1.3.1 Summary of Product Characteristics

1.3.1.1 Invented Name of the Medicinal Product

TREXIP-TZ

Ciprofloxacin with Tinidazole Tablets

1.3.1.2 Strength

Ciprofloxacin 500 mg & Tinidazole 600 mg Tablets

1.3.1.3 Dosage Form

Solid Dosage Form

1.3.1.4 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains:

Ciprofloxacin Hydrochloride BP

Equivalent to ciprofloxacin …….....500 mg.

Tinidazole BP…….600 mg.

Excipients……..Q.S.

Colour : Titanium Dioxide BP

1.3.1.5 PHARMACEUTICAL FORM

Film coated Tablets.

White coloured oval shaped film coated tablet with break line on one side

1.3.1.6. CLINICAL PARTICULARS

1.3.1.6.1 Therapeutic indications

TREXIP-TZ is indicated for the treatment of a wide variety of infections caused by susceptible gram - positive and gram - negative organisms along with anaerobes and protozoa.

- Surgical prophylaxis and surgical wound infections.

- Gynaecological infections including prophylaxis in gynaecological surgeries.
- Respiratory Tract infections like lung abscess, aspiration pneumonia, empyema and bronchiectasis.
- ENT infections like chronic sinusitis, chronic suppurative otitis media, cholesteatoma and mastoiditis.
- Orofacial and Dental infections.
- Dermatological infections like cellulitis, breast and other cutaneous abscesses, gangrene, diabetic and decubitus ulcers.
- Intra - abdominal infections and diarrhoeas of mixed bacterial and protozoal origin.

1.3.1.6.2 POSOLOGY AND METHOD OF ADMINISTRATION

Route : Oral.

Adults : 1 Tablet twice daily after meals for 5 - 10 days. depending upon severity of disease.

Children: Not recommended.

1.3.1.6.3 CONTRAINDICATIONS

TREXIP-TZ is contraindicated in persons with a history of hypersensitivity to ciprofloxacin & tinidazole or any member of the quinolone class of antimicrobial agents.

1.3.1.6.4 WARNING AND PRECAUTIONS

Theophylline	:	Serum concentration and elimination half-life of Theophyline may be increased when it is used concurrently with Ciprofloxacin
Antacids	:	Antacids containing magnesium hydroxide and/or aluminium hydroxide may interfere with the absorption of Ciprofloxacin, resulting in lower serum and urine levels.
Anticoagulants:		Prolongation of bleeding time has been reported during concomitant administration of Ciprofloxacin and Anticoagulants.
Cyclosporin	:	Transient increases in serum creatinine have been seen following concomitant administration of Cyclosporin and Ciprofloxacin.
Caffeine	:	Ciprofloxacin may interfere with the metabolism of Caffeine resulting in reduced clearance of caffeine.
Alcohol	:	Disulfiram-like antabuse reaction may occur due to

		Tinidazole. Abdominal cramps, nausea, vomiting, headache & flushing.
Disulfiram	:	Acute psychotic reaction or confusional state.
Phenobarbital	:	Increased metabolism of Metronidazole resulting in decreased & Phenytoin efficacy.
Lab tests	:	May interfere with chemical analysis for AST, SGOT, ALT, SGPT, LOH, triglyceride and hexokinase glucose. Zero values may occur.

1.3.1.6.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Ciprofloxacin Hydrochloride :

As with some other quinolones, concurrent administration of ciprofloxacin with theophylline may lead to elevated serum concentrations of theophylline and prolongation of its elimination half - life. This may result in increased risk of theophylline - related adverse reactions. If concomitant use cannot be avoided, serum levels of theophylline should be monitored and dosage adjustments made as appropriate.

Some quinolones, including ciprofloxacin, have also been shown to interfere with the metabolism of caffeine. This may lead to reduced clearance of caffeine and a prolongation of its serum half - life.

Concurrent administration of a quinolone, including ciprofloxacin, with multivalent cation - containing products such as magnesium / aluminum antacids, sucralfate, Videx® (didanosine) chewable / buffered tablets or pediatric powder, or products containing calcium, iron, or zinc may substantially decrease its absorption, resulting in serum and urine levels considerably lower than desired. for concurrent administration of these agents with ciprofloxacin.)

Histamine H_2 - receptor antagonists appear to have no significant effect on the bioavailability of ciprofloxacin.

Altered serum levels of phenytoin (increased and decreased) have been reported in patients receiving concomitant ciprofloxacin.

The concomitant administration of ciprofloxacin with the sulfonylurea glyburide has, on rare occasions, resulted in severe hypoglycemia.

Some quinolones, including ciprofloxacin, have been associated with transient elevations in serum creatinine in patients receiving cyclosporine concomitantly.

Quinolones have been reported to enhance the effects of the oral anticoagulant warfarin or its derivatives. When these products are administered concomitantly, prothrombin time or other suitable coagulation tests should be closely monitored.

Probenecid interferes with renal tubular secretion of ciprofloxacin and produces an increase in the level of ciprofloxacin in the serum. This should be considered if patients are receiving both drugs concomitantly.

As with other broad spectrum antimicrobial agents, prolonged use of ciprofloxacin may result in overgrowth of nonsusceptible organisms. Repeated evaluation of the patient' condition and microbial susceptibility testing is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Tinidazole :

Potentially hazardous interactions

Tinidazole is reported to have a disulfarim - like interaction with alcohol causing nausea, vomiting, abdominal cramps, and not flushing. Patients taking tinidazole should not drink alcohol. Tinidazole interferes with the metabolism of racemic and S-(-)- warfarin to enhance blood levels, exacerbating its anticoagulant action. While reports of this are lacking for tinidazole the similarity of structure between the two compounds suggests that this effect will occur with both and so the use of tinidazole should be avoided so far as possible in patients taking warfarin.

Potentially useful interactions

No useful interactions have been reported. An in vitro study has shown synergism between tinidazole and ampicillin, doxycycline, and sulfamethoxazole and trimethoprim combination. This synergism may contribute to the efficacy of the combination of tinidazole with doxycycline in chemoprophylaxis of anaerobic sepsis after abdominal surgery.

1.3.1.6.6 PREGNANCY AND LACTATION

PREGNANCY: TREXIP-TZ is not recommended for use in pregnancy.

NURSING MOTHERS: TREXIP-TZ is not recommended for use in nursing

mothers.

1.3.1.6.7 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.

1.3.1.6.8 UNDESIRABLE EFFECTS

Ciprofloxacin should be used with caution in patients with CNS disorders such as severe cerebral arteriosclerosis or epilepsy.

Crystalluria: Inadequate intake of water, when on Ciprofloxacin can cause Crystalluria.

Phototoxicity: Moderate to severe phototoxicity has been observed in patients who are exposed to direct sunlight with some members of the quinolone class of drugs. Metallic taste, mild nausea, headache, vomiting, anorexia, abdominal pain, furry tongue, pruritus, photosensitivity, vasculitis, skin rash, dizziness, vertigo, incoordination, insomnia, tremor, convulsion, paraesthesia, blurred vision, eosinophilia, leucopenia, myalgia, tendinitis and exacerbation of myasthenia gravis.

1.3.1.6.9 OVERDOSE

In the event of acute over dosage, reversible renal toxicity has been reported in some cases. The stomach should be emptied by inducing vomiting or gastric lavage. The patient should be carefully observed and given supportive treatment including monitoring of renal function and administration magnesium, aluminium or calcium containing antacids which can reduce the absorption of Ciprofloxacin. Adequate hydration must be maintained.

Only a small amount of Ciprofloxacin (<10 %) is removed from the body after hemodialysis or peritoneal dialysis single doses of Ciprofloxacin were relatively non toxic via the oral route of administration in mices, rats, and dogs. No deaths occurred within 14 days post

treatment observation periods at the highest oral doses tested, up to 5000 mg/kg in either rodent species or up to 2500 mg/kg in the dog. Clinical signs observed included hypoacitivity and cyanosis in both rodent species and severe vomiting in dogs. In rabbits, significant toxicity including tonic/clonic convulsions was observed at intravenous doses of Ciprofloxacin between 125 and 300 mg/kg.,

IN IMPAIRED RENAL FUNCTION: If creatinine clearance is less than 20 ml/min, half the recommended dosage may be administered.

1.3.1.7 PHARMACOLOGICAL PROPERTIES

1.3.1.7.1 Pharmacodynamic properties

Ciprofloxacin

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 and other quinolones. 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:

Enterococcus faecalis(vancomycin-susceptible isolates only)

Staphylococcus aureus(methicillin-susceptible isolates only)

Staphylococcus epidermidis(methicillin-susceptible isolates only)

Staphylococcus saprophyticus

Streptococcus pneumoniae(penicillin-susceptible isolates only)

Streptococcus pyogenes

Gram-negative Bacteria

Campylobacter jejuni	Proteus mirabilis
Citrobacter diversus	Proteus vulgaris

Citrobacter freundii	Providencia rettgeri
Enterobacter cloacae	Providencia stuartii
Escherichia coli	Pseudomonas aeruginosa
Haemophilus influenzae	Salmonella typhi
Haemophilus parainfluenzae	Serratia marcescens
Klebsiella pneumoniae	Shigella boydii
Moraxella catarrhalis	Shigella dysenteriae
Morganella morganii	Shigella flexneri
Neisseria gonorrhoeae	Shigella sonnei

Ciprofloxacin has been shown to be active against Bacillus anthracis both in vitro and by use of serum levels as a surrogate marker.

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)

Bacillus anthracis

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

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, standardized 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.

1.3.1.7.2 Pharmacokinetic properties

Ciprofloxacin-

Absorption: Rapidly and well absorbed from the GI tract with peak plasma concentrations after 2 hours (oral), may be delayed by the presence of food.

Distribution: Bile (high concentrations), CSF (10% of those in plasma in the absence of meningitis), crosses the placenta and enters the breast milk. Protein-binding is 20-40%.

Metabolism: Converted to oxo-ciprofloxacin, sulfociprofloxacin and other active metabolites.

Excretion: Mainly via the urine by active tubular secretion glomerular filtration, hepatic biliary and transluminal secretion (non-renal excretion). Elimination half-life is 3.5-4.5 hours.

Tinidazole- Oral absorption of Tinidazole is found to be 100%. Volume of distribution is found to be 0.641 l/kg and plasma protein binding is 12%. Plasma half life is 12-14 hr.

1.3.1.7.3 Preclinical safety data

Like other gyrase inhibitors, ciprofloxacin may induce joint damage during the growth phase of juvenile animals. Other preclinical effects were observed only at exposures, sufficiently in excess of the maximum human exposure, that make concern for human safety negligible in respect of animal data.

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

1.3.1.8. PHARMACEUTICAL PARTICULARS

1.3.1.8.1 List of excipients

Croscarmellose sodium
Maize Starch

Gelatin
Purified water
Magnesium stearate
Purified Talc
Croscarmellose sodium
Soluble Starch
FC Titanium Dioxide
Isopropyl Alcohol
Purified water

1.3.1.8.2 Incompatibilities: Not applicable.

1.3.1.8.3 Shelf life: Three years.

1.3.1.8.4 Special precautions for storage: Store below 30^0C.Protected from light.

1.3.1.8.5 Nature and contents of container

Available as blister pack of 10 tablets in a carton of 1 x 10 tablets.

1.3.1.8.6 Special precautions for disposal and other Special handling

None

1.3.1.9 Marketed by:

M/S. GREENLIFE PHARMACEUTICALS LTD.,
2, Bank Lane,
Off Town Planning Way,
Ilupeju, Lagos, Nigeria.

1.3.1.10 Manufactured by:

MCW HEALTHCARE PVT LTD.
236, Sector – E, Industrial Area,
Sanwer Road, Indore (M.P)