National Agency for Food & Drug Administration & Control (NAFDAC)

Registration & Regulatory Affairs (R & R) Directorate

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC) TEMPLATE

1. NAME OF THE MEDICINAL PRODUCT

CIPROFLOXACIN AND TINIDAZOLE TABLETS

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

CIPROFLOXACIN BP……..500 mg

TINIDAZOLE BP……..600 MG

Each Film coated tablet contains:
Ciprofloxacin hydrochloride BP
Equivalent to Ciprofloxacin……500 mg
Tinidazole BP……..600 mg
Excipients……Q.S
Colour: Sunset yellow FCF & Titanium dioxide

3. PHARMACEUTICAL FORM

Oral film coated tablets

4. Clinical particulars

4.1 Therapeutic indications

Ciprofloxacin and Tinidazole 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.

4.2 Posology and method ofadministration

Ciprofloxacin and Tinidazole 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.

Method of administration
Oral film coated tablet

4.3 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

4.4 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.

4.5 Interaction with other medicinal products and other forms of interaction

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		Careful monitoring of clozapine associated adverse

	Use with caution	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	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.

paediatric powder; other highly buffered drugs; or products containing calcium, iron or zinc and dairy products)		
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.

4.6 Pregnancy and Lactation

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.

4.7 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.

4.8 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 behavior (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 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.

4.9 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics 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	
Enterobcter cloacae	*Providencia rettgeri*
Escherichia coli	*Providencia stuartii*
Haemophilus influenzae	*Pseudomonas aeruginosa*
Haemophilus parainfluenzae	*Salmonella typhi*
Klebsiella pneumoniae	*Serratia marcescens*
Moraxella catarrhalis	*Shigella boydii*
Morganella morganii	*Shigella dysenteriae*
Neisseria gonorrhoeae	*Shigella flexneri*
Proteus mirabilis	*Shigella sonnei*
Proteus vulgaris	*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.

5.2 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.

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 (Cmax) 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 Cmax 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.

5.3 Preclinical safety data

There are no preclinical data of relevance to the prescriber which are additional to that already included in other sections of the Summary of Product Characteristics

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize starch

Purified water

Purified Talc

Sodium starch glycolate

Magnesium stearate

Colloiodal anhydrous silica

Colorezy white

Colour sunset yellow

Isopropyl alcohol

Dichloromethan

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months for the date of manufacturing.

6.4 Special precautions for storage

Store below 30º C. Protect from light. Keep out of reach of children

6.5 Nature and contents of container <and special equipment for use, administration or implantation>

1x10 Tablets in Alu Alu blister pack

6.6 Special precautions for disposal <and other handling>

There are no special storage precautions. Any unused product or waste material should be disposed of in accordance with local requirements.

7. <APPLICANT/MANUFACTURER>

Stallion laboratories Pvt. Ltd.

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