OFLOX OZ Tablets (Ofloxacin + Ornidazole)

Black Box 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 ofloxacin, 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 ofloxacin immediately and avoid the use of fluoroquinolones, including ofloxacin, in patients who experience any of these serious adverse reactions.

Fluoroquinolones, including ofloxacin, may exacerbate muscle weakness in patients with myasthenia gravis.

Avoid ofloxacin in patients with a known history of myasthenia gravis.

Because fluoroquinolones, including ofloxacin, have been associated with serious adverse reactions, reserve ofloxacin for use in patients who have no alternative treatment options for the following indications:

- Acute exacerbation of chronic bronchitis
- Uncomplicated cystitis

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

Composition

OFLOX-OZ Tablets
Each film-coated tablet contains:
Ofloxacin...........200 mg
Ornidazole, IP ...........500 mg

Dosage Form

Oral tablet

Pharmacology

Pharmacodynamics

Ofloxacin

Ofloxacin is a quinolone antimicrobial agent. The mechanism of action of ofloxacin and other fluoroquinolone antimicrobials involves inhibition of bacterial topoisomerase IV and DNA gyrase (both of which are type II
topoisomerases) enzymes required for DNA replication, transcription, repair and recombination.

Ofloxacin has in vitro activity against a wide range of Gram-negative and Gram-positive microorganisms. Ofloxacin is often bactericidal at concentrations equal to or slightly greater than inhibitory concentrations. Fluoroquinolones, including ofloxacin, differ in chemical structure and mode of action from aminoglycosides, macrolides and beta-lactam antibiotics, including penicillins. Fluoroquinolones may, therefore, be active against bacteria resistant to these antimicrobials.

Resistance to ofloxacin due to spontaneous mutation in vitro is a rare occurrence (range: 10–9 to 10–11). Although cross-resistance has been observed between ofloxacin and some other fluoroquinolones, some microorganisms resistant to other fluoroquinolones may be susceptible to ofloxacin.

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

**Aerobic Gram-positive Microorganisms**

*Staphylococcus aureus* (methicillin-susceptible strains)
*Streptococcus pneumoniae* (penicillin-susceptible strains)
*Streptococcus pyogenes*

**Aerobic Gram-negative Microorganisms**

*Citrobacter (diversus) koseri*
*Enterobacter aerogenes*
*Escherichia coli*
*Haemophilus influenzae*
*Klebsiella pneumoniae*
*Neisseria gonorrhoeae*
*Proteus mirabilis*
*Pseudomonas aeruginosa*

As with other drugs in this class, some strains of *Pseudomonas aeruginosa* may develop resistance fairly rapidly during treatment with ofloxacin.

**Other Microorganisms**

*Chlamydia trachomatis*

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

Ofloxacin exhibits in vitro minimum inhibitory concentrations (MIC values) of 2 mcg/mL or less against most (≥90%) strains of the following microorganisms; however, the safety and effectiveness of ofloxacin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled trials.

**Aerobic Gram-positive Microorganisms**

*Staphylococcus epidermidis* (methicillin-susceptible strains)
*Staphylococcus saprophyticus*
*Streptococcus pneumoniae* (penicillin-resistant strains)

**Aerobic Gram-negative Microorganisms**

*Acinetobacter calcoaceticus*
*Bordetella pertussis*
*Citrobacter freundii*
*Enterobacter cloacae*
*Haemophilus ducreyi*
*Klebsiella oxytoca*
*Moraxella catarrhalis*
Morganella morganii
Proteus vulgaris
Providencia rettgeri
Providencia stuartii
Serratia marcescens

Anaerobic Microorganisms
Clostridium perfringes

Other Microorganisms
Chlamydia pneumoniae
Gardnerella vaginalis
Legionella pneumophila
Mycoplasma hominis
Mycoplasma pneumoniae
Ureaplasma urealyticum

Ofloxacin is not active against Treponema pallidum.
Many strains of other streptococcal species, Enterococcus species, and anaerobes are resistant to ofloxacin.

Ornidazole
Ornidazole is a 5-nitroimidazole derivative active against protozoa and anaerobic bacteria. It is converted to reduction products that interact with DNA to cause destruction of the helical DNA structure and strand, leading to a protein synthesis inhibition and cell death in susceptible organisms.
Ornidazole is effective against *Trichomonas vaginalis, Entamoeba histolytica* and *Giardia lamblia (Giardia intestinalis)*, and also against certain anaerobic bacteria such as *Bacteroides* and *Clostridium* spp., *Fusobacterium* spp., and anaerobic cocci.

**Pharmacokinetics**

**Oral Dose**

<table>
<thead>
<tr>
<th>Oral Dose</th>
<th>Serum Concentration 2 Hours after Administration (mcg/mL)</th>
<th>Area Under the Curve (AUC (&lt;sup&gt;0-infinity&lt;/sup&gt;) (mcg•h/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>200 mg single dose</td>
<td>1.5</td>
<td>14.1</td>
</tr>
<tr>
<td>300 mg single dose</td>
<td>2.4</td>
<td>21.2</td>
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</table>

**Ofloxacin**

Following oral administration, the bioavailability of ofloxacin in the tablet formulation is approximately 98%. Maximum serum concentrations are achieved 1-2 hours after an oral dose. Absorption of ofloxacin after single or multiple doses of 200-400 mg is predictable, and the amount of drug absorbed increases proportionately with the dose. Ofloxacin has biphasic elimination. Following multiple oral doses at steady-state administration, the half-lives are approximately 4–5 hours and 20–25 hours. However, the longer half-life represents less than 5% of the total area under the curve (AUC).
Accumulation at steady-state can be estimated using a half-life of 9 hours. The total clearance and volume of distribution are approximately similar after single or multiple doses. Elimination is mainly by renal excretion. The following are mean peak serum concentrations in healthy 70-80 kg male volunteers after single oral doses of 200, 300 or 400 mg of ofloxacin or after multiple oral doses of 400 mg.
Steady-state concentrations were attained after four oral doses, and the AUC was approximately 40% higher than the AUC after single doses. Therefore, after multiple-dose administration of 200 mg and 300 mg doses, peak serum levels of 2.2 mcg/mL and 3.6 mcg/mL, respectively, are predicted at the steady state. In vitro, approximately 32% of the drug in plasma is protein-bound.

The single-dose and steady-state plasma profiles of ofloxacin injection were comparable in extent of exposure (AUC) with those of ofloxacin tablets when the injectable and tablet formulations of ofloxacin were administered in equal doses (mg/mg) to the same group of subjects. The mean steady-state $AUC_{(0 \rightarrow 12)}$ attained after the intravenous administration of 400 mg over 60 minutes was 43.5 mcg*h/mL; the mean steady-state $AUC_{(0 \rightarrow 12)}$ attained after the oral administration of 400 mg was 41.2 mcg*h/mL (two one-sided t-test, 90% confidence interval was 103 to 109) (see following chart).

**Ofloxacin Mean Steady-state (Day 5) Plasma Levels (mcg/mL) (n=19)**

![Graph showing plasma levels of ofloxacin over time](image)

Between 0 and 6 hours following the administration of a single 200 mg oral dose of ofloxacin to 12 healthy volunteers, the average urine ofloxacin concentration was approximately 220 mcg/mL. Between 12 and 24 hours after administration, the average urine ofloxacin level was approximately 34 mcg/mL.

Following oral administration of recommended therapeutic doses, ofloxacin has been detected in blister fluid, cervix, lung tissue, ovary, prostatic fluid, prostatic tissue, skin, and sputum. The mean concentration of ofloxacin in each of these various body fluids and tissues after one or more doses was 0.8 to 1.5 times the concurrent plasma level. Inadequate data are presently available on the distribution or levels of ofloxacin in the cerebrospinal fluid or brain tissue.

Ofloxacin has a pyridobenzoxazine ring that appears to decrease the extent of the parent compound metabolism. Between 65% and 80% of an administered oral dose of ofloxacin is excreted unchanged via the kidneys within 48 hours of dosing. Studies indicate that less than 5% of an administered dose is recovered in the urine as the desmethyl or N-oxide metabolites. About 4–8% of an ofloxacin dose is excreted in the faeces. This indicates a small degree of biliary excretion of ofloxacin.

The administration of ofloxacin tablets with food does not affect the $C_{max}$ and $AUC_{(\infty)}$ of the drug, but the $T_{max}$ is prolonged.

Clearance of ofloxacin is reduced in patients with impaired renal function (creatinine clearance rate ≤50 mL/min), and dosage adjustment is necessary.

Following oral administration to healthy elderly subjects (65 to 81 years of age), maximum plasma concentrations are usually achieved 1–3 hours after single and multiple twice-daily doses, indicating that the rate of oral absorption is unaffected by age or gender. Mean peak plasma concentrations in elderly subjects were 9–21% higher than those
observed in younger subjects. Gender differences in the pharmacokinetic properties of elderly subjects have been observed. Peak plasma concentrations were 114% and 54% higher in elderly females compared with elderly males following single and multiple twice-daily doses. Plasma concentrations increase dose-dependently with the increase in doses after a single oral dose and at the steady state. No differences were observed in the volume of distribution values between elderly and younger subjects. As in younger subjects, elimination is mainly by renal excretion as unchanged drug in elderly subjects, although less drug is recovered from renal excretion in elderly subjects. Consistent with younger subjects, less than 5% of an administered dose was recovered in the urine as the desmethyl and N-oxide metabolites in the elderly. A longer plasma half-life of approximately 6.4–7.4 hours was observed in elderly subjects, compared with 4–5 hours for young subjects. Slower elimination of ofloxacin is observed in elderly subjects as compared with younger subjects, which may be attributable to the reduced renal function and renal clearance observed in the elderly subjects. Because ofloxacin is known to be substantially excreted by the kidneys, and elderly patients are more likely to have decreased renal function, dosage adjustment is necessary for elderly patients with impaired renal function as recommended for all patients.

Ornidazole
Following oral administration ornidazole is rapidly absorbed. Mean absorption is 90%. Peak plasma concentrations are reached within 3 hours. The mean volume of distribution after intravenous administration is 1 litre per kg. Plasma protein-binding of ornidazole is about 13%. The active ingredient of ornidazole penetrates the cerebrospinal fluid, the body fluids and the tissues very effectively. Plasma concentrations are within the range considered to be optimal for the various indications (6–36 mg/l).

After repeated administration of 500 mg or 1,000 mg every 12 hours to healthy volunteers, an accumulation factor of 1.5–2.5 was calculated. Ornidazole is mainly metabolised to 2-hydroxymethyl and a-hydroxymethylmetabolites in the liver. Both main metabolites are less active against *Trichomonas vaginalis* and anaerobic bacteria than the unchanged ornidazole. The half-life is about 13 hours. While 85% of a single dose is eliminated within the first 5 days (most of this being metabolised), 4% of the dose is excreted as unaltered substance in the urine.

**Patients with Hepatic Impairment**
In patients with liver cirrhosis, the elimination half-life is longer (22 versus 14 hours) and clearance lower (35 versus 51 ml/min) than in healthy subjects. The dosing interval should be doubled in patients with severe hepatic impairment.

**Patients with Renal Impairment**
The pharmacokinetics of ornidazole is unaltered in renal impairment. Dose adjustment is, therefore, unnecessary in patients with impaired renal function. Ornidazole is removed by haemodialysis. An additional dose of 500 mg of ornidazole should be administered if the daily dose is 2 g/d, or an additional dose of 250 mg ornidazole if the daily dose is 1 g/d, should, therefore, be administered before the start of haemodialysis.

**Neonates and Children**
The pharmacokinetics or ornidazole in neonates and young children is similar to those in adults.

### Indications
OFLOX-OZ Tablets are indicated for the treatment of diarrhoea of mixed infection in adults only.

### Dosage And Administration
One tablet of OFLOX-OZ is recommended as twice-daily therapy.
Contraindications

OFLOX-OZ Tablets are contraindicated in persons with a history of hypersensitivity associated with the use of ofloxacin, ornidazole or any member of the quinolone or nitroimidazole group of antimicrobial agents.

Warnings And Precautions

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

Fluoroquinolones, including ofloxacin, 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 ofloxacin. Patients of any age or without pre-existing risk factors have experienced these adverse reactions. Discontinue ofloxacin immediately at the first signs or symptoms of any serious adverse reaction. In addition, avoid the use of fluoroquinolones, including ofloxacin, in patients who have experienced any of these serious adverse reactions associated with fluoroquinolones.

Tendinitis and Tendon Rupture

Fluoroquinolones, including ofloxacin, 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 rupture of 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 ofloxacin, 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 those 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 been reported in patients taking fluoroquinolones who do not have the above risk factors. Discontinue ofloxacin immediately if the patient experiences pain, swelling, inflammation or rupture of a tendon. Avoid fluoroquinolones, including ofloxacin, 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 ofloxacin, 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, dysesthesia and weakness, have been reported in patients receiving fluoroquinolones, including ofloxacin. Symptoms may occur soon after initiation of norfloxacin and may be irreversible in some patients. Discontinue ofloxacin 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 ofloxacin, in patients who have previously experienced peripheral
Exacerbation of Myasthenia Gravis

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

CNS Effects

Fluoroquinolones, including ofloxacin, 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 ofloxacin, the drug should be discontinued and appropriate measures instituted. The effects of ofloxacin on brain function or on the electrical activity of the brain have not been tested. Therefore, until more information becomes available, ofloxacin, 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.

The safety and efficacy of ofloxacin in paediatric patients and adolescents (under the age of 18 years), pregnant women, and lactating women has not been established.

In the immature rat, the oral administration of ofloxacin at 5–16 times the recommended maximum human dose based on mg/kg or 1–3 times based on mg/m$^2$ increased the incidence and severity of osteochondrosis. The lesions did not regress after 13 weeks of drug withdrawal. Other quinolones also produce similar erosions in the weight-bearing joints and other signs of arthropathy in immature animals of various species.

Hypersensitivity Reactions

Serious, and occasionally fatal, hypersensitivity and/or anaphylactic reactions have been reported in patients receiving therapy with quinolones, including ofloxacin. These reactions often occur following the first dose. Some reactions have been accompanied by cardiovascular collapse, hypotension/shock, seizure, loss of consciousness, tingling, angio-oedema (including tongue, laryngeal, throat or facial oedema/swelling), airway obstruction (including bronchospasm, shortness of breath, and acute respiratory distress), dyspnoea, urticaria, itching, and other serious skin reactions. This drug should be discontinued immediately at the first appearance of a skin rash or any other sign of hypersensitivity. Serious acute hypersensitivity reactions may require treatment with epinephrine and other resuscitative measures, including oxygen, intravenous fluids, antihistamines, corticosteroids, pressor amines, and airway management, as clinically 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 ofloxacin. 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; leucopaenia; agranulocytosis; pancytopenia; and/or other haematologic abnormalities.

The drug should be discontinued immediately at the first appearance of skin rash, jaundice, or any other sign of
hypersensitivity and supportive measures instituted. 

*Clostridium difficile*-associated diarrhoea (CDAD) has been reported with the use of nearly all antibacterial agents, including ofloxacin tablets, 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.

Ofloxacin 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 ofloxacin for gonorrhoea should have a follow-up serologic test for syphilis after three months and, if positive, treatment with an appropriate antimicrobial should be instituted.

### General

Prescribing ofloxacin tablets 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.

Adequate hydration of patients receiving ofloxacin should be maintained to prevent the formation of highly concentrated urine.

Administer ofloxacin with caution in the presence of renal or hepatic insufficiency/impairment. In patients with known or suspected renal or hepatic insufficiency/impairment, careful clinical observation and appropriate laboratory studies should be performed prior to and during therapy since elimination of ofloxacin may be reduced. In patients with impaired renal function (creatinine clearance ≤50 mg/mL), alteration of the dosage regimen is necessary.

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 as exposed to light (typically the face, ‘V’ area of the neck, extensor surfaces of the forearms, dorsa of the hands), can be associated with the use of quinolones after sun or UV light exposure. Therefore, excessive exposure to these sources of light should be avoided. Drug therapy should be discontinued if photosensitivity/phototoxicity occurs.

As with other quinolones, ofloxacin should be used with caution in any patient with a known or suspected CNS disorder that may predispose to seizures or lower the seizure threshold (e.g. severe cerebral arteriosclerosis, epilepsy) or in the presence of other risk factors that may predispose to seizures or lower the seizure threshold (e.g. certain drug therapy, renal dysfunction).

A possible interaction between oral hypoglycaemic drugs (e.g. glyburide/glibenclamide) or with insulin and fluoroquinolone antimicrobial agents has been reported, resulting in a potentiation of the hypoglycaemic action of these drugs. The mechanism for this interaction is not known. If a hypoglycaemic reaction occurs in a patient being treated with ofloxacin, discontinue ofloxacin immediately and consult a physician.

As with any potent drug, periodic assessment of organ system functions, including renal, hepatic, and haematopoietic, is advisable during prolonged therapy.
Torsades de pointes

Some quinolones, including ofloxacin, have been associated with prolongation of the QT interval on the electrocardiogram and infrequent cases of arrhythmia. Rare cases of torsades de pointes have been spontaneously reported during postmarketing surveillance in patients receiving quinolones, including ofloxacin. Ofloxacin should be avoided in patients with known prolongation of the QT interval, patients with uncorrected hypokalaemia, and patients receiving Class IA (quinidine, procainamide), or Class III (amiodarone, sotalol) anti-arrhythmic agents.

Serious Adverse Reactions

Advising patients to stop taking ofloxacin 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 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 use of ofloxacin and may occur together. Inform patients to stop taking ofloxacin immediately if they experience an adverse reaction and to call their healthcare provider.

Tendon Disorders: 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 ofloxacin 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 ofloxacin, 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 ofloxacin and contact their physicians.

CNS Effects (e.g. convulsions, dizziness, lightheadedness, increased intracranial pressure): Inform patients that convulsions have been reported in patients receiving fluoroquinolones, including ofloxacin. 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 ofloxacin 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.

Myasthenia Gravis: Inform patients that fluoroquinolones such as ofloxacin may cause worsening of myasthenia gravis symptoms, including muscle weakness and breathing problems. Patients should call their healthcare provider right away in case of any worsening muscle weakness or breathing problems.

Hypersensitivity Reactions: Inform patients that ofloxacin 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 ofloxacin. 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: 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 or more months after having taken the last dose of the antibiotic. If this occurs, instruct patients to contact their physician as soon as possible.

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 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 be advised on the following:

To drink fluids liberally.

That mineral supplements, vitamins with iron or minerals, calcium-, aluminium- or magnesium-based antacids, sucralfate 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 ofloxacin.

That ofloxacin can be taken without regard to meals.

That antibacterial drugs, including ofloxacin tablets, should only be used to treat bacterial infections. They do not treat viral infections (e.g. the common cold). When ofloxacin tablets are 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 ofloxacin tablets or other antibacterial drugs in the future.

That if they are diabetic and are being treated with insulin or an oral hypoglycaemic drug, to discontinue ofloxacin immediately if a hypoglycaemic reaction occurs and consult a physician.

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

To inform their physician of any personal or family history of QTc prolongation or pro-arrhythmic conditions such as hypokalaemia, bradycardia, or recent myocardial ischaemia; if they are taking any class IA (quinidine, procainamide), or class III (amiodarone, sotalol) anti-arrhythmic agents. Patients should notify their physicians if they have any symptoms of prolongation of the QTc interval, including prolonged heart palpitations or a loss of consciousness.

Ornidazole

Caution should be exercised in patients with diseases of the CNS, e.g. epilepsy or multiple sclerosis. The effect of other medicines can be intensified or impaired.

Drug Interactions

Ofloxacin

Antacids, Sucralfate, Metal Cations, Multivitamins

Quinolones form chelates with alkaline earth and transition metal cations. Administration of quinolones with antacids containing calcium, magnesium or aluminium, with sucralfate, with divalent or trivalent cations such as iron, or with multivitamins containing zinc or with didanosine, chewable/buffered tablets or the paediatric powder for oral solution may substantially interfere with the absorption of quinolones, resulting in systemic levels considerably lower than desired. These agents should not be taken within the 2-hour period before or within the 2-hour period after ofloxacin.
Interactions between ofloxacin and caffeine have not been detected.

Cimetidine
Cimetidine has demonstrated interference with the elimination of some quinolones. This interference has resulted in significant increases in the half-life and AUC of some quinolones. The potential for interaction between ofloxacin and cimetidine has not been studied.

Cyclosporine
Elevated serum levels of cyclosporine have been reported with concomitant use of cyclosporine with some other quinolones. The potential for interaction between ofloxacin and cyclosporine has not been studied.

Drugs Metabolised by Cytochrome P450 Enzymes
Most quinolone antimicrobial drugs inhibit cytochrome P450 enzyme activity. This may result in a prolonged half-life for some drugs that are also metabolised by this system (e.g. cyclosporine, theophylline/methylxanthines, warfarin) when co-administered with quinolones. The extent of this inhibition varies among different quinolones.

Non-Steroidal Anti-Inflammatory Drugs
The concomitant administration of a non-steroidal anti-inflammatory drug with a quinolone, including ofloxacin, may increase the risk of CNS stimulation and convulsive seizures.

Probenecid
The concomitant use of probenecid with certain other quinolones has been reported to affect renal tubular secretion. The effect of probenecid on the elimination of ofloxacin has not been studied.

Theophylline
Steady-state theophylline levels may increase when ofloxacin and theophylline are administered concurrently. As with other quinolones, concomitant administration of ofloxacin may prolong the half-life of theophylline, elevate serum theophylline levels, and increase the risk of theophylline-related adverse reactions. Theophylline levels should be closely monitored and theophylline dosage adjustments made, if appropriate, when ofloxacin is co-administered. Adverse reactions (including seizures) may occur with or without an elevation in the serum theophylline level.

Warfarin
Some quinolones have been reported to enhance the effects of the oral anticoagulant warfarin or its derivatives. Therefore, if a quinolone antimicrobial is administered concomitantly with warfarin or its derivatives, the prothrombin time or other suitable coagulation test should be closely monitored.

Antidiabetic Agents (e.g. Insulin, Glyburide/Glibenclamide)
Since disturbances of blood glucose, including hyperglycaemia and hypoglycaemia, have been reported in patients treated concurrently with quinolones and an antidiabetic agent, careful monitoring of blood glucose is recommended when these agents are used concomitantly.

Interaction with Laboratory or Diagnostic Testing
Some quinolones, including ofloxacin, may produce false-positive urine screening results for opiates using commercially available immunoassay kits. Confirmation of positive opiate screens by more specific methods may be necessary.

Ornidazole
Alcohol must not be ingested when taking ornidazole or for at least 3 days after discontinuing the medicine. Ornidazole potentiates the effect of coumarin type oral anticoagulants. The dosage of the anticoagulant has to be adjusted accordingly. Caution must be exercised when taking ornidazole together with lithium, cimetidine and antiepileptic medicines such as phenytoin and phenobarbital. Ornidazole prolongs the muscle relaxant effect of vecuronium bromide.
Ofloxacin

Pregnancy Category C

Ofloxacin has not been shown to have any teratogenic effects at oral doses as high as 810 mg/kg/day (11 times the recommended maximum human dose based on mg/m², or 50 times based on mg/kg) and 160 mg/kg/day (4 times the recommended maximum human dose based on mg/m², or 10 times based on mg/kg) when administered to pregnant rats and rabbits, respectively. Additional studies in rats with oral doses up to 360 mg/kg/day (5 times the recommended maximum human dose based on mg/m², or 23 times based on mg/kg) demonstrated no adverse effect on late foetal development, labour, delivery, lactation, neonatal viability, or growth of the newborn. Doses equivalent to 50 and 10 times the recommended maximum human dose of ofloxacin (based on mg/kg) were foetotoxic (i.e. decreased foetal body weight and increased fetal mortality) in rats and rabbits, respectively. Minor skeletal variations were reported in rats receiving doses of 810 mg/kg/day, which is more than 10 times higher than the recommended maximum human dose based on mg/m².

There are, however, no adequate and well-controlled studies in pregnant women. Ofloxacin should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Ornidazole

There is no clinical data available for ornidazole exposure in pregnancy. Studies conducted on animals do not demonstrate direct or indirect harmful effects on pregnancy/embryonic/foetal development/birth or post-natal development. The effect of ornidazole on women of childbearing potential or birth control methods is unknown. Extensive studies in various species have revealed no sign of any teratogenic or foetotoxic action of ornidazole. However, no controlled studies have been carried out in pregnant women. As a matter of principle, ornidazole should not be prescribed in early pregnancy or to nursing mothers except when absolutely necessary.

Lactation

In lactating females, a single oral 200 mg dose of ofloxacin resulted in concentrations of ofloxacin in milk that were similar to those found in plasma. Because of the potential for serious adverse reactions from ofloxacin in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

It is not known whether ornidazole is excreted in human milk. The excretion of ornidazole via milk in animals has not been researched. In making the decision whether or not to discontinue breastfeeding or whether or not ornidazole treatment should be discontinued/avoided, the benefit of breastfeeding to the infant and the benefit of ornidazole treatment for the nursing mother must be considered.

Paediatric Use

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

Ofloxacin causes arthropathy (arthrosis) and osteochondrosis in juvenile animals of several species.

Geriatric Use

Geriatric patients are at increased risk for developing severe tendon disorders, including tendon rupture, when being treated with a fluoroquinolone such as ofloxacin. This risk is further increased in patients receiving concomitant corticosteroid therapy. Tendinitis or tendon rupture can involve the Achilles tendon, hand, shoulder or other tendon sites and can occur during or after completion of therapy; cases occurring up to several months after fluoroquinolone treatment have been reported. Caution should be used when prescribing ofloxacin to elderly patients especially those on corticosteroids. Patients should be informed of this potential side effect and advised to discontinue ofloxacin and contact their healthcare provider if any symptoms of tendinitis or tendon rupture occur.

In Phase 2/3 clinical trials with ofloxacin, 688 patients (14.2%) were 65 years of age or older. Of these, 436 patients (9%)
were between the ages of 65 and 74 years and 252 patients (5.2%) were 75 years or older. There was no apparent
difference in the frequency or severity of adverse reactions in elderly adults compared with younger adults. The
pharmacokinetic properties of ofloxacin in elderly subjects are similar to those in younger subjects. Drug absorption
appears to be unaffected by age. Dosage adjustment is necessary for elderly patients with impaired renal function
(creatinine clearance rate ≤50 mL/min) due to reduced clearance of ofloxacin. In comparative studies, the frequency and
severity of most drug-related nervous system events in patients 65 years of age or older were comparable for ofloxacin
and control drugs. The only differences identified were an increase in reports of insomnia (3.9% versus 1.5%) and
headache (4.7% versus 1.8%) with ofloxacin. It is important to note that these geriatric safety data are extracted from
44 comparative studies wherein the adverse reaction information from 20 different controls (other antibiotics or placebo)
was pooled for comparison with ofloxacin. The clinical significance of such a comparison is not clear.
Elderly patients may be more sensitive to drug-associated effects on the QT interval. Therefore, precaution should be
taken when using ofloxacin with concomitant drugs that can result in prolongation of the QT interval (e.g. Class IA or
Class III anti-arrhythmics) or in patients with risk factors for torsades de pointes (e.g. known QT prolongation,
uncorrected hypokalaemia).

Effects on the Ability to Drive and Use Machines

Ofloxacin
Since there have been occasional reports of somnolence, impairment of skills, dizziness and visual disturbances, patients
should know how they react to ofloxacin before they drive or operate machinery. These effects may be enhanced by
alcohol.

Ornidazole
Somnolence, dizziness, tremor, rigidity, poor coordination, seizures, vertigo or temporary loss of consciousness may
occur in patients receiving ornidazole. If they occur, such effects may affect tasks requiring alertness, including the
patient’s ability to drive and operate machinery.

Undesirable Effects

Ofloxacin
The following is a compilation of the data for ofloxacin based on clinical experience with both the oral and intravenous
formulations. The incidence of drug-related adverse reactions in patients during Phase 2 and 3 clinical trials was 11%. Among
patients receiving multiple-dose therapy, 4% discontinued ofloxacin due to adverse experiences.

In clinical trials, the following events were considered likely to be drug-related in patients receiving multiple doses of
ofloxacin: nausea (3%), insomnia (3%), headache (1%), dizziness (1%), diarrhoea (1%), vomiting (1%), rash (1%),
pruritus (1%), external genital pruritus in women (1%), vaginitis (1%), and dysgeusia (1%).

In clinical trials, the most frequently reported adverse events, regardless of relationship to drug, were as follows: nausea
(10%), headache (9%), insomnia (7%), external genital pruritus in women (6%), dizziness (5%), vaginitis (5%), diarrhoea
(4%), and vomiting (4%).

In clinical trials, the following events, regardless of relationship to drug, occurred in 1 to 3% of patients: abdominal pain
and cramps, chest pain, decreased appetite, dry mouth, dysgeusia, fatigue, flatulence, gastrointestinal distress,
nervousness, pharyngitis, pruritus, fever, rash, sleep disorders, somnolence, trunk pain, vaginal discharge, visual
disturbances, and constipation.
Additional events, occurring in clinical trials at a rate of less than 1%, regardless of relationship to drug, were as below:
<table>
<thead>
<tr>
<th>System</th>
<th>Symptoms/Abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body as a Whole</td>
<td>asthenia, chills, malaise, extremity pain, pain, epistaxis</td>
</tr>
<tr>
<td>Cardiovascular System</td>
<td>cardiac arrest, oedema, hypertension, hypotension, palpitations, vasodilation</td>
</tr>
<tr>
<td>Gastrointestinal System</td>
<td>dyspepsia</td>
</tr>
<tr>
<td>Genital/Reproductive System</td>
<td>burning, irritation, pain and rash of the female genitalia; dysmenorrhoea; menorrhagia; metrorrhagia</td>
</tr>
<tr>
<td>Musculoskeletal System</td>
<td>arthralgia, myalgia</td>
</tr>
<tr>
<td>Nervous System</td>
<td>seizures, anxiety, cognitive change, depression, dream abnormality, euphoria, hallucinations, paraesthesia, syncope, vertigo, tremor, confusion</td>
</tr>
<tr>
<td>Nutritional/Metabolic</td>
<td>thirst, weight loss</td>
</tr>
<tr>
<td>Respiratory System</td>
<td>respiratory arrest, cough, rhinorrhoa</td>
</tr>
<tr>
<td>Skin/Hypersensitivity</td>
<td>angio-oedema, diaphoresis, urticaria, vasculitis</td>
</tr>
<tr>
<td>Special Senses</td>
<td>decreased hearing acuity, tinnitus, photophobia</td>
</tr>
<tr>
<td>Urinary System</td>
<td>dysuria, urinary frequency, urinary retention</td>
</tr>
</tbody>
</table>

The following laboratory abnormalities appeared in ≥1% of patients receiving multiple doses of ofloxacin. It is not known whether these abnormalities were caused by the drug or the underlying conditions being treated.

<table>
<thead>
<tr>
<th>System</th>
<th>Abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haematopoietic</td>
<td>anaemia, leucopaenia, leucocytosis, neutropaenia, neutrophilia, increased band forms, lymphocytopaenia, eosinophilia, lymphocytosis, thrombocytopaenia, thrombocytosis, elevated ESR</td>
</tr>
<tr>
<td>Hepatic</td>
<td>elevated: alkaline phosphatase, AST (SGOT), ALT (SGPT)</td>
</tr>
<tr>
<td>Serum Chemistry</td>
<td>hyperglycaemia, hypoglycaemia, elevated creatinine, elevated BUN</td>
</tr>
<tr>
<td>Urinary</td>
<td>glucosuria, proteinuria, alkalinuria, hyposthenuria, haematuria, pyuria</td>
</tr>
</tbody>
</table>

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 side effects more prominent and more consistent across the systemic fluoroquinolone drug class are as mentioned below:

Disturbances in attention
Disorientation
Agitation
Nervousness
Memory impairment
Delirium (serious disturbances in mental abilities)

Additional adverse events, regardless of relationship to the drug, reported from worldwide postmarketing experience with quinolones, including ofloxacin, were as below:

<table>
<thead>
<tr>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular System</td>
</tr>
<tr>
<td>cerebral thrombosis, pulmonary</td>
</tr>
<tr>
<td>oedema, tachycardia, hypotension</td>
</tr>
<tr>
<td>shock, syncope, *torsades de</td>
</tr>
<tr>
<td><em>pointes</em></td>
</tr>
<tr>
<td>Endocrine/Metabolic</td>
</tr>
<tr>
<td>hyper- or hypoglycaemia, especially in diabetic patients on insulin or oral hypoglycaemic agents</td>
</tr>
<tr>
<td>Gastrointestinal System</td>
</tr>
<tr>
<td>hepatic dysfunction, including hepatic necrosis, jaundice (cholestatic or hepatocellular), hepatitis; intestinal perforation; hepatic failure (including fatal cases); pseudomembranous colitis (the onset of pseudomembranous colitis symptoms may occur during or after antimicrobial treatment), gastrointestinal haemorrhage; hiccough, painful oral mucosa, pyrosis</td>
</tr>
<tr>
<td>Genital/Reproductive System</td>
</tr>
<tr>
<td>vaginal candidiasis</td>
</tr>
<tr>
<td>Haematopoietic</td>
</tr>
<tr>
<td>anaemia, including haemolytic and aplastic; haemorrhage, pancytopenia, agranulocytosis, leucopaenia, reversible bone marrow depression, thrombocytopenia, thrombotic thrombocytopenic purpura, petechiae, ecchymosis/bruising</td>
</tr>
<tr>
<td>Musculoskeletal</td>
</tr>
<tr>
<td>tendinitis/rupture; weakness; rhabdomyolysis</td>
</tr>
<tr>
<td>Nervous System</td>
</tr>
<tr>
<td>-------------------------------</td>
</tr>
<tr>
<td>Respiratory System</td>
</tr>
<tr>
<td>Skin/Hypersensitivity</td>
</tr>
<tr>
<td>Special Senses</td>
</tr>
<tr>
<td>Urinary System</td>
</tr>
</tbody>
</table>

**Laboratory Tests**

<table>
<thead>
<tr>
<th>Haematopoietic</th>
<th>prolongation of prothrombin time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Chemistry</td>
<td>acidosis, elevation of serum triglycerides, serum cholesterol, serum potassium, liver function tests, including GGTP, LDH, bilirubin</td>
</tr>
<tr>
<td>Urinary</td>
<td>albuminuria, candiduria</td>
</tr>
</tbody>
</table>

In clinical trials using multiple-dose therapy, ophthalmologic abnormalities, including cataracts and multiple punctate lenticular opacities, have been noted in patients undergoing treatment with other quinolones. The relationship of the drugs to these events is not presently established.

Stevens-Johnson syndrome/toxic epidermal necrolysis have been reported with ofloxacin.

Crystalluria and cylindruria have been reported with other quinolones.

**Ornidazole**

Adverse effects have been categorised as follows: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1000), very rare (<1/10,000), and not known (cannot be estimated from the available data).
Diseases of the Vascular and Lymph System

Rare: leucopaenia

Nervous System Disorders

Very rare: somnolence, headache, dizziness, tremor, rigidity, coordination impairments, seizures, fatigue, vertigo, temporary loss of consciousness and sensory or mixed peripheral neuropathy.

Gastrointestinal Disorders

Uncommon: nausea, vomiting, diarrhoea, epigastric discomfort, dry mouth, loss of appetite.

Rare: impairment of the sense of taste

Hepatobiliary Diseases

Unknown: jaundice, abnormal liver function tests

Skin and subcutaneous tissue diseases

Rare: pruritus and skin reactions

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.

Overdosage

Ofloxacin

Information on overdosage with ofloxacin is limited. One incident of accidental overdosage has been reported. In this case, an adult female received 3 grams of ofloxacin intravenously over 45 minutes. A blood sample obtained 15 minutes after the completion of the infusion revealed an ofloxacin level of 39.3 mcg/mL. In 7 hours, the level had fallen to 16.2 mcg/mL, and by 24 hours to 2.7 mcg/mL. During the infusion, the patient developed drowsiness, nausea, dizziness, hot and cold flushes, subjective facial swelling and numbness, slurring of speech, and mild-to-moderate disorientation. All complaints except the dizziness subsided within 1 hour after discontinuation of the infusion. The dizziness, most bothersome while standing, resolved in approximately 9 hours. Laboratory testing reportedly revealed no clinically significant changes in routine parameters in this patient.

Ornidazole

In cases of overdosage, the symptoms mentioned under Undesirable Effects occur in a more severe form. No specific antidote is known. The administration of diazepam is recommended if cramps occur

Storage And Handling Instructions

Store in a cool, dry place. Protect from light.

Packaging Information

OFLOX OZ Tablets..................Blister pack of 10 tablets

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Last Reviewed: Apr 2019