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

**Warning**

SERIOUS ADVERSE REACTIONS INCLUDING TENDINITIS, TENDON RUPTURE, PERIPHERAL NEUROPATHY, CENTRAL NERVOUS SYSTEM (CNS) EFFECTS AND EXACERBATION OF MYASTHENIA GRAVIS

See the full prescribing information for complete boxed warning

Fluoroquinolones, including norfloxacin have been associated with disabling and potentially irreversible serious adverse reactions that have occurred together, including:
- tendinitis and tendon rupture;
- peripheral neuropathy; and,
- CNS effects

Discontinue norfloxacin immediately and avoid the use of fluoroquinolones, including ciprofloxacin, in patients who experience any of these serious adverse reactions.

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

Because fluoroquinolones, including norfloxacin, have been associated with serious adverse reactions, reserve norfloxacin for use in patients who have no alternative treatment options for uncomplicated urinary tract infections (including cystitis).

This drug may cause low blood sugar and mental health-related side effects

**TINIDAZOLE: POTENTIAL RISK FOR CARCINOGENICITY**

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. Its use should be reserved for the conditions described in INDICATIONS AND USAGE.

**Composition**

NORFLOX-TZ Tablets

Each film-coated tablet contains:

Norfloxacin IP…….400 mg

Tinidazole IP…….600 mg

Lactic Acid Bacillus …..120 x 10^6 spores

(Appropriate overages added)

Colours: Titanium Dioxide and Lake Quinoline Yellow WS

**Dosage Form**

Oral tablet
**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 catalysed 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 *in vitro* activity against a broad range of Gram-positive and Gram-negative aerobic bacteria. 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
Serratia marcescens
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
Edwardsiella tarda
Enterobacter agglomerans
Haemophilus ducreyi
Klebsiella oxytoca
Morganella morganii
Providencia alcalifaciens
Providencia rettgeri
Providencia stuartii
Pseudomonas fluorescens
Pseudomonas stutzeri
Other
Ureaplasma urealyticum
Norfloxacin is not generally active against obligate anaerobes.
Norfloxacin has not been shown to be active against Treponema pallidum
Tinidazole
Tinidazole is an antiprotozoal, antibacterial agent. The nitro group of tinidazole is reduced by cell extracts of Trichomonas. The free nitro radicals 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 spp. 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.

### Pharmacokinetics

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 \(\mu g/mL\) 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</th>
<th>Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal parenchyma</td>
<td>7.3 (\mu g/g)</td>
</tr>
<tr>
<td>Prostate</td>
<td>2.5 (\mu g/g)</td>
</tr>
<tr>
<td>Seminal fluid</td>
<td>2.7 (\mu g/mL)</td>
</tr>
<tr>
<td>Testicle</td>
<td>1.6 (\mu g/g)</td>
</tr>
<tr>
<td>Uterus/Cervix</td>
<td>3.0 (\mu g/g)</td>
</tr>
<tr>
<td>Vagina</td>
<td>4.3 (\mu g/g)</td>
</tr>
<tr>
<td>Fallopian tube</td>
<td>1.9 (\mu g/g)</td>
</tr>
<tr>
<td>Bile</td>
<td>6.9 (\mu g/mL) (after two 200 mg doses)</td>
</tr>
</tbody>
</table>

At 2–3 hours after a single 400 mg dose, urinary concentrations of 200 \(\mu g/mL\) or more are attained in the urine. In healthy volunteers, mean urinary concentrations of norfloxacin remain above 30 \(\mu g/mL\) 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 \(\mu g\) 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 m²), 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) \(\mu g\text{•hr/mL}\) and 2.02 (0.77) \(\mu g/mL\), respectively, were observed in healthy elderly volunteers. The extent of systemic exposure was slightly higher than that seen in younger adults (AUC, 6.4 \(\mu g\text{•hr/mL}; C_{max}, 1.5 \(\mu g/mL\)). 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. 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 ($C_{\text{max}}$) of 47.7 (±7.5) microg/mL with a mean time to peak concentration ($T_{\text{max}}$) of 1.6 (±0.7) hours, and a mean area under the plasma concentration-time curve (AUC, 0-infinity) of 901.6 (± 126.5) microg/hr/mL at 72 hours. The elimination half-life ($T_{1/2}$) was 13.2 (±1.4) hours. Mean plasma levels decreased to 14.3 microg/mL at 24 hours, 3.8 microg/mL at 48 hours and 0.8 microg/mL at 72 hours following administration. Steady-state conditions are reached in 2½ to 3 days of multi-day dosing. Administration of tinidazole tablets with food resulted in a delay in the $T_{\text{max}}$ of approximately 2 hours and a decline in the $C_{\text{max}}$ 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 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. 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 <22 mL/min) is not significantly different from the pharmacokinetics seen in healthy subjects. However, during haemodialysis, clearance of tinidazole is significantly increased; the half-life is reduced from 12.0 hours to 4.9 hours. Approximately 43% of the amount present in the body is eliminated during a 6-hour haemodialysis session. The pharmacokinetics of tinidazole in patients undergoing routine continuous peritoneal dialysis has not been investigated. 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 diarrhoea 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 tinidazole or other nitroimidazole derivatives.
In patients with a history of hypersensitivity, tendinitis, or tendon rupture associated with the use of norfloxacin or any member of the quinolone group of antimicrobial agents.
In pregnancy and during lactation.
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

Disabling and Potentially Irreversible Serious Adverse Reactions, Including Tendinitis and Tendon Rupture, Peripheral Neuropathy, and CNS Effects:

Fluoroquinolones, including norfloxacin, have been associated with disabling and potentially irreversible serious adverse reactions from different body systems that can occur together in the same patient. 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 norfloxacin. Patients of any age or without pre-existing risk factors have experienced these adverse reactions.
Discontinue norfloxacin immediately at the first signs or symptoms of any serious adverse reaction. In addition, avoid the use of fluoroquinolones, including norfloxacin, in patients who have experienced any of these serious adverse reactions associated with fluoroquinolones.

Tendinitis and Tendon Rupture

Fluoroquinolones, including norfloxacin, have been associated with an increased risk of tendinitis and tendon rupture in all ages. This adverse reaction most frequently involves the Achilles tendon, and has also been reported with the rotator cuff (the shoulder), the hand, the biceps, the thumb, and other tendons. Tendinitis or tendon rupture can occur within hours or days of starting norfloxacin, or as long as several months after completion of fluoroquinolone therapy. Tendinitis and tendon rupture can occur bilaterally. The risk of developing fluoroquinolone-associated tendinitis and tendon rupture is increased in patients over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants. Other factors that may independently increase the risk of tendon rupture include strenuous physical activity, renal failure, and previous tendon disorders such as rheumatoid arthritis. Tendinitis and tendon rupture have also occurred in patients taking fluoroquinolones who do not have the above risk factors. Discontinue norfloxacin immediately if the patient experiences pain, swelling, inflammation or rupture of a tendon. Avoid fluoroquinolones, including norfloxacin, in patients who have a history of tendon disorders or have experienced tendinitis or tendon rupture. Patients should be advised to rest at the first sign of tendinitis or tendon rupture, and to contact their healthcare provider regarding changing to a non-quinolone antimicrobial drug.

Peripheral Neuropathy

Fluoroquinolones, including norfloxacin, 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 norfloxacin. Symptoms may occur soon after initiation of norfloxacin and may be irreversible in some patients. Discontinue norfloxacin immediately if the patient experiences symptoms of peripheral neuropathy including pain, burning, tingling, numbness, and/or weakness, or other alterations in sensations including light touch, pain, temperature, position sense and vibratory sensation, and/or motor strength in order to minimise the development of an irreversible condition. Avoid fluoroquinolones, including norfloxacin, in patients who have previously experienced peripheral neuropathy.

CNS Effects

Fluoroquinolones, including norfloxacin, have been associated with an increased risk of CNS effects, including convulsions, increased intracranial pressure (including pseudotumour cerebri), and toxic psychoses. Quinolones may also cause 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 which predispose to seizures.

Exacerbation of Myasthenia Gravis

Fluoroquinolones, including norfloxacin, 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 norfloxacin in patients with a known history of myasthenia gravis.

Safety in Children, Adolescents, Nursing Mothers, and during Pregnancy

Safety and efficacy of oral norfloxacin in paediatric patients, adolescents (under the age of 18 years), pregnant women, and nursing mothers have not been established.

The oral administration of single doses of norfloxacin, 6 times the recommended human clinical dose (on 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.

Other serious and sometimes fatal adverse reactions, 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 insufficiency or failure
- Hepatitis; jaundice; acute hepatic necrosis or failure
- Anaemia, including haemolytic and aplastic; thrombocytopenia, including thrombotic thrombocytopenic purpura; leucopaenia; 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.
Hypersensitivity Reactions

Serious, and occasionally fatal, hypersensitivity (anaphylactic) reactions, some following the first dose, have been reported in patients receiving fluoroquinolone therapy, including norfloxacin. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, tingling, pharyngeal or facial oedema, dyspnœa, 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.

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 C. difficile. C. difficile produces toxins A and B, which contribute to the development of CDAD. Hypertoxin-producing strains of C. 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 C. difficile may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of C. difficile, and surgical evaluation should be instituted as clinically indicated. 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 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. 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.
Advise patients to stop taking norfloxacin if they experience an adverse reaction and to call their healthcare provider for advice on completing the full course of treatment with another antibacterial drug. Inform patients of the following serious adverse reactions that have been associated with norfloxacin or other fluoroquinolone use:

**Disabling and Potentially Irreversible Serious Adverse Reactions That May Occur Together:** Inform patients that disabling and potentially irreversible serious adverse reactions, including tendinitis and tendon rupture, peripheral neuropathies, and CNS effects, have been associated with the use of norfloxacin and may occur together. Inform patients to stop taking norfloxacin immediately if they experience an adverse reaction and to call their healthcare provider.

**Tendinitis and Tendon Rupture:** Instruct patients to contact their healthcare provider if they experience pain, swelling, or inflammation of a tendon, or weakness or inability to use one of their joints; rest and refrain from exercise; and discontinue norfloxacin treatment. The risk of severe tendon disorders with fluoroquinolones is higher in older patients (usually over 60 years of age), in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants.

**Peripheral Neuropathies:** Inform patients that peripheral neuropathies have been associated with the use of norfloxacin, and that symptoms may occur soon after initiation of therapy and may be irreversible. If symptoms of peripheral neuropathy including pain, burning, tingling, numbness, and/or weakness develop, patients should immediately discontinue norfloxacin and contact their physicians.

**CNS Effects (e.g. convulsions, dizziness, light-headedness, increased intracranial pressure):** Inform patients that convulsions have been reported in patients receiving fluoroquinolones, including norfloxacin. Instruct patients to notify their physician before taking this drug if they have a history of convulsions. Inform patients that they should know how they react to norfloxacin before they operate an automobile or machinery or engage in other activities requiring mental alertness and coordination. Instruct patients to notify their physician if persistent headache with or without blurred vision occurs.

**Exacerbation of Myasthenia Gravis:** Inform patients that fluoroquinolones such as norfloxacin may cause worsening of myasthenia gravis symptoms, including muscle weakness and breathing problems. Patients should call their healthcare provider right away if they have any worsening muscle weakness or breathing problems.

**Hypersensitivity Reactions:** Inform patients that norfloxacin can cause hypersensitivity reactions, even following a single dose, and to discontinue the drug at the first sign of a skin rash, hives or other skin reactions, a rapid heartbeat, difficulty in swallowing or breathing, any swelling suggesting angio-oedema (e.g. swelling of the lips, tongue, face, tightness of the throat, hoarseness), or other symptoms of an allergic reaction.

**Hepatotoxicity:** Inform patients that severe hepatotoxicity (including acute hepatitis and fatal events) has been reported in patients taking norfloxacin. Instruct patients to inform their physician if they experience any signs or symptoms of liver injury, including loss of appetite, nausea, vomiting, fever, weakness, tiredness, right upper quadrant tenderness, itching, yellowing of the skin and eyes, light-coloured bowel movements or dark-coloured urine.

**Diarrhoea:** Inform patients that diarrhoea is a common problem caused by antibiotics, which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as 2 months or more than 8 months after having taken the last dose of the antibiotic. If this occurs, instruct patients to contact their physician as soon as possible.

**Prolongation of the QT interval:** Inform patients of the following:

- that norfloxacin may cause changes in the electrocardiogram (QTc interval prolongation).
- that norfloxacin needs to be avoided in patients receiving class IA (e.g. quinidine, procainamide) or class III (e.g. amiodarone, sotalol) anti-arrhythmic agents.
that norfloxacin needs to be used with caution in subjects receiving drugs that affect the QTc interval such as cisapride, erythromycin, antipsychotics, and tricyclic antidepressants.

to inform their physicians of any personal or family history of QTc prolongation or pro-arrhythmic conditions such as hypokalaemia, bradycardia or recent myocardial ischaemia.

*Photosensitivity/Phototoxicity:* Inform patients that photosensitivity/phototoxicity has been reported in patients receiving fluoroquinolones. Patients should minimise or avoid exposure to natural or artificial sunlight (tanning beds or UVA/B treatment) while taking quinolones. If patients need to be outdoors while using quinolones, they should wear loose-fitting clothes that protect the skin from sun exposure and discuss other sun protection measures with their physician. If a sunburn-like reaction or skin eruption occurs, patients should contact their physician.

Other Information for Patients

Patients should also be advised on the following:

to drink fluids liberally.

that norfloxacin should be taken at least 1 hour before or at least 2 hours after a meal or ingestion of milk and/or other dairy products.

that multivitamins or other products containing iron or zinc, antacids or didanosine, chewable/buffered tablets or the paediatric powder for oral solution, should not be taken within the 2-hour period before or within the 2-hour period after taking norfloxacin.

that some quinolones may increase the effects of theophylline and/or caffeine.

that convulsions have been reported in patients taking quinolones, including norfloxacin, and to notify their physician before taking this drug if there is a history of this condition.

Patients should be counselled that antibacterial drugs, including norfloxacin, should only be used to treat bacterial infections. They do not treat viral infections (e.g. the common cold). When norfloxacin is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment; and, (2) increase the likelihood that bacteria will develop resistance and will not be treatable by norfloxacin or other antibacterial drugs in the future.

Laboratory Tests

As with any potent antibacterial agents, 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 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.

Drug Interactions

Norfloxacin

Quinolones, including norfloxacin, have been shown *in vitro* to inhibit cytochrome (CY) P1A2. Concomitant use with drugs metabolised 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 Oral Coumarin Anticoagulants: As with metronidazole, tinidazole may enhance the effect of warfarin
and other coumarin anticoagulants, resulting in a prolongation of prothrombin time. The dosage of oral anticoagulants may need to be adjusted during tinidazole co-administration and up to 8 days after discontinuation.

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

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

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

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

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

### Potential Effects of Other Drugs on Tinidazole

**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 minimise any potential effect on the oral bioavailability of tinidazole.

**Oxytetracycline:** Oxytetracycline was reported to antagonise 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+ to NADH or NADH to NAD+). Potential interference is due to the similarity of absorbance peaks of NADH and tinidazole. Tinidazole, like metronidazole, may produce transient leucopaenia and neutropaenia; 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 Tablets should be avoided in pregnancy.
Lactation

NORFLOX-TZ Tablets are not recommended for use by nursing mothers.

Paediatric Use

Safety and effectiveness of oral norfloxacin in paediatric patients and adolescents below the age of 18 years have not been established.

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, palpititation, 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 white blood cells 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 characterised as generalised 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-Barré syndrome, ataxia, paraesthesia, hypoesthesia, psychic disturbances, including psychotic reactions and confusion.

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

Haematologic
Neutropaenia; leucopaenia; agranulocytosis; haemolytic anaemia, sometimes associated with glucose-6 phosphate dehydrogenase deficiency; thrombocytopaenia.

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.

The drug may cause low blood sugar and mental health-related side effects. Low blood sugar levels, also called hypoglycaemia, can lead to coma. The mental health-related side effects that were more prominent and more consistent across the systemic fluoroquinolone drug class are as mentioned below;

Disturbances in attention
Disorientation
Agitation
Nervousness
Memory impairment

Serious disturbances in mental abilities called delirium

Tinidazole

Clinical Studies Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Among 3,669 patients treated with a single 2 g dose of tinidazole, in both controlled and uncontrolled trichomoniasis and
Giardiasis clinical studies, adverse reactions were reported by 11% of patients. For multi-day dosing in controlled and uncontrolled amoebiasis studies, adverse reactions were reported by 13.8% of 1,765 patients. Common adverse reactions (>1% incidence) reported by body system were as follows:

**CNS:** weakness/fatigue/malaise, dizziness, convulsions, transient peripheral neuropathy, numbness, paraesthesia, vertigo, ataxia, giddiness, insomnia, drowsiness, hypoaesthesia, sensory disturbances, dysgeusia.

**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, allergic dermatitis, pruritus.

**Renal:** darkened urine, chromaturia.

**Cardiovascular:** palpitations.

**Haematopoietic:** transient neutropaenia, transient leucopaenia.

**Other:** headache, Candida overgrowth, increased vaginal discharge, oral candidiasis, hepatic abnormalities, including raised transaminase level, arthralgias, myalgias and arthritis, fever.

Rare reported adverse reactions include bronchospasm, dyspnoea, coma, confusion, depression, furry tongue, pharyngitis, and reversible thrombocytopaenia.

**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 amoebiasis studies, were gastrointestinal (decreased appetite, and flatulence); renal (UTI, 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.

If you experience any side-effects, talk to your doctor or pharmacist or write to drugsafety@cipla.com. You can also report side effects directly via the national pharmacovigilance program of India by calling on 18002677779 (Cipla Number) or you can report to PvPI on 1800 180 3024.

By reporting side-effects, you can help provide more information on the safety of this product.

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**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.
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 Tablets: Blister pack of 10 tablets

*Last Updated: Apr 2019*

*Last Reviewed: Apr 2019*

**NORFLOX-TZ Tablets**

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