SUMMARY OF PRODUCTS CHARACTERISTICS

1. Name of the Finished Pharmaceutical Product

1.1 Product name: CIPROSTAT TN

Generic name: CIPROFLOXACIN AND TINIDAZOLE TABLETS

1.2 Strength:
Each film coated tablet contains:
Ciprofloxacin Hydrochloride BP
Eq. to Ciprofloxacin 500 mg
Tinidazole BP 600 mg
Excipients Q.S.
Colour: Sunset Yellow FCF & Titanium Dioxide

1.3 Pharmaceutical dosage forms:
Film coated tablet

2. Qualitative and Quantitative composition:

Sr. No.	Ingredients	Label Claim (mg)	Actual Qty/Tablet (mg)	Actual Qty/Batch (kg)	Function
Active Ingredient					
1.	Ciprofloxacin Hydrochloride BP Eq. to Ciprofloxacin*	500.00	582.00	58.20	Anti-bacterial
2.	Tinidazole BP	600.00	600.00	60.00	Antiprotozoal
Excipients					
3.	Maize Starch BP	-	4.00	0.40	Diluent
4.	Maize Starch BP	-	22.00	2.20	Binder
5.	Purified Water BP**	-	Q.S.	Q.S.	Solvent
6.	Purified Talc BP	-	10.00	1.00	Glidant
7.	Sodium Starch Glycolate BP	-	20.00	2.00	Disintegrant
8.	Magnesium Stearate BP	-	10.00	1.00	Lubricant
9.	Colloidal Anhydrous Silica BP	-	2.00	0.20	Lubricant
Total weight of uncoated tablet			**1250.00 mg**	**125.0 kg**	
Coating					
10.	Colorezy White IHS***	-	37.50	3.75	Colorant
11.	Sunset Yellow FCF IHS	-	1.50	0.15	Colorant
12.	Isopropyl Alcohol BP**	-	Q.S.	Q.S.	Solvent
13.	Methylene Chloride BP**	-	Q.S.	Q.S.	Solvent
Total weight of coated tablet			**1289.00 mg**	**128.90 kg**	

* Quantity to be calculated on the basis of its potency

Calculation

Ciprofloxacin Hydrochloride Eq. to Ciprofloxacin (100% Potency) 500 mg

$$= \frac{\text{Label claim } \times 100 \times \text{molecular weighr of Ciprofloxacin Hydrochloride}}{\text{Potency } \times \text{Molecular Weight of Ciprofloxacin}}$$

$$= \frac{500 \times 100 \times 385.7}{100 \times 331.34}$$

= 582.00 mg

** The Materials which will not remain in the final tablets.

***COMPOSITION OF COLOREZY WHITE

Sr. No.	Components	Quantity per kg
1.	Hypromellose BP	608.0 gm
2.	Polyethylene glycol-6000 BP	120.0 gm
3.	Titanium Dioxide BP	132.0 gm
4.	Polysorbate 80 BP	24.0 gm
5.	Purified Talc BP	120.0 gm

3. Pharmaceutical forms

Oral dosage form.

4. Clinical Particulars

4.1 Therapeutic Indications

CIPROFLOXACIN AND TINIDAZOLE TABLETS are indicated for treatment of Gynaecological infections, Intra-abdominal infections, Respiratory tract infections, Urinary tract infections, acute uncomplicated cystitis, chronic bacterial prostatitis, acute sinusitis, skin and skin structure infections, bone and joint infections, complicated intra-abdominal infections infectious diarrhea, typhoid fever (enteric fever).

4.2 Posology and Method of administration

XIPROTN 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:

For oral administration.

4.3 Contraindications

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 breast-feeding is recommended during tinidazole therapy and for 3 days following the last dose.

4.4 Special warning and precaution 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.

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.

Exacerbation of Myasthenia Gravis

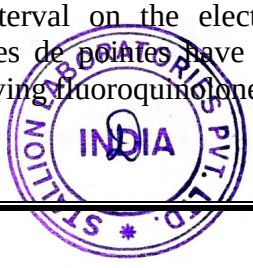
Fluoroquinolones, including ciprofloxacin, have neuromuscular blocking activity and may exacerbate muscle weakness in patients with myasthenia gravis. Postmarketing serious adverse reactions, including deaths and requirement for ventilatory support, have been associated with fluoroquinolone use in patients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

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.

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.



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.

- 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.

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 interactions
Antacids, sucralfate, calcium, Fe & Zn preparation reduce absorption of ciprofloxacin. Concurrent use with ciclosporin may lead to transient increases in serum creatinine levels. Increases plasma levels and elimination half-life of theophylline; potentiates oral anticoagulant effects; disulfiram-like effect with alcohol. May affect metabolism of caffeine resulting in reduced clearance of caffeine.

4.7 Fertility, pregnancy and lactation

Pregnancy
Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

Lactation
Ciprofloxacin is excreted in human milk. The amount of ciprofloxacin absorbed by the nursing infant is unknown. Because of the potential for serious adverse reactions 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.

4.8 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.

4.10 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

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.
Other side effects:
Gastrointestinal: Metallic/bitter taste, Nausea, Anorexia, Dyspepsia/cramps/epigastric discomfort, Vomiting, Constipation, Weakness/fatigue/malaise, Dizziness and Headache

4.12 Overdose and Treatments

If poisoning or excessive over dosage is suspected it is recommended, on general principles, that vomiting be induced or gastric lavage be performed, and such symptomatic supportive therapy be administered as appears indicated.

5. Pharmacological properties

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Anthelmintics, benzimidazoles and related substances, ATC code: J01MA02, P01AB02

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. 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

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

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

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

Pharmacokinetic Properties:

Ciprofloxacin

Absorption

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

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

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 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.

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
Not available

6. Pharmaceutical Particulars
6.1 List of Excipients

Maize Starch BP
Sodium Starch Glycolate BP
Colloidal Anhydrous Silica BP
Colorezy White IHS
Sunset Yellow FCF IHS
Isopropyl Alcohol BP
Purified Water BP
Methylene Chloride BP
Purified talc BP

6.2 Incompatibilities
Not applicable

6.3 Shelf Life
36 months

6.4 Special precautions for storage
Store at a temperature not exceeding 30ºC in a dry place. Protect from light. Keep out of reach of children.

6.5 Nature and contents of container

10 x 1 x 10 Alu-Alu blister Pack

Primary Packing: Alu-Alu Blister of 1 X 10 Tablets packed in printed aluminium foil on one side and Plain aluminium foil on another side.

Secondary Packing: Such 10 Carton s are packed in final printed carton of approved pack size along with insert.

6.6 Special precautions for disposal and other handling
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Marketing authorisation holder and manufacturing site addresses
STALLION LABORATORIES PVT.LTD.
C-1B 305/2, 3, 4& 5, G.I.D.C, KERALA (BAVLA),
DIST. AHMEDABAD,
GUJARAT, INDIA.

8. Marketing authorisation numbers
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9. Date of First Registration/Renewal of the Registration
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10. Date of revision of Text
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11. Dosimetry (If Applicable)
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12. Instructions for Preparation of Radiopharmaceuticals (If Applicable)