NORFLOX-TZ Tablets (Norfloxacin + Tinidazole + Lactic acid bacillus)

Black Box Warning

Fluoroquinolones, including norfloxacin, are associated with an increased risk of tendinitis and tendon rupture in all ages. This risk is further increased in older patients, usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants.

Fluoroquinolones, including norfloxacin, may exacerbate muscle weakness in persons with myasthenia gravis. Avoid norfloxacin in patients with a known history of myasthenia gravis.

Carcinogenicity has been seen in mice and rats treated long-term with metronidazole, another nitroimidazole agent. Although such data have not been reported for tinidazole, the two drugs are structurally related and have similar biologic effects.

Composition

NORFLOX-TZ
Each Film coated Tablet contains
Norfloxacin IP......400 mg
Tinidazole IP......600 mg
Lactic Acid Bacillus......120 x 10⁶ spores
(Appropriate overages added)
Colours :Titanium Dioxide and Lake Quinoline Yellow WS

Dosage Form/s

Oral tablets

Pharmacology

Pharmacodynamics

Norfloxacin

Norfloxacin has in vitro activity against a broad range of gram-positive and gram-negative aerobic bacteria. The fluorine atom at the 6 position provides increased potency against gram-negative organisms, and the piperazine moiety at the 7 position is responsible for antipseudomonal activity.

Norfloxacin inhibits bacterial deoxyribonucleic acid synthesis and is bactericidal. At the molecular level, three specific events are attributed to norfloxacin in Escherichia coli cells:

- Inhibition of the ATP-dependent DNA supercoiling reaction catalyzed by DNA gyrase
- Inhibition of the relaxation of supercoiled DNA
- Promotion of double-stranded DNA breakage
Resistance to norfloxacin due to spontaneous mutation in vitro is a rare occurrence (range: 10⁻⁹ to 10⁻¹² cells). Resistant organisms have emerged during therapy with norfloxacin in less than 1% of patients treated. Organisms in which development of resistance is greatest are as follows:

- Pseudomonas aeruginosa
- Klebsiella pneumoniae
- Acinetobacter spp.
- Enterococcus spp.

For this reason, when there is a lack of satisfactory clinical response, repeat culture and susceptibility testing should be done. Nalidixic acid-resistant organisms are generally susceptible to norfloxacin in vitro; however, these organisms may have higher minimum inhibitory concentrations (MICs) to norfloxacin than nalidixic acid-susceptible strains. There is generally no cross-resistance between norfloxacin and other classes of antibacterial agents. Therefore, norfloxacin may demonstrate activity against indicated organisms resistant to some other antimicrobial agents, including the aminoglycosides, penicillins, cephalosporins, tetracyclines, macrolides, and sulphonamides, including combinations of sulphamethoxazole and trimethoprim. Antagonism has been demonstrated in vitro between norfloxacin and nitrofurantoin.

Norfloxacin has been shown to be active against most strains of the following microorganisms both in vitro and in clinical infections:

- Gram-positive Aerobes
  - Enterococcus faecalis
  - Staphylococcus aureus
  - Staphylococcus epidermidis
  - Staphylococcus saprophyticus
  - Streptococcus agalactiae
- Gram-negative Aerobes
  - Citrobacter freundii
  - Enterobacter aerogenes
  - Enterobacter cloacae
  - Escherichia coli
  - Klebsiella pneumoniae
  - Neisseria gonorrhoeae
  - Proteus mirabilis
  - Proteus vulgaris
  - Pseudomonas aeruginosa
  - Serratiamarcescens

The following in vitro data are available, but their clinical significance is unknown.

Norfloxacin exhibits in vitro MICs of ≤4 μg/mL against most (>90%) strains of the following microorganisms; however, the safety and effectiveness of norfloxacin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

- Gram-negative Aerobes
  - Citrobacter diversus
  - Edwardsiellatarda
  - Enterobacteragglomerans
  - Haemophilus ducreyi
  - Klebsiella oxytoca
Morganellamorganii
Providenciaalcalifaciens
Providenciaretgeri
Providenciastuartii
Pseudomonasfluorescens
Pseudomonastutzeri
Other
Ureaplasmaurealyticum

Norfloxacin is not generally active against obligate anaerobes. Norfloxacin has not been shown to be active against *Treponemapallidum*

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 nitrates 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. *Gardnerellavaginalis*, *Mobiluncusspp.* 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.
*Gardnerellavaginalis*
*Prevotella* spp.

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.

### Pharmacokinetics

Norfloxacin
In fasting healthy volunteers, at least 30-40% of an oral dose of norfloxacin is absorbed. Absorption is rapid following single doses of 200 mg, 400 mg and 800 mg. At the respective doses, mean peak serum and plasma concentrations of 0.8, 1.5 and 2.4 μg/mL are attained approximately 1 hour after dosing. The presence of food and/or dairy products may decrease absorption. The effective half-life of norfloxacin in serum and plasma is 3-4 hours. Steady-state concentrations of norfloxacin will be attained within 2 days of dosing.

The following are the mean concentrations of norfloxacin in various fluids and tissues measured 1-4 hours post-dose after two 400 mg doses, unless otherwise indicated:
<table>
<thead>
<tr>
<th>Tissue/Compartment</th>
<th>Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal parenchyma</td>
<td>7.3 μg/g</td>
</tr>
<tr>
<td>Prostate</td>
<td>2.5 μg/g</td>
</tr>
<tr>
<td>Seminal fluid</td>
<td>2.7 μg/mL</td>
</tr>
<tr>
<td>Testicle</td>
<td>1.6 μg/g</td>
</tr>
<tr>
<td>Uterus/Cervix</td>
<td>3.0 μg/g</td>
</tr>
<tr>
<td>Vagina</td>
<td>4.3 μg/g</td>
</tr>
<tr>
<td>Fallopian tube</td>
<td>1.9 μg/g</td>
</tr>
<tr>
<td>Bile</td>
<td>6.9 μg/mL (after two 200 mg doses)</td>
</tr>
</tbody>
</table>

At 2-3 hours after a single 400 mg dose, urinary concentrations of 200 μg/mL or more are attained in the urine. In healthy volunteers, mean urinary concentrations of norfloxacin remain above 30 μg/mL for at least 12 hours following a 400 mg dose. The urinary pH may affect the solubility of norfloxacin. Norfloxacin is least soluble at urinary pH of 7.5, with greater solubility occurring at pHs above and below this value. The serum protein binding of norfloxacin is between 10 and 15%.

Norfloxacin is eliminated through metabolism, biliary excretion, and renal excretion. After a single 400 mg dose of norfloxacin, mean antimicrobial activities equivalent to 278, 773, and 82 μg of norfloxacin/g of the faeces were obtained at 12, 24, and 48 hours, respectively. Renal excretion occurs by both glomerular filtration and tubular secretion as evidenced by the high rate of renal clearance (approximately 275 mL/min). Within 24 hours of drug administration, 26-32% of the administered dose is recovered in the urine as norfloxacin with an additional 5-8% being recovered in the urine as six active metabolites of lesser antimicrobial potency. Only a small percentage (less than 1%) of the dose is recovered thereafter. Faecal recovery accounts for another 30% of the administered dose. In elderly subjects (average creatinine clearance 91 mL/min/1.73 m), approximately 22% of the administered dose was recovered in urine, and renal clearance averaged 154 mL/min.

In healthy elderly volunteers (65-75 years of age with normal renal function for their age), norfloxacin is eliminated more slowly because of their slightly decreased renal function. Following a single 400 mg dose of norfloxacin, a mean (± SD) AUC and C_{max} of 9.8 (2.83) μg hr/mL and 2.02 (0.77) μg/mL, respectively, were observed in healthy elderly volunteers. The extent of systemic exposure was slightly higher than that seen in younger adults (AUC, 6.4 μg hr/mL; C_{max}, 1.5 μg/mL). Drug absorption appears unaffected. However, the effective half-life of norfloxacin in these elderly subjects was 4 hours.

There is no information on accumulation of norfloxacin with repeated administration in elderly patients. However, no dosage adjustment is required based on age alone. In elderly patients with reduced renal function, the dosage should be adjusted as for other patients with renal impairment.

The disposition of norfloxacin in patients with creatinine clearance rates greater than 30 mL/min/1.73 m² is similar to that in healthy volunteers. In patients with creatinine clearance rates equal to or less than 30 mL/min/1.73 m², the renal elimination of norfloxacin decreases so that the effective serum half-life is 6.5 hours. In these patients, alteration of dosage is necessary. Drug absorption appears unaffected by decreasing renal function.

Tinidazole

After oral administration, tinidazole is rapidly and completely absorbed. Administration of tinidazole tablets with food resulted in a delay in the T_{max} of approximately 2 hours and a decline in the C_{max} of approximately 10%, compared with fasted conditions. However, administration of tinidazole with food did not affect the AUC or T_{1/2} in this study.
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.

Tinidazole is significantly metabolized in humans prior to excretion. Tinidazole is partly metabolized 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.

The plasma half-life of tinidazole is approximately 12 to 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.

The pharmacokinetics of tinidazole in patients with severe renal impairment (creatinine clearance

There are no data on tinidazole pharmacokinetics in patients with impaired hepatic function. Reduction of metabolic elimination of metronidazole, a chemically-related nitroimidazole, in patients with hepatic dysfunction has been reported in several studies.

## Indications

Treatment of diarrhea and dysentery of amoebic, bacterial or mixed origins.

## Dosage And Administration

The dosage is one tablet twice daily for 5 days.

## Contraindications

- In patients hypersensitive to quinolone or to tinidazole or any other excipient
- History of hypersensitivity, tendinitis, or tendon rupture associated with the use of norfloxacin or any member of the quinolone group of antimicrobial agents
- Tinidazole should be avoided in patients with organic neurological disorders.
- Tinidazole is contraindicated in patients having, or with a history of, blood dyscrasia, although no persistent haematological abnormalities have been noted in clinical or animal studies.

## Warnings And Precautions

**Tendinopathy and Tendon Rupture**

Fluoroquinolones, including norfloxacin, are associated with an increased risk of tendinitis and tendon rupture in all ages. This adverse reaction most frequently involves the Achilles' tendon, and rupture of the Achilles' tendon may require surgical repair. Tendinitis and tendon rupture in the rotator cuff (the shoulder), the hand, the biceps, the thumb, and other tendon sites have also been reported. The risk of developing fluoroquinolone-associated tendinitis and tendon rupture is further increased in older patients, usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants. Factors, in addition to age and corticosteroid use, 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. Tendon rupture can occur during or after completion of
therapy; cases occurring up to several months after completion of therapy have been reported. Norfloxacin should be discontinued if the patient experiences pain, swelling, inflammation or rupture of a tendon. Patients should be advised to rest at the first sign of tenosynovitis or tendon rupture, and to contact their healthcare provider regarding changing to a non-quinolone antimicrobial drug.

**Exacerbation of Myasthenia Gravis**

Fluoroquinolones, including norfloxacin, have neuromuscular blocking activity and may exacerbate muscle weakness in persons with myasthenia gravis. Post-marketing serious adverse events, including death and requirement for ventilatory support, have been associated with fluoroquinolone use in persons with myasthenia gravis. Avoid norfloxacin in patients with a known history of myasthenia gravis.

**Safety in Children and Adolescents, and during Pregnancy and Lactation**

The safety and efficacy of oral norfloxacin in paediatric patients, adolescents (below the age of 18 years), pregnant women, and nursing mothers have not been established. The oral administration of single doses of norfloxacin, six times the recommended human clinical dose (on an mg/kg basis), caused lameness in immature dogs. Histologic examination of the weight-bearing joints of these dogs revealed permanent lesions of the cartilage. Other quinolones also produced erosions of the cartilage in weight-bearing joints and other signs of arthropathy in immature animals of various species.

**Central Nervous System Effects/Disorders**

Convulsions have been reported in patients receiving norfloxacin. Convulsions, increased intracranial pressure, and toxic psychoses have been reported in patients receiving drugs in this class. Quinolones may also cause central nervous system (CNS) stimulation, which may lead to tremors, restlessness, lightheadedness, confusion, and hallucinations. If these reactions occur in patients receiving norfloxacin, the drug should be discontinued and appropriate measures instituted.

The effects of norfloxacin on brain function or on the electrical activity of the brain have not been tested. Therefore, until more information becomes available, norfloxacin, like all other quinolones, should be used with caution in patients with known or suspected CNS disorders, such as severe cerebral arteriosclerosis, epilepsy, and other factors that predispose to seizures.

**Hypersensitivity Reactions**

Serious, and occasionally fatal, hypersensitivity (anaphylactic) reactions, some following the first dose, have been reported in patients receiving quinolone therapy, including norfloxacin. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, tingling, pharyngeal or facial oedema, dyspnoea, urticaria and itching. Only a few patients had a history of hypersensitivity reactions. If an allergic reaction to norfloxacin occurs, discontinue the drug. Serious acute hypersensitivity reactions require immediate emergency treatment with epinephrine. Oxygen, intravenous fluids, antihistamines, corticosteroids, pressor amines, and airway management, including intubation, should be administered as indicated.

Other serious and sometimes fatal events, some due to hypersensitivity, and some due to uncertain aetiology, have been reported rarely in patients receiving therapy with quinolones, including norfloxacin. These events may be severe and generally occur following the administration of multiple doses. Clinical manifestations may include one or more of the following:

- Fever, rash or severe dermatologic reactions (e.g. toxic epidermal necrolysis, Stevens-Johnson syndrome)
- Vasculitis; arthralgia; myalgia; serum sickness
- Allergic pneumonitis
- Interstitial nephritis; acute renal impairment or failure
- Hepatitis; jaundice; acute hepatic necrosis or failure
- Anaemia, including haemolytic and aplastic; thrombocytopenia, including thrombotic thrombocytopenic purpura; leucopenia; agranulocytosis; pancytopenia; and/or other haematologic abnormalities.
The drug should be discontinued immediately at the first appearance of a skin rash, jaundice, or any other sign of hypersensitivity, and supportive measures should be instituted.

**Clostridium Difficile-associated Diarrhoea**

*Clostridium difficile*-associated diarrhoea (CDAD) has been reported with the use of nearly all antibacterial agents, including norfloxacin and may range in severity from mild diarrhoea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *Clostridium difficile.*

*Clostridium difficile* produces toxins A and B, which contribute to the development of CDAD. Hypertoxin-producing strains of *Clostridium difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhoea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over 2 months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *Clostridium difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *Clostridium difficile*, and surgical evaluation should be instituted as clinically indicated.

**Peripheral Neuropathy**

Rare cases of sensory or sensorimotor axonal polyneuropathy affecting small and/or large axons resulting in paraesthesias, hypoesthesias, dysesthesias and weakness have been reported in patients receiving quinolones, including norfloxacin. Norfloxacin should be discontinued if the patient experiences symptoms of neuropathy, including pain, burning, tingling, numbness and/or weakness, or is found to have deficits in light touch, pain, temperature, position sense, vibratory sensation and/or motor strength in order to prevent the development of an irreversible condition.

**Syphilis Treatment**

Norfloxacin has not been shown to be effective in the treatment of syphilis. Antimicrobial agents used in high doses for short periods of time to treat gonorrhoea may mask or delay the symptoms of incubating syphilis. All patients with gonorrhoea should have a serologic test for syphilis at the time of diagnosis. Patients treated with norfloxacin should have a follow-up serologic test for syphilis after 3 months.

**General**

Needle-shaped crystals were found in the urine of some volunteers who received either placebo, 800 mg norfloxacin, or 1,600 mg norfloxacin (at or twice the recommended daily dose, respectively) while participating in a double-blind, crossover study comparing single doses of norfloxacin with placebo. While crystalluria is not expected to occur under usual conditions with a dosage regimen of 400 mg b.i.d., as a precaution, the daily recommended dosage should not be exceeded and the patient should drink sufficient fluids to ensure a proper state of hydration and adequate urinary output.

Alteration in the dosage regimen is necessary for patients with impaired renal function.

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 quinolone antibiotics after sun or UV light exposure. Therefore, excessive exposure to these sources of light should be avoided. Drug therapy should be discontinued if phototoxicity occurs.

Rarely, haemolytic reactions have been reported in patients with latent or actual defects in glucose-6 phosphate dehydrogenase activity, who take quinolone antibacterial agents, including norfloxacin. Quinolones, including norfloxacin, may exacerbate the signs of myasthenia gravis and lead to life-threatening weakness of the respiratory muscles. Caution should be exercised when using quinolones, including norfloxacin, in patients with myasthenia gravis.
Prescribing norfloxacin 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.

Laboratory Tests
As with any potent antibacterial agent, periodic assessment of organ system functions, including renal, hepatic and haematopoietic, is advisable during prolonged therapy.

Neurological Adverse Reactions
Convulsive seizures and peripheral neuropathy, the latter characterized 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.

Drug Interactions
Norfloxacin
Quinolones, including norfloxacin, have been shown in vitro to inhibit cytochrome (CY) P1A2. Concomitant use with drugs metabolized by CYP1A2 (e.g. caffeine, clozapine, ropinirole, tacrine, theophylline, tizanidine) may result in increased substrate drug concentrations when given in usual doses. Patients taking any of these drugs concomitantly with norfloxacin should be carefully monitored.

Elevated plasma levels of theophylline have been reported with concomitant quinolone use. There have been reports of theophylline-related side effects in patients on concomitant therapy with norfloxacin and theophylline. Therefore, monitoring of theophylline plasma levels should be considered and the dosage of theophylline adjusted as required.

Elevated serum levels of cyclosporine have been reported with concomitant use of cyclosporine with norfloxacin. Therefore, cyclosporine serum levels should be monitored and appropriate cyclosporine dosage adjustments made when these drugs are used concomitantly.

Quinolones, including norfloxacin, may enhance the effects of oral anticoagulants, including warfarin or its derivatives or similar agents. When these products are administered concomitantly, prothrombin time or other suitable coagulation tests should be closely monitored.

The concomitant administration of quinolones including norfloxacin with glyburide (a sulphonylurea agent) has, on rare occasions, resulted in severe hypoglycaemia. Therefore, monitoring of blood glucose is recommended when these agents are co-administered.

Diminished urinary excretion of norfloxacin has been reported during the concomitant administration of probenecid and norfloxacin.

The concomitant use of nitrofurantoin is not recommended since nitrofurantoin may antagonize the antibacterial effect of norfloxacin in the urinary tract.

Multivitamins, or other products containing iron or zinc, antacids or sucralfate, should not be administered concomitantly with, or within 2 hours of, the administration of norfloxacin, because they may interfere with absorption, resulting in lower serum and urine levels of norfloxacin.

Didanosine chewable/buffered tablets or the paediatric powder for oral solution should not be administered concomitantly with, or within 2 hours of, the administration of norfloxacin, because these products may interfere with
absorption resulting in lower serum and urine levels of norfloxacin.

Some quinolones have also been shown to interfere with the metabolism of caffeine. This may lead to reduced clearance of caffeine and a prolongation of the plasma half-life that may lead to accumulation of caffeine in plasma when products containing caffeine are consumed while taking norfloxacin. The concomitant administration of a non-steroidal anti-inflammatory drug (NSAID) with a quinolone, including norfloxacin, may increase the risk of CNS stimulation and convulsive seizures. Therefore, norfloxacin should be used with caution in individuals receiving NSAIDS concomitantly.

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 Coumarin Anticoagulants:** As with metronidazole, tinidazole may enhance the effect of warfarin and other coumarin anticoagulants, resulting in a prolongation of prothrombin time. The dosage of oral anticoagulants may need to be adjusted during tinidazole co-administration and up to 8 days after discontinuation.

**Alcohols, Disulfiram:** Alcoholic beverages and preparations containing ethanol or propylene glycol should be avoided during tinidazole therapy and for 3 days afterward because abdominal cramps, nausea, vomiting, headaches and flushing may occur. Psychotic reactions have been reported in alcoholic patients using metronidazole and disulfiram concurrently. Though no similar reactions have been reported with tinidazole, tinidazole should not be given to patients who have taken disulfiram within the last 2 weeks.

**Lithium:** Metronidazole has been reported to elevate serum lithium levels. It is not known if tinidazole shares this property with metronidazole, but consideration should be given to measuring serum lithium and creatinine levels after several days of simultaneous lithium and tinidazole treatment to detect potential lithium intoxication.

**Phenytoin, Fosphenytoin:** Concomitant administration of oral metronidazole and intravenous phenytoin was reported to result in prolongation of the half-life and reduction in the clearance of phenytoin. Metronidazole did not significantly affect the pharmacokinetics of orally-administered phenytoin.

**Cyclosporine, Tacrolimus:** There are several case reports suggesting that metronidazole has the potential to increase the levels of cyclosporine and tacrolimus. During tinidazole co-administration with either of these drugs, the patient should be monitored for signs of calcineurin-inhibitor associated toxicities.

**Fluorouracil:** Metronidazole was shown to decrease the clearance of fluorouracil, resulting in an increase in side effects without an increase in therapeutic benefits. If the concomitant use of tinidazole and fluorouracil cannot be avoided, the patient should be monitored for fluorouracil-associated toxicities.

**Potential Effects of Other Drugs on Tinidazole**

**CYP3A4 Inducers and Inhibitors:** Simultaneous administration of tinidazole with drugs that induce liver microsomal enzymes, i.e. CYP3A4 inducers such as phenobarbital, rifampin, phenytoin and fosphenytoin (a pro-drug of phenytoin), may accelerate the elimination of tinidazole, decreasing the plasma level of tinidazole. Simultaneous administration of drugs that inhibit the activity of liver microsomal enzymes, i.e. CYP3A4 inhibitors such as cimetidine and ketoconazole, may prolong the half-life and decrease the plasma clearance of tinidazole, increasing the plasma concentrations of tinidazole.

Cholestyramine: Cholestyramine was shown to decrease the oral bioavailability of metronidazole by 21%. Thus, it is advisable to separate the dosing of cholestyramine and tinidazole to minimize any potential effect on the oral bioavailability of tinidazole. Oxytetracycline: Oxytetracycline was reported to antagonize the therapeutic effect of metronidazole.

**Laboratory Test Interactions**

Tinidazole, like metronidazole, may interfere with certain types of determinations of serum chemistry values, such as
aspartate aminotransferase (AST, SGOT), alanine aminotransferase (ALT, SGPT), lactate dehydrogenase (LDH), triglycerides, and hexokinase glucose. Values of zero may be observed. All of the assays in which interference has been reported involve enzymatic coupling of the assay to oxidation-reduction of nicotinamide adenine dinucleotide (NAD + NADH). Potential interference is due to the similarity of absorbance peaks of NADH and tinidazole. Tinidazole, like metronidazole, may produce transient leucopenia and neutropenia; however, no persistent haematological abnormalities attributable to tinidazole have been observed in clinical studies. Total and differential leucocyte counts are recommended if re-treatment is necessary.

Pregnancy
NORFLOX-TZ should be avoided in pregnancy.

Lactation
NORFLOX-TZ is not recommended for use by lactating mothers.

Pediatric Use
Use of NORFLOX TZ in prepubertal children or growing adolescents is contraindicated.

Undesirable Effects

Norfloxacin
Single-Dose Studies
In clinical trials involving 82 healthy subjects and 228 patients with gonorrhoea, treated with a single dose of norfloxacin, 6.5% reported drug-related adverse experiences. However, the following incidence figures were calculated without reference to drug relationship.

The most common adverse experiences (>1.0%) were: dizziness (2.6%), nausea (2.6%), headache (2.0%), and abdominal cramping (1.6%).

Additional reactions (0.3-1.0%) were anorexia, diarrhoea, hyperhidrosis, asthenia, anal/rectal pain, constipation, dyspepsia, flatulence, tingling of the fingers, and vomiting.

Laboratory adverse changes considered drug-related were reported in 4.5% of patients/subjects. These laboratory changes were increased AST (SGOT) (1.6%), decreased WBCs (1.3%), decreased platelet count (1.0%), increased urine protein (1.0%), decreased haematocrit and haemoglobin (0.6%), and increased eosinophils (0.6%).

Multiple-Dose Studies
In clinical trials involving 52 healthy subjects and 1,980 patients with UTIs or prostatitis treated with multiple doses of norfloxacin, 3.6% reported drug-related adverse experiences. However, the incidence figures below were calculated without reference to drug relationship.

The most common adverse experiences (>1.0%) were: nausea (4.2%), headache (2.8%), dizziness (1.7%), and asthenia (1.3%).

Additional reactions (0.3-1.0%) were abdominal pain, back pain, constipation, diarrhoea, dry mouth, dyspepsia/heartburn, fever, flatulence, hyperhidrosis, loose stools, pruritus, rash, somnolence, and vomiting.

Less frequent reactions (0.1-0.2%) included abdominal swelling, allergies, anorexia, anxiety, bitter taste, blurred vision, bursitis, chest pain, chills, depression, dysmenorrhoea, oedema, erythema, foot or hand swelling, insomnia, mouth ulcer, myocardial infarction, palpitation, pruritus ani, renal colic, sleep disturbances, and urticaria.

Abnormal laboratory values observed in these patients/subjects were: eosinophilia (1.5%), elevation of ALT (SGPT) (1.4%), decreased WBCs and/or neutrophil count (1.4%), elevation of AST (SGOT) (1.4%), and increased alkaline phosphatase (1.1%). Those occurring less frequently included increased BUN, increased LDH, increased serum
creatinine, decreased haematocrit, and glycosuria.

Postmarketing Experience

The most frequently reported adverse reaction in postmarketing experience was rash. CNS effects characterized as generalized seizures, myoclonus and tremors have been reported with norfloxacin. Visual disturbances have been reported with drugs in this class. The following additional adverse reactions have been reported since the drug was marketed:

Hypersensitivity Reactions

Hypersensitivity reactions have been reported, including anaphylactoid reactions, angio-oedema, dyspnoea, vasculitis, urticaria, arthritis, arthralgia, and myalgia.

Skin

Toxic epidermal necrolysis, Stevens-Johnson syndrome and erythema multiforme, exfoliative dermatitis, photosensitivity/phototoxicity reactions.

Gastrointestinal

Pseudomembranous colitis, hepatitis, jaundice, including cholestatic jaundice and elevated liver function tests, pancreatitis (rare), and stomatitis. The onset of pseudomembranous colitis symptoms may occur during or after antibacterial treatment.

Hepatic

Hepatic failure, including fatal cases.

Cardiovascular

On rare occasions, prolonged QTc interval and ventricular arrhythmia, including torsades de pointes.

Renal

Interstitial nephritis, renal failure.

Nervous System/Psychiatric

Peripheral neuropathy, Guillain-Barr syndrome, ataxia, paraesthesia, hypoesthesia, psychic disturbances, including psychotic reactions and confusion.

Musculoskeletal

Tendinitis, tendon rupture; exacerbation of myasthenia gravis; elevated creatine kinase (CK).

Haematologic

Neutropenia; leucopenia; agranulocytosis; haemolytic anaemia, sometimes associated with glucose-6 phosphate dehydrogenase deficiency; thrombocytopenia.

Special Senses

Hearing loss, tinnitus, diplopia, dysgeusia.

Other adverse events reported with quinolones include the following: Agranulocytosis, albuminuria, candiduria, crystalluria, cylindruria, dysphagia, elevation of blood glucose, elevation of serum cholesterol, elevation of serum potassium, elevation of serum triglycerides, haematuria, hepatic necrosis, symptomatic hypoglycaemia, nystagmus, postural hypotension, prolongation of prothrombin time, and vaginal candidiasis.

Tinidazole

Common adverse reactions reported by body system are as follows:

CNS: Weakness/fatigue/malaise, dizziness, convulsions and transient peripheral neuropathy, including numbness and paraesthesia. Other CNS reports include vertigo, ataxia, giddiness, insomnia, drowsiness.

Gastrointestinal: Metallic/bitter taste, nausea, anorexia, tongue discolouration, stomatitis, diarrhoea, dyspepsia/cramps/epigastric discomfort, constipation, vomiting, glossitis.

Hypersensitivity: Urticaria, pruritus, rash, flushing, sweating, dryness of mouth, fever, burning sensation, thirst, salivation, angio-oedema, angioneurotic oedema.
Renal: Darkened urine.
Cardiovascular: Palpitations.
Haematopoietic: Transient neutropenia, transient leucopenia.
Other: Candida overgrowth, increased vaginal discharge, oral candidiasis, hepatic abnormalities, including raised transaminase level, arthralgias, myalgias, and arthritis, fever, tiredness.
Rare reported adverse reactions include bronchospasm, dyspnoea, coma, confusion, depression, furry tongue, pharyngitis and reversible thrombocytopenia.
Adverse Reactions in Paediatric Patients
In pooled paediatric studies, adverse reactions reported in paediatric patients taking tinidazole were similar in nature and frequency to adult findings, including nausea, vomiting, diarrhoea, taste change, anorexia and abdominal pain.

Bacterial Vaginosis: The most common adverse reactions in treated patients (incidence >2%), which were not identified in the trichomoniasis, giardiasis and amebiasis studies, are gastrointestinal (decreased appetite, and flatulence); renal (urinary tract infection, painful urination and urine abnormality); and other reactions, including pelvic pain, vulvo-vaginal discomfort, vaginal odour, menorrhagia, and upper respiratory tract infection.

Postmarketing Experience
The following adverse reactions have been identified and reported during the post-approval use of tinidazole. Because the reports of these reactions are voluntary and the population is of uncertain size, it is not always possible to reliably estimate the frequency of the reaction or establish a causal relationship to drug exposure.
Severe acute hypersensitivity reactions have been reported on initial or subsequent exposure to tinidazole.
Hypersensitivity reactions may include urticaria, pruritus, angio-oedema, Stevens-Johnson syndrome and erythema multiforme.

Overdosage

Norfloxacin
No significant lethality was observed in male and female mice and rats at single oral doses up to 4 g/kg.
In the event of acute overdosage, the stomach should be emptied by inducing vomiting or by gastric lavage, and the patient carefully observed and given symptomatic and supportive treatment. Adequate hydration must be maintained.

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.

Storage And Handling Instructions

Store in a cool and dry place. Protect from moisture.

Packaging Information

NORFLOX-TZ: Blister pack of 10 tablets
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