/Instructions in this font/colour are from the World Health Organisation Public Assessment Report WHOPAR guidelines.]

[Additional instructions and examples]

{<example text>}

1. NAME OF THE MEDICINAL PRODUCT
CIPROTAB TN (Ciprofloxacin & Tinidazole Tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film coated tablet contains:

Ciprofloxacin Hydrochloride USP	
Eq. to Ciprofloxacin	500 mg
Tinidazole BP	600 mg
Excipients	q.s

Approved colors are used.

3. PHARMACEUTICAL FORM
Tablet; Orange opaque oblong shape gelatin coated tablets (Soflets) imprinted with 'Ciprotab TN'

4. Clinical particulars
4.1 Therapeutic indications

CIPROTAB TN (Ciprofloxacin & Tinidazole Tablets) is indicated in the following cases:
CIPROTAB TN is indicated for the treatment of a wide variety of infections caused by sensitive gram-positive and gram-negative organisms as well as anaerobes and protozoa.
- Surgical prophylaxis and surgical wound infections
- Gynecological infections, including prophylaxis in gynecological surgeries
- Respiratory tract infections such as lung abscess, aspiration pneumonia, empyema and bronchiectasis
- ENT infections such as chronic sinusitis, chronic suppurative otitis media, cholesteatoma and mastoiditis.
- Oral and dental infections
- Dermatological infections such as cellulitis, breast and other skin abscesses, gangrene, diabetic and decubitus ulcers

4.2 P o s o l o g y and method of administration
Ciprotab-TN should be taken one hour before or two hours after meals.
Adults: one tablet twice a day.
In case of renal failure: -
If the creatinine clearance is less than 20 ml / min, half of the recommended dose may be administered

Method of administration
Oral

4.3 Contraindications
Hypersensitivity to the quinolone group or to the nitroimidazole group of compounds and to those patients with a history of blood dyscrasias.

4.4 Special warnings and precautions for use
Drugs interactions: -

Theophylline: The serum concentration and elimination half-life of theophylline may be increased when used at the same time as ciprofloxacin.

Antacids:

Antacids containing magnesium hydroxide and / or aluminum hydroxide may interfere with absorption of ciprofloxacin, causing serum and urine levels to drop. Alcohol should be avoided due to disulfiram-type reactions. Theophylline, antacids and anticoagulants should not be taken at the same time.

4.5 Interaction with other medicinal products and other forms of interaction

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

Medicines which are affected by and affect ciprofloxacin

Medicines affected by ciprofloxacin		
Drugs	Recommendation	comments
Tizanidine	Contraindicated	Concomitant administration of tizanidine and ciprofloxacin is contraindicated due to the potentiation of the hypotensive and sedative effects of tizanidine.
Theophylline	Avoid use (Exposure to plasma is likely to be increased and prolonged)	Co-administration of ciprofloxacin and theophylline may lead to an increased risk of developing CNS or other side effects in a patient. If concomitant use cannot be avoided, monitor serum theophylline levels and adjust dosage as needed.
Theophylline levels and adjust the dosage as needed	Avoid use	Ciprofloxacin may further prolong the QT interval in patients receiving drugs known to prolong the QT interval (eg, class IA or III antiarrhythmics, tricyclic antidepressants, macrolides, antipsychotics).
Oral anti-diabetic drugs	Use with caution Potentiated hypoglycemic effect	Hypoglycaemia, sometimes severe, has been reported when ciprofloxacin and oral antidiabetic drugs, mainly sulfonylureas (eg glyburide, glimepiride), have been co-administered, possibly enhancing the action of the oral antidiabetic agent. Dead were reported. Monitor blood sugar levels when ciprofloxacin is co-administered with oral diabetes medicines.

Phenytoin	Use with caution Altered serum phenytoin levels (increased and decreased)	To avoid loss of seizure control associated with decreased phenytoin levels and to prevent undesirable effects associated with phenytoin overdose when stopping ciprofloxacin in patients receiving both agents, monitor phenytoin therapy. including serum phenytoin concentration during and shortly after administration of ciprofloxacin with phenytoin.
Cyclosporine	Use with caution (transient increases in serum creatinine)	Monitor renal function (especially serum creatinine) when ciprofloxacin is co-administered with cyclosporine.
Anticoagulant drugs	Use with caution (increase in anticoagulant effect)	The risk may vary depending on the underlying infection, the age and general condition of the patient, so the contribution of ciprofloxacin to the increase in the international normalized ratio (INR) is difficult to assess. . Monitor prothrombin time and INR frequently during and soon after administration of ciprofloxacin with an oral anticoagulant (eg warfarin).
Methotrexate	Use with caution Inhibition of renal tubular transport of methotrexate which may lead to increased plasma levels of methotrexate	Potential increased risk of toxic reactions associated with methotrexate. Therefore, carefully monitor patients on methotrexate therapy when concomitant ciprofloxacin therapy is indicated.
Ropinirole	Use with caution	Monitoring of ropinirole-related adverse reactions and appropriate adjustment of the ropinirole dose is recommended during and shortly after co-administration of ciprofloxacin.
Clozapine	Use with caution	Careful monitoring of adverse reactions associated with clozapine and appropriate adjustment of the clozapine dosage during and shortly after co-administration of ciprofloxacin is advised.

Nonsteroidal anti-inflammatory drugs	Use with caution	Nonsteroidal anti-inflammatory drugs (but not acetylsalicylic acid) in combination with very high doses of quinolones have been shown to cause seizures in preclinical and postmarketing studies.
Sildenafil	Use with caution Exposure doubled	Monitor the toxicity of sildenafil.
Monitor for sildenafil toxicity. Avoid use	Five times more exposure to duloxetine	If unavoidable, monitor the toxicity of duloxetine
Caffeine / xanthine derivatives Use with caution	Reduced clearance resulting in high levels and prolongation of serum half-life	Ciprofloxacin inhibits the formation of paraxanthin after administration of caffeine (or products containing pentoxifylline). Monitor the toxicity of xanthine and adjust the dose if necessary.
Zolpidem	Zolpidem	Co-administration with ciprofloxacin may increase the blood levels of zolpidem; simultaneous use is not recommended
Drug (s) affecting the pharmacokinetics of ciprofloxacin		
Antacids, sucralfate, multivitamins and other products containing multivalent cations (magnesium / aluminum antacids; polymer phosphate binders (eg sevelamer, lanthanum carbonate); sucralfate; Videx® (didanosine) chewable / buffered tablets or pediatric powder; other highly buffered drugs; or products containing calcium, iron or zinc and dairy products) Probenecid	Ciprofloxacin should be taken at least 2 hours before or 6 hours after administration of products containing multivalent cations Use with caution (interferes with renal tubular secretion of ciprofloxacin and increases serum ciprofloxacin levels)	Decreased absorption of ciprofloxacin, resulting in decreased serum and urine levels. Potentiation of ciprofloxacin toxicity may occur.

Tinidazole
Although not specifically identified in studies with tinidazole, the following drug interactions have been reported for metronidazole, a chemically related nitroimidazole. Therefore, these drug interactions can occur with tinidazole.
Potential effects of tinidazole on other drugs
Warfarin and other oral coumarin anticoagulants: As with metronidazole, tinidazole may increase the effect of warfarin and other coumarin anticoagulants, resulting in prothrombin time. The dosage of oral anticoagulants may need to be adjusted during concomitant administration of tinidazole and up to 8 days after stopping.

Alcohols, disulfiram: Alcoholic beverages and preparations containing ethanol or propylene glycol should be avoided during treatment with tinidazole and for 3 days thereafter, as cramps, nausea, vomiting, headache and flushing may occur. Psychotic reactions have been reported in alcoholic patients using metronidazole and disulfiram simultaneously. Although no similar reactions have been reported with tinidazole, tinidazole should not be administered to patients taking disulfiram within the last 2 weeks.

Lithium: Metronidazole has been reported to elevate serum lithium levels. It is not known whether 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 and intravenous metronidazole Phenytoin would result in prolonged half-life and reduced phenytoin clearance. Metronidazole did not significantly alter the pharmacokinetics of oral drugs.
Phenytoin, Cyclosporine, Tacrolimus: Several case reports suggest that metronidazole has the potential to increase cyclosporine and tacrolimus levels. During co-administration of tinidazole with either of these drugs, the patient should be monitored for any signs of calcineurin inhibitor associated toxicities.

Fluorouracil: Metronidazole has been shown to decrease the clearance of fluorouracil, leading to increased side effects without increasing therapeutic benefits. If the concomitant use of tinidazole and fluorouracil cannot be avoided, the patient should be monitored for toxicities.

Potential Effects of Other Drugs on Tinidazole
CYP3A4 inducers and inhibitors: simultaneous administration of tinidazole with drugs that induce hepatic microsomal enzymes, i.e. CYP3A4 inducers such as phenobarbital, rifampin, phenytoin and fosphenytoin (a prodrug of phenytoin), may accelerate the elimination of tinidazole, decreasing the plasma level of tinidazole. Co-administration of drugs which inhibit the activity of hepatic microsomal enzymes, i.e. CYP3A4 inhibitors such as cimetidine and ketoconazole, may prolong the half-life and decrease the plasma clearance of tinidazole. Increasing plasma concentrations of tinidazole.

Cholestyramine: Cholestyramine has been shown to decrease the oral bioavailability of metronidazole by 21%. Thus, it is advisable to separate the dosage of cholestyramine and tinidazole to minimize any potential effect on the oral bioavailability of tinidazole.

Oxytetracycline: Oxytetracycline has been reported to antagonize the therapeutic effect of metronidazole.

Laboratory Test Interactions Tinidazole, like metronidazole, may interfere with certain types of serum chemical determinations, such as aspartate aminotransferase (AST, SGOT), alanine aminotransferase (ALT, SGPT), lactate dehydrogenase (LDH), triglycerides and glucose hexokinase. Values of zero can be observed. All tests in which interference has been reported involve coupling of the assay to the redox assay of nicotinamide adenine dinucleotide (NAD +
NADH). The potential interference is due to the similarity of the absorbance peaks of NADH and tinidazole.

Tinidazole, like metronidazole, can produce transient leukopenia and neutropenia; however, no persistent hematologic abnormalities attributable to tinidazole were observed during studies. The total and differential white blood cell count is recommended if further treatment is needed.

4.6 Pregnancy and Lactation
Ciprotab-TN is not recommended for use in pregnancy / is not recommended for use in nursing the mothers.

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 operate machinery may be impaired.
Medicines of similar chemical structure, including tinidazole, have been associated with various neurological disorders such as dizziness, vertigo, ataxia, peripheral neuropathy (paresthesia, sensory disturbances, hypoaesthesia) and rarely convulsions. If abnormal neurological signs develop during treatment with tinidazole, the drug should be discontinued.

4.8 Undesirable effects
CNS stimulation: Ciprofloxacin should be used with caution in patients with CNS disorders such as severe cerebral arteriosclerosis or epilepsy.

Phototoxicity: Moderate to severe phototoxicity has been observed in exposed patients to direct sunlight with certain members of the quinolone class.
Metallic taste, mild nausea, headache, vomiting, anorexia, abdominal pain, hairy tongue, pruritus, photosensitivity, vasculitis, rash, dizziness, dizziness, incoordination

4.9 Overdose

Ciprofloxacin

In case of acute overdose, reversible renal toxicity has been reported in some cases. Empty stomach by inducing vomiting or gastric lavage. Observe the patient carefully and give supportive therapy, including monitoring renal function, urine pH, and acidification, if necessary, to prevent crystalluria and administration of antacid magnesium, aluminum or calcium, which may reduce blood pressure. Absorption of ciprofloxacin. Adequate hydration must be maintained. Only a small amount of ciprofloxacin (less than 10%) is eliminated from the body after hemodialysis or peritoneal dialysis.

Tinidazole

No overdose has been reported with tinidazole in humans. There is no specific antidote for the treatment of overdose with tinidazole; therefore, treatment should be symptomatic and supportive. Gastric lavage may be helpful. Hemodialysis may be considered because approximately 43% of the amount present in the body is eliminated during a 6 hour hemodialysis session.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

1.Ciprofloxacin

Pharmacotherapeutic group: Fluoroquinolones

ATC code: J01MA02

Mechanism of Action of 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:

Bactéries Gram-positives
Bacillus anthracis
Enterococcus faecalis
Staphylococcus aureus (isolats sensibles à la méthicilline uniquement)
Staphylococcus epidermidis (isolats sensibles à la méthicilline uniquement)
Staphylococcus saprophyticus
Streptococcus pneumoniae
Streptococcus pyogenes
Bactéries Gram-négatives

Gram-positive bacteria	Providencia rettgeri
Bacillus anthracis	Providencia stuartii
Enterococcus faecalis	Pseudomonas aeruginosa
Staphylococcus aureus (methicillin sensitive isolates only)	Salmonella typhi
	Serratia marcescens
Staphylococcus epidermidis (methicillin sensitive isolates only)	Shigella boydii
	Shigella dysenteriae
Staphylococcus saprophyticus	Shigella flexneri
Streptococcus pneumoniae	Shigella sonnei
Streptococcus pyogenes	Yersinia pestis
Gram-negative bacteria	

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

Gram-positive bacteria
Staphylococcus haemolyticus (methicillin sensitive isolates only)
Staphylococcus hominis (methicillin sensitive 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

2. Tinidazole
Pharmacotherapeutic group: anti-infectives for systemic use.
ATC code: J 01XD02

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

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

Bacteria culture and sensitivity tests are not routinely performed to diagnose bacterial vaginosis; standard methodology for susceptibility testing of potential pathogenic bacteria, namely 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 protozoa: Trichomonas vaginalis; Giardia duodenalis (also called G. lamblia); and Entamoeba histolytica.

For protozoan parasites, there are no standardized susceptibility tests for use in microbiology laboratories. The development of resistance to tinidazole by G. duodenalis, E. histolytica or bacteria associated with bacterial vaginosis has not been investigated.

About 38% of T. vaginalis isolates with 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 administered as an oral tablet is rapidly and well absorbed from the gastrointestinal tract after oral administration. Absolute bioavailability is approximately 70% with no loss through first pass metabolism.

Maximum ciprofloxacin serum concentrations and area under the curve (AUC) are graphed for the dose range of 250 to 1000 mg.

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

Peak serum concentrations are reached 1 to 2 hours after oral administration. Average concentrations 12 hours after administration of 250, 500 or 750 mg are respectively 0.1, 0.2 and 0.4 µg / mL. The serum elimination half-life in subjects with normal renal function is approximately 4 hours. Serum concentrations increase proportionally at doses up to 1000 mg.

An oral dose of 500 mg given every 12 hours has been shown to produce an AUC equivalent to that produced by an intravenous (IV) infusion of 400 mg of ciprofloxacin given over 60 minutes every 12 hours.

An oral dose of 750 mg administered every 12 hours has been shown to produce AUC equivalent to that produced by an IV infusion of 400 mg given over 60 minutes every 8 hours.
An oral dose of 750 mg results in a Cmax similar to that seen with an IV dose of 400 mg. At 250 mg the oral dose administered every 12 hours produces an AUC equivalent to that produced by an infusion of 200 mg of 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 the ciprofloxacin tablet is given concomitantly with food, there is a delay in absorption of the drug, resulting in peak concentrations that occur almost 2 hours after administration rather than 1 hour. Whereas no delay is observed when ciprofloxacin suspension is administered with food. The however, the overall absorption of the ciprofloxacin tablet or ciprofloxacin suspension is not substantially affected. The pharmacokinetics of ciprofloxacin in suspension are also not affected by food. Avoid the concomitant administration of ciprofloxacin with dairy products (such as milk or yogurt) or juices fortified with calcium alone, since a decrease in absorption is possible; however, ciprofloxacin can be taken with a meal containing these products.

For oral administration, a dose of 500 mg, administered as 10 ml of ciprofloxacin 5% 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 probably not high enough to cause significant protein binding interactions with other drugs.

Following oral administration, ciprofloxacin is widely distributed throughout the body. Tissue Concentrations often exceed serum concentrations in men and women, particularly in the genitals. tissue, including the prostate. Ciprofloxacin is present in active form in saliva, nose and bronchial secretions, sinus lining, sputum, skin bladder 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 watery and vitreous fluids of the eye.

Metabolism: Four metabolites have been identified in human urine, which together represent 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 mainly metabolized by CYP1A2 results in increased plasma concentrations of these drugs and 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 unchanged After an oral dose of 250 mg, urinary concentrations of ciprofloxacin typically exceed 200 µg / Ml First 2 hours and are approximately 30 µg / mL 8 to 12 hours after administration. The urinary excretion of ciprofloxacin is almost completed within 24 hours of administration. Renal clearance of ciprofloxacin, which is about 300 ml / minute, exceeds normal glomerular filtration flow rate of 120 ml / minute. Thus, active tubular secretion seems to play an important role in its elimination. Co-administration of probenecid with ciprofloxacin results in an approximately 50% reduction in the renal clearance of ciprofloxacin and a 50% increase in its concentration in the circulation. Although the bile concentrations of ciprofloxacin are several times higher than those in serum after oral administration, only a small amount of the administered dose is recovered in the bile as unchanged drug. An additional 1 to 2% of the dose is recovered from the bile as the metabolites. About 20-35% of an oral dose is recovered in the faeces within 5 days after dosing. This can result from bile clearance or trans intestinal elimination.

5.3 Preclinical safety data

Ciprofloxacin

Non-clinical data from conventional studies on dose toxicity, repeated dose toxicity, carcinogenic potential or reproductive toxicity. Like a number of other quinolones, ciprofloxacin is phototoxic in animals at exposure levels. Photomutagenicity / photocarcinogenicity data show low photomutagenicity or phototumorigenic effect of ciprofloxacin in vitro and in animal experiments. This effect was comparable to that of other gyrase inhibitors.

Joint tolerance

As indicated for other gyrase inhibitors, ciprofloxacin causes damage to the large carrier weight joints in immature animals. The extent of cartilage damage varies with age, species and dose; damage can be reduced by reducing the weight of the joints. Studies with mature animals (rat, dog) did not reveal any sign of cartilage damage. In a study in young beagle dogs, ciprofloxacin caused severe joint changes at therapeutic doses after two weeks of treatment, which were still seen after 5 months.

Tinidazole

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize Starch
Sodium Starch Glycolate
Magnesium Stearate
Instacoat Aqua White (IC-A-223)

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store below 30 ^{0}C. Protect from direct sun light.
Keep all medicines out of the reach of children.
Store tablets in the blisters in the provided carton

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

1 Alu- Alu blister of 10 tablets is packed in a printed carton along with pack insert.
Pack sizes: 1x10 tablets

6.6 Special precautions for disposal <and other handling>

Any unused product or waste material should be disposed of in accordance with local requirements.

7. <APPLICANT/MANUFACTURER>

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