OFLOX-OZ Tablets (Ofloxacin + Ornidazole)

For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

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

- o tendinitis and tendon rupture;
- o peripheral neuropathy; and,
- o 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:

- o Acute exacerbation of chronic bronchitis
- o Uncomplicated cystitis

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

Qualitative and Quantitative Composition

OFLOX-OZ Tablets

Each film-coated tablet contains:

Ofloxacin IP…….200 mg

Ornidazole, IP ……. 500 mg

Colour: Titanium Dioxide

Dosage Form(S) And Strength(S)

Oral tablet containing ofloxacin 200 mg and ornidazole 500 mg

Clinical Particulars

Therapeutic Indications

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

Posology and Method of 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.

Special Warnings and Precautions for Use

Ofloxacin

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, dysaesthesia 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 neuropathy.

Exacerbation of Myasthenia Gravis

Fluoroquinolones, including ofloxacin, have neuromuscular-blocking activity and may exacerbate muscle weakness in persons with myasthenia gravis. Post marketing 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, light-headedness, 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; thrombocytopaenia, including thrombotic thrombocytopaenic purpura; leucopaenia; agranulocytosis; pancytopaenia; 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 3 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 are 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 hypoglyacemic 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 post marketing 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

Advise 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 administration.

Caffeine

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 (CYP450) 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.

Use in Special Populations

Pregnant Women

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/m^2, or 50 times based on mg/kg) and 160 mg/kg/day (4 times the recommended maximum human dose based on mg/m^2, 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/m^2, 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 foetal 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/m^2.

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

Lactating Women

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 Patients

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.

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

Geriatric Patients

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:

Body as a Whole	asthenia, chills, malaise, extremity pain, pain, epistaxis
Cardiovascular System	cardiac arrest, oedema, hypertension, hypotension, palpitations, vasodilation
Gastrointestinal System	dyspepsia
Genital/Reproductive System	burning, irritation, pain and rash of the female genitalia; dysmenorrhoea; menorrhagia; metrorrhagia
Musculoskeletal System	arthralgia, myalgia
Nervous System	seizures, anxiety, cognitive change, depression, dream abnormality, euphoria, hallucinations, paraesthesia, syncope, vertigo, tremor, confusion
Nutritional/Metabolic	thirst, weight loss
Respiratory System	respiratory arrest, cough, rhinorrhoea
Skin/Hypersensitivity	angio-oedema, diaphoresis, urticaria, vasculitis
Special Senses	decreased hearing acuity, tinnitus, photophobia
Urinary System	dysuria, urinary frequency, urinary retention

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.

Haematopoietic	anaemia, leucopaenia, leucocytosis, neutropaenia, neutrophilia, increased band forms, lymphocytopaenia, eosinophilia, lymphocytosis, thrombocytopaenia, thrombocytosis, elevated ESR
Hepatic	elevated: alkaline phosphatase, AST (SGOT), ALT (SGPT)

Serum Chemistry	hyperglycaemia, hypoglycaemia, elevated creatinine, elevated BUN
Urinary	glucosuria, proteinuria, alkalinuria, hyposthenuria, haematuria, pyuria

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)

Post marketing Adverse Events

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

Clinical

Cardiovascular System	cerebral thrombosis, pulmonary oedema, tachycardia, hypotension/shock, syncope, *torsades de pointes*
Endocrine/Metabolic	hyper- or hypoglycaemia, especially in diabetic patients on insulin or oral hypoglycaemic agents
Gastrointestinal System	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
Genital/Reproductive System	vaginal candidiasis

Haematopoietic	anaemia, including haemolytic and aplastic; haemorrhage, pancytopaenia, agranulocytosis, leucopaenia, reversible bone marrow depression, thrombocytopaenia, thrombotic thrombocytopaenic purpura, petechiae, ecchymosis/bruising
Musculoskeletal	tendinitis/rupture; weakness; rhabdomyolysis
Nervous System	nightmares; suicidal thoughts or acts, disorientation, psychotic reactions, paranoia; phobia, agitation, restlessness, aggressiveness/hostility, manic reaction, emotional lability; peripheral neuropathy that may be irreversible, ataxia, incoordination; exacerbation of myasthenia gravis and extrapyramidal disorders; dysphasia, light-headedness
Respiratory System	dyspnoea, bronchospasm, allergic pneumonitis, stridor
Skin/Hypersensitivity	anaphylactic (anaphylactoid) reactions/shock; purpura, serum sickness, erythema multiforme/Stevens-Johnson syndrome, erythema nodosum, exfoliative dermatitis, hyperpigmentation, toxic epidermal necrolysis, conjunctivitis, photosensitivity/phototoxicity reaction, vesiculobullous eruption
Special Senses	diplopia, nystagmus, blurred vision, disturbances of taste, smell, hearing and equilibrium, usually reversible following discontinuation
Urinary System	anuria, polyuria, renal calculi, renal failure, interstitial nephritis, haematuria

Laboratory Tests

Haematopoietic	prolongation of prothrombin time
Serum Chemistry	acidosis, elevation of serum triglycerides, serum cholesterol, serum potassium, liver function tests, including GGTP, LDH, bilirubin
Urinary	albuminuria, candiduria

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.

Reporting of Side Effects

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 Programme of India by calling on 1800 180 3024 or you can report to Cipla Ltd on 1800 267 7779. By reporting side effects, you can help provide more information on the safety of this product.

Overdose

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

Pharmacological Properties

Mechanism of Action

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.

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.

Pharmacodynamic Properties

Ofloxacin

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 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.

Pharmacokinetic Properties

Ofloxacin

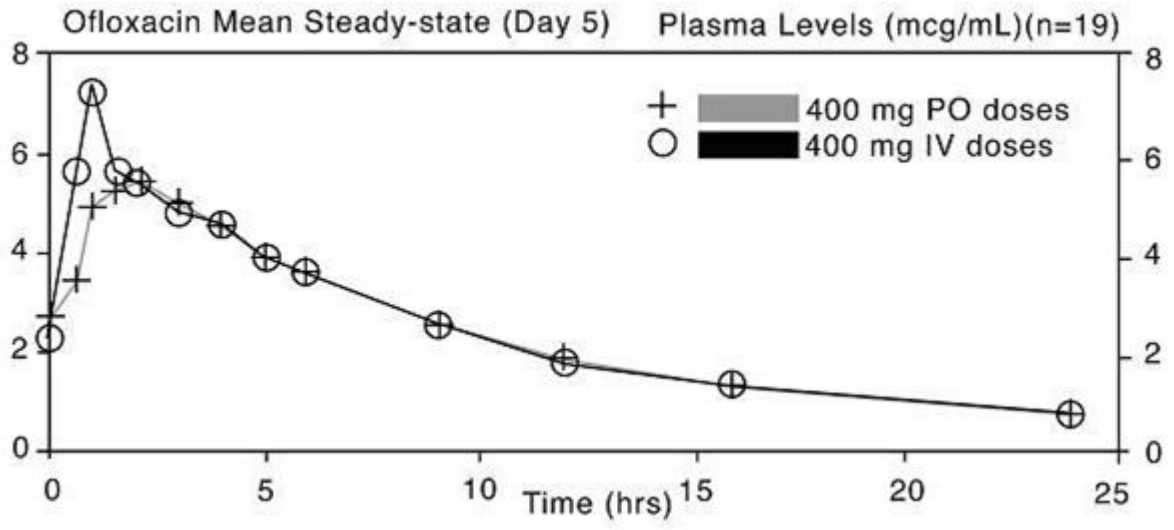
Following oral administration, the bioavailability of ofloxacin in the tablet formulation is approximately 98%. Maximum serum concentrations are achieved 1–2 hours after an oral dose. Absorption of ofloxacin after single or multiple doses of 200–400 mg is predictable, and the amount of drug absorbed 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.

Oral Dose	Serum Concentration 2 Hours after Administration (mcg/mL)	Area Under the Curve ($AUC_{(0\text{-infinity})}$) (mcg•h/mL)
200 mg single dose	1.5	14.1
300 mg single dose	2.4	21.2
400 mg single dose	2.9	31.4
400 mg steady-state	4.6	61

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 $AUC_{(0 \text{ to } 12)}$ attained after the intravenous administration of 400 mg over 60 minutes was 43.5 mcg•h/mL; the mean steady-state $AUC_{(0 \text{ to } 12)}$ 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).



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 $AUC_{(infinity)}$ 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 [this interpretation was based on study results collected from two separate studies]. 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-hydroxymethyl metabolites 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.

Nonclinical Properties

Animal Toxicology or Pharmacology

Ofloxacin

Ofloxacin, as well as other drugs of the quinolone class, has been shown to cause arthropathies (arthrosis) in immature dogs and rats. In addition, these drugs are associated with an increased incidence of osteochondrosis in rats as compared with the incidence observed in vehicle-treated rats. There is no evidence of arthropathies in fully mature dogs at intravenous doses up to 3 times the recommended maximum human dose (on an mg/m^2 basis or 5 times based on mg/kg basis), for a 1-week exposure period.

Long-term, high-dose systemic use of other quinolones in experimental animals has caused lenticular opacities; however, this finding was not observed in any animal studies with ofloxacin. Reduced serum globulin and protein levels were observed in animals treated with other quinolones. In one ofloxacin study, minor decreases in serum globulin and protein levels were noted in female cynomolgus monkeys dosed orally with 40 mg/kg ofloxacin daily for 1 year. These changes, however, were considered to be within normal limits for monkeys.

Crystalluria and ocular toxicity were not observed in any animals treated with ofloxacin.

Preclinical Safety Data

Preclinical effects in conventional studies of safety pharmacology, acute toxicity, repeated dose toxicity, reproductive studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use. Joint toxicity was observed at exposure in the human therapeutic range in juvenile rats and dogs. Ofloxacin exhibits a neurotoxic potential and causes reversible testicular alterations at high doses.

Mutagenicity studies showed no evidence for mutagenicity of ofloxacin. However, like some other quinolones Ofloxacin is phototoxic in animals at exposure in the human therapeutic range. The

phototoxic, photomutagenic and photocarcinogenic potential of ofloxacin is comparable with that of other gyrase inhibitors.

Preclinical data from conventional genotoxicity studies reveal no special hazard to humans, but carcinogen potential has not been investigated.

Reproduction Toxicity

Ofloxacin

Ofloxacin has no effect on fertility, peri- or postnatal development, and therapeutic doses did not lead to any teratogenic or other embryotoxic effects in animals. Ofloxacin crosses the placenta and levels reached in the amniotic fluid are about 30% of the maximal concentrations measured in maternal serum.

Ornidazole

Not seen.

Description

Ofloxacin

Ofloxacin tablets are a synthetic broad-spectrum antimicrobial agent for oral administration. Chemically, ofloxacin, a fluorinated carboxyquinolone, is the racemate, (±)-9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic acid. The chemical structure is $C_{18}H_{20}FN_3O_4$. The molecular weight is 361.4.

Ornidazole

Ornidazole is an antibiotic used to treat protozoan infections. Its chemical formula is $C_7H_{10}ClN_3O_3$.

Pharmaceutical Particulars

Incompatibilities

Not applicable.

Shelf-Life

As on the pack.

Packaging Information

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

Storage and Handling Instructions

Store at a temperature not exceeding 30° C. Protect from light and moisture.

Patient Counselling Information

What are OFLOX-OZ tablets and what are they used for?

OFLOX-OZ tablets contain ofloxacin and ornidazole. These tablets are indicated for the treatment of diarrhoea of mixed infection in adults only.

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.

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.

Important information about OFLOX-OZ tablets

OFLOX-OZ Tablets contain ofloxacin and ornidazole. Do not take OFLOX-OZ Tablets if you have allergy and tell your doctor in case of any of the following:

Ofloxacin

- If you are allergic to ofloxacin or any of the other ingredients of this medicine. Signs of an allergic reaction include a rash, swallowing or breathing problems, swelling of your lips, face, throat or tongue.
- If you have previously had an allergic reaction to another quinolone antibiotic e.g. ciprofloxacin or norfloxacin.
- If you suffer from epilepsy or are at risk of fits.
- If you have a history of inflammation and swelling of the tendons (tendonitis) which can affect areas such as the wrist or the achilles tendon after treatment with a quinolone antibiotic e.g. ciprofloxacin, norfloxacin, or nadifloxacin.
- If you suffer from or there is a family history of glucose-6-phosphate dehydrogenase deficiency (an inherited disorder that affects the red blood cells)
- If you are pregnant, think you may be pregnant or are planning to have a baby.
- If you are breastfeeding.
- If you are under the age of 18 years or are still growing.

Do not take this medicine if any of the above apply to you. If you are not sure, talk to your doctor or pharmacist before taking ofloxacin.

Warnings and precautions

Before taking this medicine

You should not take fluoroquinolone/quinolone antibacterial medicines, including ofloxacin, if you have experienced any serious adverse reaction in the past when taking a quinolone or fluoroquinolone. In this situation, you should inform your doctor as soon as possible.

Talk to your doctor or pharmacist before taking ofloxacin if any of the following apply:

- If you have been diagnosed with an enlargement or ‘bulge’ of a large blood vessel (aortic aneurysm

or large vessel peripheral aneurysm)
- If you have experienced a previous episode of aortic dissection (a tear in the aorta wall)
- If you have a family history of aortic aneurysm or aortic dissection or other risk factors or predisposing conditions (e.g. connective tissue disorders such as Marfan syndrome, or vascular Ehlers-Danlos syndrome, or vascular disorders such as Takayasu arteritis, giant cell arteritis, Behcet's disease, high blood pressure, or known atherosclerosis)
- If you feel sudden, severe pain in your abdomen, chest or back, go **immediately** to an emergency room.
- You have or have ever had a history of mental illness.
- You have problems with your liver or kidneys.
- You have heart disease or problems with your heartbeat.
- You were born with or have family history of prolonged QT interval (seen on ECG [electrical recording of the heart]).
- Have salt imbalance in the blood (especially low level of potassium or magnesium in the blood).
- Have a very slow heart rhythm (called 'bradycardia').
- Have a weak heart (heart failure).
- Have a history of heart attack (myocardial infarction).
- You are female or elderly.
- You are taking other medicines that result in abnormal ECG changes
- You have an illness of the nervous system called 'myasthenia gravis' (muscle weakness).
- If you are diabetic or suffer from low blood sugar.

During treatment

When taking this medicine, If your eyesight becomes impaired or if your eyes seem to be otherwise affected, consult an eye specialist **immediately**.

If you:

- experience a severe skin rash or allergic reaction, or
- develop severe diarrhoea, (which may be bloody) with stomach pain and fever, or
- notice pain, tenderness, or restricted movement of the tendons, or
- notice numbness or tingling in the hands and feet

stop taking this medicine and talk to your doctor **straightaway**.

Pain and swelling in the joints and inflammation or rupture of tendons may occur rarely. Your risk is increased if you are elderly (above 60 years of age), have received an organ transplant, have kidney problems or if you are being treated with corticosteroids. Inflammation and ruptures of tendons may occur within the first 48 hours of treatment and even up to several months after stopping of ofloxacin therapy. At the first sign of pain or inflammation of a tendon (for example in your ankle, wrist, elbow, shoulder or knee), **stop taking** ofloxacin, contact your doctor and rest the painful area. Avoid any unnecessary exercise as this might increase the risk of a tendon rupture.

You may rarely experience symptoms of nerve damage (neuropathy) such as pain, burning, tingling, numbness and/or weakness especially in the feet and legs or hands and arms. If this happens, **stop taking** ofloxacin and inform your doctor **immediately** in order to prevent the development of potentially irreversible condition.

Prolonged, disabling and potentially irreversible serious side effects

Fluoroquinolone/quinolone antibacterial medicines, including ofloxacin, have been associated with

very rare but serious side effects, some of them being long-lasting (continuing for months or years), disabling or potentially irreversible. This includes tendon, muscle and joint pain of the upper and lower limbs, difficulty in walking, abnormal sensations such as pins and needles, tingling, tickling, numbness or burning (paraesthesia), sensory disorders including impairment of vision, taste and smell, and hearing, depression, memory impairment, severe fatigue, and severe sleep disorders.

If you experience any of these side effects after taking ofloxacin, contact your doctor **immediately** prior to continuing treatment. You and your doctor can then decide on continuing the treatment by considering an antibiotic from another class.

If you are not sure if any of the above apply to you, talk to your doctor or pharmacist before taking ofloxacin.

Other medicines and ofloxacin

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Ornidazole

Do not take these tablets in case of the following:

- You have had an allergic reaction to ornidazole other nitroimidazole derivatives such as metronidazole or any ingredients listed at the end of this leaflet.
- The package is torn or shows signs of tampering.
- The expiry date printed on the pack has passed.

If you are not sure if you should be taking ornidazole, talk to your doctor.

Before you take OFLOX-OZ Tablets, tell your HCP about other medication.

OFLOX-OZ Tablets contain ofloxacin and ornidazole, which may react with other medications. Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Ofloxacin

You **must** tell your doctor if you are taking other medicines that can alter your heart rhythm:

- Medicines that belong to the group of anti-arrhythmics (e.g. quinidine, hydroquinidine, disopyramide, amiodarone, sotalol, dofetilide, ibutilide).
- Tricyclic antidepressants (e.g. clomipramine, amitriptyline).
- Some antimicrobials that belong to the group of macrolides (e.g. erythromycin, clarithromycin, azithromycin).
- Some antipsychotics used to treat mental health conditions such as schizophrenia and bipolar disorder.

Tell your doctor if you are taking any of the following medicines:

- Medicines or dietary supplements that contain iron (for anaemia) or zinc.
- Sucralfate used for stomach ulcers.
- Antacids used for indigestion that contain magnesium or aluminium.
- Corticosteroids used for treatment of inflammation and swelling or over-active immune system.

These may increase the risk of you developing a tendon rupture.
- Painkillers called non-steroidal anti-inflammatory drugs (NSAIDs), e.g. ibuprofen or diclofenac, or theophylline, used to treat asthma or chronic obstructive pulmonary disease as these could make you more prone to fits if taken with ofloxacin.
- Glibenclamide, a medicine to control your blood sugar, as the amount of these medicines in the blood may increase and have a greater effect.
- Drugs that may affect your kidney function, e.g. cimetidine (used for stomach ulcers or indigestion), probenecid (used for gout) and methotrexate (used for rheumatism) as they can increase the level of ofloxacin in the blood.
- Medicines to thin your blood, e.g. warfarin. Taking these with ofloxacin can increase the time it takes for your blood to clot.
- If you are taking didanosine (a medicine used to treat HIV infections), you should not take the chewable, buffered tablets until at least 2 hours after taking ofloxacin.
- Diuretics such as furosemide.

This medicine **should not** be taken within 2 hours of taking iron or zinc tablets, antacids, or sucralfate, as these medicines can stop ofloxacin from working properly.

If you are due to have urine tests for porphyrin (a pigment in the blood), or for opiates (strong painkillers), tell your doctor or nurse you are taking this medicine.

Pregnancy and breastfeeding

Do not take ofloxacin if you are pregnant or breastfeeding, think you may be pregnant or are planning to have a baby. If you become pregnant while taking ofloxacin, **stop taking the tablets** and contact your doctor **immediately**.

Driving and using machines

Taking ofloxacin may make you feel sleepy, dizzy or could affect your eyesight. Do not drive or use machines until you know how this medicine affects you. Drinking alcohol may make these symptoms worse.

Ornidazole

Before starting medication, tell your doctor about all your current conditions/other medicines:

- You are pregnant or plan to become pregnant. It is not known whether ornidazole is harmful to an unborn baby when taken by a pregnant woman. Ornidazole is not recommended for use in pregnant women unless the benefits of treatment outweigh the risk to the unborn baby.
- You are breastfeeding or plan to breastfeed. It is not known whether ornidazole passes into breast milk. Your doctor will discuss the risks and benefits of using ornidazole if you are breastfeeding.
- You have any other health problems, especially epilepsy, multiple sclerosis or liver disease.
- You are allergic to any other medicines, foods, dyes or preservatives

If you have not told your doctor about any of the above, tell them before you start taking ornidazole.

Taking other medicines

Tell your doctor if you are taking any other medicines including any that you have bought from a pharmacy. Some medicines and ornidazole may interfere with each other. These include

- warfarin, a blood-thinning agent

- vecuronium bromide, a muscle relaxant

These medicines may be affected by ornidazole or may affect how well it works. You may need to use different amounts of your medicine, or you may need to take different medicines. Your doctor will advise you.

Your doctor and pharmacist may have more information on medicines to be careful with or avoid while taking ornidazole. Ask your doctor or pharmacist if you are not sure about the above list of medicines.

How should I take OFLOX-OZ Tablets?

- One tablet of **OFLOX-OZ** is recommended as twice-daily therapy.
- Always take this medicine exactly as your doctor or pharmacist has told you.
- Check with your doctor or pharmacist if you are not sure.
- For oral use. You should swallow these tablets whole with water. Do not chew them.
- The tablets can be taken with or without food.
- If you take it on an empty stomach, it may cause a stomach upset
- When undergoing treatment with these tablets, avoid strong sunlight and do not use sun lamps or solaria as your skin may be more sensitive to light.
- If you are taking iron tablets (for anaemia), antacids (for indigestion or heartburn) or sucralfate (for stomach ulcers) or didanosine chewable or buffered tablets (for HIV), it is important not to take these 2 hours before or after taking **OFLOX-OZ Tablets**. If you feel the effect of your medicine is too weak or strong, do not change the dose yourself, but ask your doctor.
- When taking **OFLOX-OZ Tablets**, if your eyesight becomes impaired or if your eyes seem to be otherwise affected, consult an eye specialist immediately
- In case of missed dose, if it is almost time for your next dose, skip the dose you missed and take your next dose when you are meant to.
- If you are not sure what to do, ask your doctor or pharmacist.

What are the possible side effects OFLOX-OZ Tablets?

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Ofloxacin

Stop taking OFLOX-OZ Tablets and tell your doctor or go to your nearest hospital casualty department straightaway if you have any of the following serious side effects because you may need medical attention:

Uncommon *(may affect up to 1 in 100 people)*

- Resistance of infection causing organisms to this treatment, (you may fail to respond to treatment).

Rare *(may affect up to 1 in 1,000 people)*

- You have an allergic reaction. Such reactions may appear in the form of anaphylaxis (a severe form of allergic reaction) with symptoms such as
    - severe skin rash
    - swelling of the face, lips, mouth, tongue or throat (angio-oedema)

- anaphylactic shock (sudden wheezing, swelling of your lips, tongue and throat or body, rash, fainting or difficulties in swallowing)

- Inflammation of the bowel, which may cause severe watery diarrhoea, which may have blood in it, possibly with stomach cramps and a high temperature.
- Swelling of the tendons with the following symptoms; pain, tenderness, sometimes restricted movement (tendonitis). This can lead to tendon rupture, especially of the large tendon at the back of the ankle (Achilles tendon). The risk of this occurring is increased if you are also taking corticosteroids, e.g. prednisolone.
- Numbness or tingling in the hands and feet or being very sensitive to touch, numbness or weakness of the arms and legs.
- Blurred, double or altered colour vision. If your eyesight becomes impaired or if your eyes seem to be otherwise affected, consult an eye specialist **immediately**.

Very rare *(may affect up to 1 in 10,000 people)*

- A condition in which the amount of oxygen-carrying pigment (haemoglobin) in the blood is below normal or an illness resulting from the destruction of red blood cells with the following symptoms; feeling tired, faint, dizzy, being short of breath when exercising and having pale skin. These may be signs of anaemia or haemolytic anaemia.
- Other blood disorders when the numbers of different types of cells in the blood may fall, which may cause fever, chills, sore throat, ulcers in the mouth and throat (leucopaenia, agranulocytosis).
- Fits (seizures).
- Skin rash, which may blister and looks like small targets (central dark spots surrounded by a paler area, with a dark ring around the edge) (erythema multiforme).
- A widespread rash with blisters and skin peeling on much of the body surface (toxic epidermal necrolysis).
- Narrowing, blockage or leakage of blood vessels, in exceptional cases leading to severe skin reactions and death of areas of the skin.
- Severe kidney problems, which may result in your kidneys stopping working. Signs may include a rash, high temperature, general aches and pains, or blood in the urine.
- Liver problems, such as inflammation of the liver (hepatitis) or blockage in the bile duct that may cause your eyes or skin to go yellow (jaundice) or you may notice the following symptoms: nausea, vomiting, loss of appetite, feeling generally unwell, fever, itching, light-coloured bowel motions, dark-coloured urine.

Not known *(frequency cannot be estimated from the available data)*

- Abnormally fast heart rhythm, life-threatening irregular heart rhythm, alteration of the heart rhythm (called 'prolongation of QT interval', seen on ECG [electrical activity of the heart]).
- Severe depression or mental illness. Some people who are depressed think of harming or killing themselves.
- A serious reduction in all types of blood cells (pancytopaenia), which may result from a failure of the bone marrow to produce these.
- A widespread rash with blisters and peeling skin, particularly around the mouth, nose, eyes and genitals (Stevens-Johnson syndrome).
- Swelling of the lungs with the following symptoms: coughing, difficulty breathing, wheezing
- Temporary paralysis or weakness of the muscles (rhabdomyolysis), disease of the muscles with the following symptoms: aching muscles, muscle tenderness or weakness, not caused by exercise.
- Inflammation of the pancreas (pancreatitis) – you may have severe pain in the stomach and back.
- Loss of consciousness (coma), due to a severe reduction in blood sugar levels

- Skin redness with excessive scaling (exfoliative dermatitis)
- Loss of appetite, skin and eyes becoming yellow in colour, dark-coloured urine, itching, or tender stomach (abdomen). These may be signs of liver problems which may include a fatal failure of the liver.

Tell your doctor or pharmacist if any of the following side effects gets serious or lasts longer than a few days:

Uncommon *(may affect up to 1 in 100 people)*

- Feeling sick (nausea) or being sick (vomiting), diarrhoea or stomach pains.
- Headaches, sleep disturbances including difficulty sleeping (insomnia).
- Cough and inflamed sore nose or throat (nasopharyngitis).

Rare *(may affect up to 1 in 1,000 people)*

- Loss of appetite.
- Feeling confused or anxious, nightmares, seeing, feeling or hearing things that are not there, depression and mental illness.
- Changes in kidney function shown in blood tests.
- Feeling faint, lightheaded or dizzy, which may be due to low blood pressure.

Very rare *(may affect up to 1 in 10,000 people)*

- Unusual bleeding or bruising more easily than normal (thrombocytopaenia).
- Increase in some white blood cells (eosinophilia).
- Unusual purple discolouration under the skin, which may be due to bleeding or bruising due to leaky or damaged blood vessels .

Not known *(frequency cannot be estimated from the available data)*

- A red, scaly rash with bumps under the skin and blisters (exanthemous pustolosis).
- Muscular weakness, muscle tear.
- Feeling weak or irritable, sweating and/or trembling. This could be due to lowering of blood sugar (glucose) levels especially in patients with diabetes or existing low blood sugar.
- Feeling of nervousness, tremor, unusual (involuntary) muscle movements.
- Digestive problems such as stomach upset (indigestion/heartburn), constipation, or wind.
- General pain, pains in your muscles and stiffness in the bones/joints (arthritis), feeling unwell (asthenia), or fever.

  Very rare cases of long-lasting (up to months or years) or permanent adverse drug reactions, such as tendon inflammations, tendon rupture, joint pain, pain in the limbs, difficulty in walking, abnormal sensations such as pins and needles, tingling, tickling, burning, numbness or pain (neuropathy), depression, fatigue, sleep disorders, memory impairment, as well as impairment of hearing, vision, and taste and smell have been associated with administration of quinolone and fluoroquinolone antibiotics, in some cases irrespective of pre-existing risk factors.

Ornidazole

Tell your doctor or pharmacist as soon as possible if you do not feel well while you are taking **OFLOX-OZ Tablets**. All medicines can have side effects. Sometimes they are serious, most of the time they are not. You may need medical treatment if you get some of the side effects.

Tell your doctor if you notice any of the following and they worry you:

- Sleepiness/tiredness
- Headache
- Nausea and/or vomiting
- Dizziness or vertigo (a spinning sensation)
- Tremor
- Taste disturbances
- Skin reactions
- Numbness or tingling in your fingers or toes

Tell your doctor immediately or go to your nearest Accident and Emergency Centre if you notice any of the following:

- Rigidity
- Poor co-ordination
- Seizures
- Loss of consciousness
- Allergic reaction. Some of the symptoms of an allergic reaction may include severe skin rash, itching, hives, swelling of the face, lips, mouth or throat which may cause difficulty in swallowing or breathing, swelling of the hands, feet or ankles.

These may be serious side effects. You may need urgent medical attention.

This is not a complete list of all possible side effects. Others may occur in some people and there may be some side effects not yet known.

Tell your doctor if you notice anything else that is making you feel unwell, even if it is not on this list.

Ask your doctor or pharmacist if you don’t understand anything in this list.

How should I store OFLOX-OZ Tablets?

- Keep this medicine out of the sight and reach of children.
- Do not take this medicine after the expiry date shown on the pack. The expiry date refers to the last day of that month.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment
- Keep your tablets in the blister pack until it is time to take them.
- Keep **OFLOX-OZ Tablets** in a cool dry place where the temperature stays below 30°C.
- Do not store it, or any other medicine, in a bathroom or near a sink.
- Do not leave it in the car or on windowsills. Heat and dampness can destroy some medicines.

General information about the safe and effective use of OFLOX-OZ Tablets

- This medicine **should not** be taken within 2 hours of taking iron or zinc tablets, antacids, or sucralfate, as these medicines can stop ofloxacin (a component of **OFLOX-OZ Tablets**) from working properly.
- If you are due to have urine tests for porphyrin (a pigment in the blood), or for opiates (strong painkillers), tell your doctor or nurse you are taking this medicine.
- **Do not** take **OFLOX-OZ Tablets** if you are pregnant or breastfeeding, think you may be pregnant or are planning to have a baby. If you become pregnant while taking, **stop taking the tablets** and contact your doctor **immediately**.

- Taking **OFLOX-OZ Tablets** may make you feel sleepy, dizzy or could affect your eyesight. Do not drive or use machines until you know how this medicine affects you. Drinking alcohol may make these symptoms worse.
- If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.
- Do not drink alcoholic drinks while taking **OFLOX-OZ Tablets** or for at least 3 days after finishing treatment.
- Do not stop taking or change the dose without first checking with your doctor.
- Do not give **OFLOX-OZ Tablets** to anyone else even if they have the same condition as you.
- Do not use **OFLOX-OZ Tablets** to treat other complaints unless your doctor says to.

What are the ingredients in OFLOX-OZ Tablets?

Each film-coated tablet contains:

Ofloxacin IP.....200 mg

Ornidazole, IP ..... 500 mg

Colour: Titanium Dioxide

Details of The Manufacturer/Marketer

Manufactured by: Cipla Ltd

Kumrek, Rangpo, East Sikkim, Sikkim 737132

Marketed by:

Cipla Ltd

Regd. Office: Cipla House, Peninsula Business Park,

Ganpatrao Kadam Marg, Lower Parel,

Mumbai – 400 013, India

Details of Permission or Licence Number with Date

M. L. No. M/447/2007 dated 23.12.2016

Date of Revision

26/11/2020