain, digestive problems such as stomach upset (indigestion/heartburn), or wind

· increased amounts of certain substances in the blood (transaminases and/or bilirubin)

· rash, itching, or hives

· joint pain in adults

· poor kidney function

· pains in your muscles and bones, feeling unwell (asthenia), or fever

· increase in blood alkaline phosphatase (a certain substance in the blood)

Rare (may affect up to 1 in 1,000 people):

· muscle pain, inflammation of the joints, increased muscle tone and cramping - inflammation of the bowel (colitis) linked to antibiotic use (can be fatal in very rare cases)

· changes to the blood count (leukopenia, leukocytosis, neutropenia, anaemia), increased or decreased amounts of a blood clotting factor (thrombocytes)

· allergic reaction, swelling (oedema), or rapid swelling of the skin and mucous membranes (angio-oedema)

· increased blood sugar (hyperglycaemia)

· decreased blood sugar (hypoglycaemia)

· confusion, disorientation, anxiety reactions, strange dreams, depression (potentially leading to thoughts of suicide, suicide attempts, or complete suicide), or hallucinations

· pins and needles, unusual sensitivity to stimuli of the senses, decreased skin sensitivity, tremors, or giddiness

· eyesight problems including double vision

· tinnitus, loss of hearing, impaired hearing

· rapid heartbeat (tachycardia)

· expansion of blood vessels (vasodilation), low blood pressure, or fainting

· shortness of breath, including asthmatic symptoms

· liver disorders, jaundice (cholestatic icterus), or hepatitis - sensitivity to light

· kidney failure, blood or crystals in the urine, urinary tract inflammation

· fluid retention or excessive sweating

· increased levels of the enzyme amylase

Very rare (may affect up to 1 in 10,000 people):

- a special type of reduced red blood cell count (haemolytic anaemia); a dangerous drop in a type of white blood cells (agranulocytosis); a drop in the number of red and white blood cells and platelets (pancytopenia), which may be fatal; and bone marrow depression, which may also be fatal - allergic reactions called serum sickness like reaction

· mental disturbances (psychotic reactions potentially leading to thoughts of suicide, suicide attempts, or completed suicide) migraine, disturbed coordination, unsteady walk (gait disturbance), disorder of sense of smell (olfactory disorders), pressure on the brain (intracranial pressure and pseudotumor cerebri)

· visual colour distortions

· inflammation of the wall of the blood vessels (vasculitis)

· pancreatitis - death of liver cells (liver necrosis) very rarely leading to life-threatening liver failure

· small, pin-point bleeding under the skin (petechiae); various skin eruptions or rashes

· worsening of the symptoms of myasthenia gravis

Not known (frequency cannot be estimated from the available data)

· abnormal fast heart rhythm, life-threatening irregular heart rhythm, alteration of the heart rhythm (called 'prolongation of QT interval', seen on ECG, electrical activity of the heart)

· influence on blood clotting (in patients treated with Vitamin K antagonists)

· Feeling highly excited (mania) or feeling great optimism and overactivity (hypomania).

· Syndrome associated with impaired water excretion and low levels of sodium (SIADH)

Other side effects include: - Increase of your blood sugar levels (hyperglycaemia) or lowering of your blood sugar levels leading to coma (hypoglycaemic coma). This is important for people that have

diabetes.

Very rare cases of long lasting (up to months or years) or permanent adverse drug reactions, such as tendon inflammations, tendon rupture, joint pain, pain in the limbs, difficulty in walking, abnormal sensations such as pins and needles, tingling, tickling, burning, numbness or pain (neuropathy), depression, fatigue, sleep disorders, memory impairment, as well as impairment of hearing, vision, and taste and smell have been associated with administration of quinolone and fluoroquinolone antibiotics, in some cases irrespective of pre-existing risk factors

Tinidazole

Like all medicines, this medicine causes side effects, although not everybody gets them. Tell your doctor immediately if you experience any of the following symptoms after taking this medicine.

Although they are very rare, the symptoms can be severe.

· sudden wheeziness, difficulty in breathing, swelling of eyelids, face or lips or tongue

· fits or seizures

The common side effects (that may affect up to 1 in 10 people) are listed below. These may go away during treatment as your body adjusts to the medicine.

Tell your doctor if any of these side effects continue to bother you.

· nausea (feeling sick) or vomiting, loss of appetite, diarrhoea, stomach pain or cramps

· headache

· vertigo

· skin rash or itching (especially affecting the whole body).

The frequency of the following side effects is not known (cannot be estimated from the available data). You should contact your doctor if you notice any of the following: • numbness, tingling, pain or weakness in hands or feet

· clumsiness or unsteadiness

· fever or chills and painful ulcers in the mouth

· sore or swollen mouth/tongue

· redness of the face or neck

· dizziness

· tiredness

· dark urine

· tongue discolouration or unpleasant metallic taste.

Tinidazole can sometimes cause a temporary reduction in white blood cells which does not usually

give you any symptoms.

6. How should I store CIPLOX-TZ Tablets?

Keep this medicine out of the sight and reach of children. Do not use this medicine after the expiry date which is stated on the carton and blister after EXP. The expiry date refers to the last day of that month. This medicinal product does not require any special storage conditions. Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

7. General information about the safe and effective use of CIPLOX-TZ Tablets

Ciprofloxacin

Talk to your doctor or pharmacist before taking this medicine.

· You should not take fluoroquinolone/quinolone antibacterial medicines, including Ciprofloxacin, if you have experienced any serious adverse reaction in the past when taking a quinolone or fluoroquinolone. In this situation, you should inform your doctor as soon as possible.

· if you have ever had kidney problems because your treatment may need to be adjusted

· if you suffer from epilepsy or other neurological conditions.

· if you have a history of tendon problems during previous treatment with antibiotics such as Ciprofloxacin

· if you are diabetic because you may experience a risk of hypoglycaemia with ciprofloxacin.

· if you have myasthenia gravis (a type of muscle weakness) because symptoms can be exacerbated.

· if you have heart problems. Caution should be taken when using Ciprofloxacin, if you were born with or have family history of prolonged QT interval (seen on ECG, electrical recording of the heart), have salt imbalance in the blood (especially low level of potassium or magnesium in the blood), have a very slow heart rhythm (called 'bradycardia'), have a weak heart (heart failure), have a history of heart attack (myocardial infarction), you are female or elderly or you are taking other medicines that result in abnormal ECG changes

· if you or a member of your family is known to have a deficiency in glucose-6- phosphate dehydrogenase (G6PD), since you may experience a risk of anaemia with ciprofloxacin.

· if you have been diagnosed with an enlargement or "bulge" of a large blood vessel (aortic aneurysm or large vessel peripheral aneurysm).

· if you have experienced a previous episode of aortic dissection (a tear in the aorta wall).

· if you have a family history of aortic aneurysm or aortic dissection or other risk factors or predisposing conditions (e.g. connective tissue disorders such as Marfan syndrome, or vascular Ehlers-Danlos syndrome, or vascular disorders such as Takayasu arteritis, giant cell arteritis, Behcet's disease, high blood pressure, or known atherosclerosis). If you feel sudden, severe pain in your abdomen, chest or back, go immediately to an emergency room. For the treatment of some genital tract infections, your doctor can prescribe another antibiotic in addition to ciprofloxacin. If

there is no improvement in symptoms after 3 days of treatment, please consult your doctor.

While taking ciprofloxacin Tell your doctor immediately, if any of the following occurs while taking Ciprofloxacin. Your doctor will decide whether treatment with Ciprofloxacin needs to be stopped.

· Severe, sudden allergic reaction (an anaphylactic reaction/shock, angiooedema). Even with the first dose, there is a small chance that you may experience a severe allergic reaction with the following symptoms: tightness in the chest, feeling dizzy, sick or faint, or experiencing dizziness when standing up. If this happens, stop taking Ciprofloxacin and contact your doctor immediately.

· Pain and swelling in the joints and inflammation or rupture of tendons may occur rarely. Your risk is increased if you are elderly (above 60 years of age), have received an organ transplant, have kidney problems or if you are being treated with corticosteroids. Inflammation and ruptures of tendons may occur within the first 48 hours of treatment and even up to several months after stopping of Ciprofloxacin therapy. At the first sign of pain or inflammation of a tendon (for example in your ankle, wrist, elbow, shoulder or knee), stop taking this medicine, contact your doctor and rest the painful area. Avoid any unnecessary exercise as this might increase the risk of a tendon rupture.

· If you suffer from epilepsy or other neurological conditions such as cerebral ischemia or stroke, you may experience side effects associated with the central nervous system. If seizure happens, stop taking Ciprofloxacin and contact your doctor immediately.

· You may experience psychiatric reactions the first time you take Ciprofloxacin. If you suffer from depression or psychosis, your symptoms may become worse under treatment with Ciprofloxacin. In rare cases, depression or psychosis can progress to thoughts of suicide, suicide attempts, or completed suicide. If this happens, contact your doctor immediately.

· Hypoglycemia has been reported most often in diabetic patients, predominantly in elderly population. If this happens, contact your doctor immediately.

· You may rarely experience symptoms of nerve damage (neuropathy) such as pain, burning, tingling, numbness and/ or weakness especially in the feet and legs or hands and arms. If this happens, stop taking Ciprofloxacin and inform your doctor immediately in order to prevent the development of potentially irreversible condition.

· If your eyesight becomes impaired or if your eyes seem to be otherwise affected, consult an eye specialist immediately.

· Diarrhoea may develop while you are taking antibiotics, including Ciprofloxacin, or even several weeks after you have stopped taking them. If it becomes severe or persistent or you notice that your stool contains blood or mucus, stop taking Ciprofloxacin and contact your doctor immediately, as this can be life-threatening. Do not take medicines that stop or slow down bowel movements.

· Tell the doctor or laboratory staff that you are taking Ciprofloxacin if you have to provide a blood or urine sample.

· If you suffer from kidney problems, tell the doctor because your dose may need to be adjusted.

· Ciprofloxacin may cause liver damage. If you notice any symptoms such as loss of appetite, jaundice (yellowing of the skin), dark urine, itching, or tenderness of the stomach, contact your doctor immediately.

· Ciprofloxacin may cause a reduction in the number of white blood cells and your resistance to infection may be decreased. If you experience an infection with symptoms such as fever and serious deterioration of your general condition, or fever with local infection symptoms such as sore throat/pharynx/mouth or urinary problems you should see your doctor immediately. A blood test will be taken to check possible reduction of white blood cells (agranulocytosis). It is important to inform your doctor about your medicine.

· Your skin becomes more sensitive to sunlight or ultraviolet (UV) light when taking Ciprofloxacin. Avoid exposure to strong sunlight, or artificial UV light such as sunbeds.

· Prolonged, disabling and potentially irreversible serious side effects
Fluoroquinolone/quinolone antibacterial medicines, including Ciprofloxacin, have been associated with very rare but serious side effects, some of them being long lasting (continuing months or years), disabling or potentially irreversible. This includes tendon, muscle and joint pain of the upper and lower limbs, difficulty in walking, abnormal sensations such as pins and needles, tingling, tickling, numbness or burning (paraesthesia), sensory disorders including impairment of vision, taste and smell, and hearing, depression, memory impairment, severe fatigue, and severe sleep disorders. If you experience any of these side effects after taking Ciprofloxacin, contact your doctor immediately prior to continuing treatment. You and your doctor will decide on continuing the treatment considering also an antibiotic from another class

Tinidazole

Do not take Tinidazole 500mg film-coated tablets if:

· you have a blood disorder or a history of blood disorders

· you have central nervous system (CNS) disease, including epilepsy

· you are in the first 13 weeks of pregnancy or trying to become pregnant or you are breast-feeding.

Talk to your doctor, pharmacist or nurse, if during therapy with this medicine abnormal neurological signs develop (such as, dizziness, vertigo, difficulty in controlling movements) as you may be told to stop your treatment.

Pregnancy and Breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. It is preferable to avoid the use of this medicine during pregnancy.

Do not take this medicine during breast feeding because this medicine is excreted in breast milk and can be harmful for your child.

Driving and using machines: This medicine may make you feel less alert. Some neurological adverse events can occur. Therefore, make sure you know how you react to this medicine before driving a vehicle or operating machinery. If in doubt, talk to your doctor

8. What are the ingredients in CIPLOX-TZ Tablets?

CIPLOX-TZ Tablets
Each film-coated tablet contains:

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

Tinidazole, IP ..... 600 mg

Details of the Manufacturer

Mfd. By Cipla Ltd.

Registered Office:

Cipla House, Peninsula Business Park,

Ganpatrao Kadam Marg

Lower Parel

Mumbai – 400 013, India

Details of Permission or Licence Number with Date

Lic.No.: M/447/2007 dated 12/01/2020

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