CIPNOX PLUS
(CIPROFLOXACIN AND TINIDAZOLE TABLETS)

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

1. Name of the medicinal product

CIPNOX PLUS

(CIPROFLOXACIN AND TINIDAZOLE TABLETS)

2. Qualitative and quantitative compositionPharmaceutical form

Each film coated tablet contains:

Ciprofloxacin Hydrochloride BP

eq. to Ciprofloxacin 500 mg

Tinidazole BP 600 mg

Colour: Titanium Dioxide BP & Sunset yellow

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 of administration

Dosage and Administration

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

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

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.

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 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

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-loweringeffect 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 levelsof henytoin increased and decreased)	To avoid the loss of seizure control associated with decreased phenytoin levels and to prevent phenytoin overdose- related adverse Reactions uponciprofloxacin.

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

4.6 Fertility, 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

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 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.

Tinidazole

Pharmacotherapeutic group: Anti-infective for systemic useATC 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 bacterialpathogens, 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: 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 microbiologylaboratories.

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 substantialloss 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. Serumconcentrations 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 Cmax 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
Cmax (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 thedrug, 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 maybe 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 tocause 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, CSFconcentrations 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 leadto 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 rateof 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 themetabolism 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

6.0 PHARMACEUTICAL EXCIPIENTS

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

None known

6.3 Shelf life

36 months for the date of manufacturing.

6.4 Special precautions

Store at temperature below 30°C. Protect from light.

6.5 Nature and contents of container

1x10 Tablets in Alu Alu blister pack

6.6 Instruction for use handling and disposal:

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

7. Manufacturer name

Alpa Laboratories Limited

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8. Marketing Authority

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