Not to be sold by retail without the prescription of a Registered Medical Practitioner

Prescribing Information

1. Generic Name

Ofloxacin and Ornidazole Tablets IP

(Brand Name: O-CEBRAN ® -OZ Tablets)

Ofloxacin: WARNINGs

Fluoroquinolones, including ofloxacin, are associated with an increased risk of tendinitis and tendon rupture in all ages. This risk is further increased in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants. Fluoroquinolones, including ofloxacin, may exacerbate muscle weakness in persons with myasthenia gravis. Avoid ofloxacin in patients with a known history of myasthenia gravis.

2. Qualitative and Quantitative Composition

Each Film-Coated Tablet Contains:

Ofloxacin IP …….. 200 mg.

Ornidazole IP …… 500 mg.

Colours: Lake of Sunset Yellow FCF & Titanium Dioxide IP.

3. Dosage Form and Strength

Dosage Form: Tablets.

Dosage Strength: Ofloxacin 200 mg with Ornidazole 500 mg per tablet.

4. Clinical Particulars

4.1 Therapeutic Indication

O-CEBRAN-OZ Tablets are indicated for the treatment of diarrhoea caused by mixed infections (bacterial and protozoal) in adults.

4.2Posology and Method of Administration

Adults (with normal renal function): One tablet to be administered orally twice daily.

O-CEBRAN-OZ Tablets should be administered during or immediately after a meal.

Or, as prescribed by physician.

4.3Contraindications

O-CEBRAN-OZ Tablets are contraindicated in the following:

- Known or suspected hypersensitivity to ofloxacin/other quinolones or to ornidazole/other 5-nitroimidazoles or to any component of the formulation.

- Pregnancy and lactation.
- Anuric patients.
- In patients with epilepsy.
- Patients with history of tendon disorders (tendinitis) related to use of fluoroquinolones.
- Patients with latent or actual defects in glucose-6-phosphate dehydrogenase (G6PD) activity.

4.4Special Warnings and Precautions for Use

Ofloxacin

Caution - safety issues with fluoroquinolone antibiotics: Fluoroquinolone antibiotics may cause significant decreases in blood sugar and certain mental health side effects. Low blood sugar levels, also called hypoglycemia, can lead to coma. The mental health side effects more prominent and more consistent across the systemic fluoroquinolone drug class include:

- Disturbances in attention.
- Disorientation.
- Agitation.
- Nervousness.
- Memory impairment.
- Serious disturbances in mental abilities called delirium.

Fluoroquinolone antibiotics - increased risk of ruptures or tears in the aorta blood vessel in certain patients: Fluoroquinolone antibiotics can increase the occurrence of rare but serious events of ruptures or tears in the main artery of the body, called the aorta. These tears, called aortic dissections or ruptures of an aortic aneurysm, can lead to dangerous bleeding or even death.

Information for healthcare professionals (HCPs):

- Avoid prescribing fluoroquinolone antibiotics to patients who have an aortic aneurysm or are at risk for an aortic aneurysm, such as patients with peripheral atherosclerotic vascular diseases, hypertension, certain genetic conditions such as **Marfan syndrome and Ehlers-Danlos syndrome, and elderly patients.**
- Prescribe fluoroquinolones to these patients only when no other treatment options are available.
- Advise all patients to seek immediate medical treatment for any symptoms associated with aortic aneurysm.
- Stop fluoroquinolone treatment immediately if a patient reports side effects suggestive of aortic aneurysm or dissection.

Information for patients:

- Seek medical attention immediately if you experience sudden, severe, and constant pain in the stomach, chest or back.

- Be aware that symptoms of an aortic aneurysm often do not show up until the aneurysm becomes large or bursts, so report any unusual side effects from taking fluoroquinolones to your health care professional immediately.
- Inform your health professional before starting an antibiotic prescription, if you have a history of aneurysms, blockages or hardening of the arteries, high blood pressure, or genetic conditions such as Marfan syndrome or Ehlers-Danlos syndrome.
- Do not stop the antimicrobial without first talking to your health care professional.

Central nervous system effects: Convulsions, increased intracranial pressure, and toxic psychosis have been reported in patients receiving quinolones, including ofloxacin. Quinolones, including ofloxacin, may also cause central nervous system stimulation which may lead to tremors, restlessness/agitation, nervousness/anxiety, lightheadedness, confusion, hallucinations, paranoia and depression, nightmares, insomnia, and rarely suicidal thoughts or acts. These reactions may occur following the first dose. If these reactions occur in patients receiving ofloxacin, the drug should be discontinued and appropriate measures instituted.

Patients with history of psychotic disorder: As with all quinolones, ofloxacin should be used with caution in patients 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).

Hypersensitivity reactions: Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving therapy with quinolones, including ofloxacin. These reactions often occur following the first dose. Some reactions were accompanied by cardiovascular collapse, hypotension/shock, seizure, loss of consciousness, tingling, angioedema (including tongue, laryngeal, throat or facial edema/swelling), airway obstruction (including bronchospasm, shortness of breath and acute respiratory distress), dyspnea, urticaria/hives, itching, and other serious skin reactions. A few patients had a history of hypersensitivity reactions. The drug should be discontinued immediately at the first appearance of a skin rash or any other sign of hypersensitivity.

Peripheral neuropathy: Rare cases of sensory or sensorimotor axonal polyneuropathy affecting small and/or large axons resulting in paresthesias, hypoesthesias, dysesthesias and weakness have been reported in patients receiving quinolones, including ofloxacin. Ofloxacin should be discontinued if the patient experiences symptoms of neuropathy including pain, burning, tingling, numbness, and/or weakness or other alterations of sensation including light touch, pain, temperature, position sense, and vibratory sensation in order to prevent the development of an irreversible condition.

***Clostridium difficile*-associated diarrhea (CDAD):** Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic-associated colitis".

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including ofloxacin, and may range in severity from mild to life-threatening. Therefore, it is important to

consider this diagnosis in patients who present with diarrhea subsequent to the administration of any antibacterial agents.

Tendon effects: Ruptures of the shoulder, hand, Achilles tendon or other tendons that required surgical repair or resulted in prolonged disability have been reported in patients receiving quinolones, including ofloxacin. Post-marketing surveillance reports indicate that the risk may be increased in patients receiving corticosteroids, especially in the elderly. Ofloxacin should be discontinued if the patient experiences pain, inflammation, or rupture of a tendon. Patients should rest and refrain from exercise until the diagnosis of tendonitis or tendon rupture has been confidently excluded. Tendon rupture can occur during or after therapy with quinolones, including ofloxacin.

Photosensitivity/phototoxicity: Moderate to severe phototoxicity reactions have been observed in patients exposed to direct sunlight while receiving some drugs in this class, including ofloxacin. Excessive sunlight should be avoided. Therapy should be discontinued if phototoxicity (e.g., a skin eruption) occurs.

Torsades de pointes/ QT interval prolongation: Some quinolones, including ofloxacin, have been associated with prolongation of the QT interval on the electrocardiogram and infrequent cases of arrhythmia. Rare cases of torsade 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 hypokalemia, and patients receiving class IA (e.g., quinidine, procainamide), or class III (e.g., amiodarone, sotalol) antiarrhythmic agents.

Renal and/or hepatic impairment: Administer ofloxacin with caution in the presence of renal or hepatic insufficiency/impairment. In patients with known or suspected renal or hepatic 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 (based on creatinine clearance), alteration of the dosage regimen is necessary. Periodic assessment of organ system functions, including renal, hepatic, and hematopoietic, is advisable during prolonged therapy.

Patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency: Patients with latent or actual defects in G6PD activity may be prone to haemolytic reactions when treated with quinolone antibacterial agents, and so ofloxacin should be used with caution.

Myasthenia gravis: Ofloxacin should be used with caution in patients with a history of myasthenia gravis.

Hypoglycemia: If a hypoglycemic reaction occurs in a patient being treated with antidiabetic drugs along with ofloxacin, discontinue ofloxacin immediately and consult a physician.

General: Adequate hydration of patients receiving ofloxacin should be maintained to prevent the formation of highly concentrated urine. Also, excessive alkalinity of the urine should be avoided because of the risk of crystalluria.

Ornidazole

Coadministration with alcohol: When given in conjunction with alcohol, ornidazole may provoke a disulfiram-like reaction in some individuals. Thus, patients are advised not to drink alcoholic beverages while taking ornidazole.

CNS effects: Somnolence, dizziness, tremor, rigidity, poor coordination, seizures, vertigo or temporary loss of consciousness may occur in patients receiving ornidazole.

Long term use: Peripheral neuropathy, transient epileptiform seizures, and leucopenia have sometimes been associated with prolonged or intensive treatment with ornidazole. Clinical and laboratory monitoring is advised in patients receiving ornidazole for more than 10 days.

Patient with hepatic impairment, brain damage, hematopoiesis disorders: Caution must be exercised if the ornidazole is prescribed in patients with hepatic impairment (dose must be reduced), brain damage, hematopoiesis disorders (high risk of leucopenia or neutropenia), and patients who abuse alcohol.

4.5Drug Interactions

Ofloxacin

Antacids, sucralfate, metal cations, and multivitamins: Quinolones form chelates with alkaline earth and transition metal cations. Administration of quinolones with antacids containing calcium, magnesium, or aluminum, with sucralfate, with divalent or trivalent cations such as iron, or with multivitamins containing zinc or with didanosine may substantially interfere with the absorption of quinolones resulting in systemic levels considerably lower than desired. These agents should not be taken within the two-hour period before or within the two-hour period after ofloxacin administration.

Cimetidine: Cimetidine has demonstrated interference with the elimination of some quinolones. This interference has resulted in significant increases in 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 metabolized 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 metabolized 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 (NSAIDs): The concomitant administration of a NSAID 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 hyperglycemia and hypoglycemia, 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.

Interactions 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

Disulfiram: Acute psychoses or confusion have been associated with the concomitant use of ornidazole and disulfiram.

Phenytoin, lithium, and fluorouracil: Ornidazole is reported to impair the metabolism or excretion of several drugs including warfarin, phenytoin, lithium, fluorouracil with the consequent potential for an increased incidence of adverse effects.

Coumarin: Ornidazole potentiates the effect of the coumarin range oral anticoagulants, which requires appropriate adjustment of the dose.

Vecuronium bromide: Ornidazole prolongs the myorelaxant effect of vecuronium bromide.

Cytochrome P450 inducer agents: Plasma concentrations of ornidazole decreases by the concomitant administration of phenytoin, phenobarbital, or rifampicin as these drugs may accelerate the metabolism of ornidazole.

Cimetidine: Concentration of ornidazole increases in case of concurrent administration of liver microsomal system inhibitors, particularly H_2-receptor blockers (e.g., cimetidine).

Other nitroimidazole drugs: Isolated cases of peripheral nephritis, psychic depression and epilepsy-like convulsions were reported in cases of concurrent use of other 5-nitroimidazole derivatives (e.g., metronidazole, tinidazole).

4.6Use in Special Populations

Pregnant Women

Ofloxacin use in animal studies has shown damage to the joint cartilage in immature animals, but no teratogenic effects. There is no clinical data available for ornidazole exposure in pregnancy. Use of ornidazole should be avoided during pregnancy, especially during the first trimester and particularly with high dose regimens. O-CEBRAN-OZ Tablets are contraindicated for use during pregnancy.

Lactating Women

Ofloxacin is excreted into human breast milk in small amounts. Because of the potential for arthropathy and other serious toxicity in the nursing infant due to ofloxacin, breast feeding should be discontinued during treatment with ofloxacin. Ornidazole is distributed into breast milk giving it a bitter taste, which may impair feeding. Unnecessary exposure of the infant to the drug should be avoided, and breast feeding should generally be interrupted during treatment with O-CEBRAN-OZ Tablets and for 1 to 2 days afterwards.

Paediatric Patients

Ofloxacin and other fluoroquinolones have been reported to cause degenerative changes in weight bearing joints of young animals (beagle dogs). Thus, ofloxacin is contraindicated for use in children or growing adolescents. Ornidazole can be administered to children. Based on ofloxacin content of the formulation, O-CEBRAN-OZ Tablets are contraindicated for use in children.

Geriatric Patients

Generally no adjustment of dosage is required in the geriatric population with normal body functions. Dosage adjustment is necessary in patients with impaired renal function due to reduced clearance of ofloxacin. Because elderly patients are more likely to have decreased renal and/or liver function, dosage should be reduced accordingly, and it may be useful to monitor renal/hepatic function.

Renal Impairment Patients

Ofloxacin dosage should be reduced in patients with impairment of renal function (creatinine clearance <50 ml/min). In patients with creatinine clearance 20 to 50 ml/min, ofloxacin dosage should be reduced by half (100 to 200 mg daily); if creatinine clearance is < 20 ml/min, ofloxacin 100 mg should be given every 24 hours. The elimination of ornidazole is reported to be largely unaltered in patients with impaired renal functions.

Hepatic Impairment Patients

The excretion of both ofloxacin and ornidazole may be reduced in patients with severe hepatic dysfunction (e.g., liver cirrhosis). In such patients, ofloxacin dose should not exceed 400 mg daily. In view of the prolonged half-life and reduced clearance of ornidazole reported in patients with hepatic dysfunction, the interval between doses should be doubled in patients with severe hepatic

impairment. Thus, caution must be exercised while administering O-CEBRAN-OZ Tablets in patients with hepatic dysfunction.

4.7Effect on Ability to Drive and Use Machines

Adverse effects such as dizziness, lightheadedness, poor coordination, vertigo, and visual disturbances are possible after taking this medicine. These effects may impair the patient's ability to concentrate and react. Patients should know how they react to this medicine before they drive or operate machinery. If affected, they should not drive or operate machinery.

4.8Undesirable Effects

O-CEBRAN-OZ Tablets are generally well tolerated. Adverse effects are rare, mild, and transient in nature.

Ofloxacin

Clinical Trials Experience

The most common adverse events were nausea, insomnia, headache, dizziness, diarrhea, vomiting, rash, pruritus, external genital pruritus in women, vaginitis, and dysgeusia.

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 have been reported rarely with ofloxacin administration.

Additional events, occurring in clinical trials at a rate of less than 1%, regardless of relationship to drug, were:

Body as a Whole: Asthenia, chills, malaise, extremity pain, pain, epistaxis.

Cardiovascular System: Cardiac arrest, edema, hypertension, hypotension, palpitations, vasodilation.

Gastrointestinal System: Dyspepsia.

Genital/Reproductive System: Burning, irritation, pain and rash of the female genitalia; dysmenorrhea; menorrhagia; metrorrhagia; vaginal candidiasis.

Musculoskeletal System: Arthralgia, myalgia.

Nervous System: Seizures, anxiety, cognitive change, depression, dream abnormality, euphoria, hallucinations, paresthesia, syncope, vertigo, tremor, confusion.

Nutritional/Metabolic: Thirst, weight loss.

Respiratory System: Respiratory arrest, cough, rhinorrhea.

Skin/Hypersensitivity: Angioedema, diaphoresis, urticaria, vasculitis.

Special Senses: Decreased hearing acuity, tinnitus, photophobia.

Urinary System: Dysuria, urinary frequency, urinary retention.

Post-Marketing Experience

Stevens-Johnson Syndrome (SJS) / Toxic Epidermal Necrolysis (TEN) as an adverse drug reaction reported with the use of ofloxacin.

Additional adverse events, regardless of relationship to drug, reported from worldwide marketing experience with quinolones, including ofloxacin:
Cardiovascular System: Cerebral thrombosis, pulmonary edema, tachycardia, hypotension/shock, syncope, torsade de pointes.
Endocrine/Metabolic: Hyper-or hypoglycemia, especially in diabetic patients on insulin or oral hypoglycemic 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), GI hemorrhage; hiccough, painful oral mucosa, pyrosis.
Genital/Reproductive System: Vaginal candidiasis.
Hematopoietic: Anemia, including hemolytic and aplastic; hemorrhage, pancytopenia, agranulocytosis, leukopenia, reversible bone marrow depression, thrombocytopenia, thrombotic thrombocytopenic 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, ataxia, incoordination; exacerbation of myasthenia gravis and extrapyramidal disorders; dysphasia, lightheadedness.
Respiratory System: Dyspnea, bronchospasm, allergic pneumonitis, stridor.
Skin/Hypersensitivity: Anaphylactic reactions/shock; purpura, serum sickness, erythema multiforme, erythema nodosum, exfoliative dermatitis, hyperpigmentation, 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, hematuria, albuminuria, candiduria.

Abnormal Laboratory Tests

Prolongation of prothrombin time; elevation of serum triglycerides, serum cholesterol, serum potassium; abnormal liver function tests including gamma-glutamyl transpeptidase (GGTP), lactate dehydrogenase (LDH), and bilirubin.

Ornidazole

Digestive System: Metallic after-taste, dry mouth, coated tongue, nausea, loss of appetite, stomach pain, diarrhea, vomiting, altered liver function test results.
Nervous System: Headache, vertigo, tremor, muscle rigidity, movement coordination disorders, ataxia, convulsions, confused consciousness, signs of sensory or mixed peripheral neuropathy.
Allergic Reactions: Skin rash, itching, nettle rash, and angioneurotic edema (very rare).
Other: Moderate leucopenia, darkened urine color, cardiovascular disorders.

4.9Overdose

Ofloxacin

The most important signs to be expected following acute overdose are CNS symptoms such as confusion, dizziness, impairment of consciousness and convulsive seizures as well as gastrointestinal (GI) reactions such as nausea and mucosal erosions. In the case of overdose, steps to remove any unabsorbed ofloxacin e.g., gastric lavage, administration of adsorbents and sodium sulphate, if possible during the first 30 minutes, are recommended; antacids are recommended for protection of the gastric mucosa. Elimination of ofloxacin may be increased by forced diuresis. In the event of overdose, symptomatic treatment should be implemented. ECG monitoring should be undertaken, because of the possibility of QT interval prolongation.

Ornidazole

Somnolence, headache and gastrointestinal disturbances like nausea and vomiting may occur. Disturbances of the CNS such as dizziness, tremor, rigidity, poor coordination, seizures, tiredness, vertigo, temporary loss of consciousness and signs of sensory or mixed peripheral neuropathy have been observed in isolated cases in more severe form with ornidazole overdose. No specific antidote is known for ornidazole. The administration of diazepam is recommended if cramps occur.

5. Pharmacological Properties

5.1 Mechanism of Action

Ofloxacin

Ofloxacin is a fluoroquinolone class of antimicrobial agent. The mechanism of action of ofloxacin and other fluoroquinolone antimicrobials involves inhibition of bacterial topoisomerase IV and deoxyribonucleic acid (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.

Ornidazole

Ornidazole is a newer 5-nitroimidazole class of antibiotic with superior efficacy and longer duration of action. It has an antibacterial effect similar to that of metronidazole and other 5-nitroimidazoles. Ornidazole kills susceptible microorganisms by interfering with DNA functioning.

Ornidazole act selectively against microorganisms with enzyme systems capable of reducing the nitro group and catalyzing the interaction between ferredoxin proteins and nitro compounds. After the drug penetrates the microbial cell, the mechanism of its action is based on reducing the nitro group under the influence of the microorganism's nitroreductases and the activity of the reduced nitroimidazole. The reduction products create compounds with DNA causing it to degrade, and disrupt the DNA replication and transcription processes. Furthermore, the drug's metabolism products have cytotoxic properties and disrupt cellular respiration processes.

5.2Pharmacodynamic Properties

Ofloxacin

Ofloxacin is a broad-spectrum antimicrobial agent. Ofloxacin acts against wide range of gram-positive, gram-negative, and other atypical microorganisms.

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

Aerobic gram-positive bacteria

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

Aerobic gram-negative bacteria

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

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) of 2 μg/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 bacteria

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

Aerobic gram-negative bacteria

- *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 bacteria

- *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 has antiprotozoal and antibacterial actions. Ornidazole is effective against some anaerobic bacteria, such as *Gardnerella vaginalis, Bacteroides, Clostridium spp., Fusobacterium,* and anaerobic cocci.

Ornidazole has an antiprotozoal action against *Balantidium coli, Blastocytes hominis, Trichomonas vaginalis, Trichotomous foetus, Giardia intestinalis (Giardiasis lamblia)* and *Entamoeba histolytica*.

5.3Pharmacokinetic Properties

Ofloxacin

Absorption: Following oral administration, the bioavailability of ofloxacin (in the tablet formulation) is approximately 98%. Maximum serum concentrations are achieved 1 to 2 hours after an oral dose.

Distribution: The total clearance and volume of distribution are approximately similar after single or multiple doses. *In vitro*, approximately 32% of the drug in plasma is protein bound.

Metabolism and Excretion: Ofloxacin is mainly excreted by renal route. Between 65 to 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 to 8% of ofloxacin dose is excreted in the feces. Ofloxacin has biphasic elimination. Following multiple oral doses at steady-state administration, the half-lives are approximately 4 to 5 hours and 20 to 25 hours. Accumulation at steady-state can be estimated using a half-life of 9 hours.

Ornidazole

Absorption: Following oral administration, ornidazole is rapidly absorbed. Mean absorption is 90%. Peak plasma concentrations are reached within 3 hours.

Distribution: Plasma protein binding of ornidazole is about 13%. Ornidazole penetrates the cerebrospinal fluid, the body fluids and the tissues very effectively. Plasma concentrations are within the range of 6 to 36 mg/l (considered to be optimal for various indications).

Metabolism and Excretion: Ornidazole is metabolized in the liver and is excreted in the urine, mainly as conjugates and metabolites, and to a lesser extent in the faeces. Biliary excretion may be important in the elimination of ornidazole and its metabolites. The plasma elimination half-life of ornidazole is 12 to 14 hours. About 85% of a single dose is eliminated within the first 5 days, most of this being metabolized. Up to 4% of the dose is excreted as unaltered substance in the urine.

6. Nonclinical Properties

6.1 Animal Toxicology

Ofloxacin

Mutagenicity studies showed no evidence for mutagenicity of ofloxacin. Ofloxacin was not mutagenic in the Ames bacterial test, *in vitro* and *in vivo* cytogenetic assay, sister chromatid exchange (Chinese Hamster and Human Cell Lines), unscheduled DNA Repair (UDS) using human fibroblasts, dominant lethal assays, or mouse micronucleus assay. Ofloxacin was positive in the UDS test using rat hepatocytes and Mouse Lymphoma Assay.

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. 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.

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 fetal development, labor, 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 fetotoxic (i.e., decreased fetal 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.

Ornidazole

Acute oral LD50 value of ornidazole reported in mice was 1420 mg/kg. In sub-acute toxicity study, ornidazole was orally administered to dogs at the doses of 250 mg/kg for 3 to 14 weeks, showed neurotoxicity as early as week 3 of the study. This toxicity was reversible after termination of the drug therapy. Ornidazole was also administered to dogs by intravenous route for 4 weeks; only a slight sedative effect was observed, with ataxia and salivation lasting 15 to 30 minutes after high dose injection (150 mg/kg/day).

No teratogenic effect was observed with ornidazole in mice, rat, and rabbits when administered during pregnancy.

Reproduction studies were performed with ornidazole, a compound with trichomonacidal activity. Male rats were treated for 61 days prior to mating and female rats were treated for 2 weeks prior to mating and throughout gestation and lactation at doses of 0 (control), 25, 100, and 400 mg of ornidazole/kg/day. A decrease in the pregnancy rate was observed in high-dose rats without altered mating performance. Crossover matings between high-dose treated and control male and female rats showed that male but not female fertility was affected and that the effect on fertility was reversible within several days after the cessation of treatment. Testicular and epididymal weights were not altered in treated male rats. Histopathological examination revealed that spermatogenesis and the testes were normal and that the epididymides of treated male rats contained normal appearing sperm.

7. Description

O-CEBRAN-OZ Tablets are Orange Coloured, elongated, biconvex, one side scored & film coated tablets.

O-CEBRAN-OZ Tablets contain 200 mg of ofloxacin and 500 mg of ornidazole for oral administration in adults and adolescents.

Ofloxacin

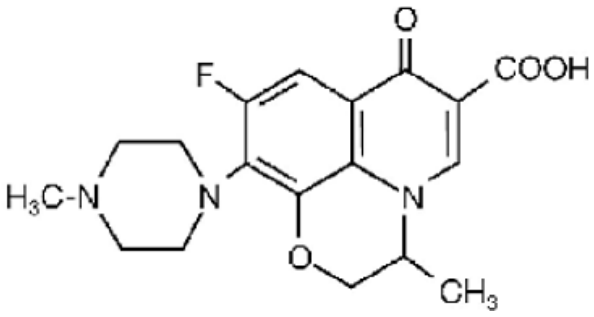
Ofloxacin is a synthetic broad-spectrum antimicrobial agent. Ofloxacin is an off-white to pale yellow crystalline powder.

Molecular Weight: 361.4 g/mol.

Molecular Formula: $C_{18}H_{20}FN_3O_4$.

Chemical Name: (±)-9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7oxo-7H-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid.

Structural Formula:



Ornidazole

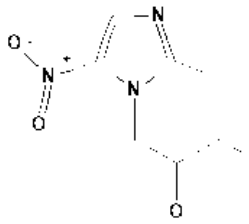
Ornidazole is a synthetic 5-nitroimidazole class of antimicrobial agent. Ornidazole is used for treatment of infections caused by both anaerobic bacteria and protozoa.

Molecular Weight: 219.62 g/mol.

Molecular Formula: C7H10ClN3O3.

Chemical Name: 1-chloro-3-(2-methyl-5-nitroimidazol-1-yl)propan-2-ol.

Structural Formula:



Inactive ingredients (excipients) of O-CEBRAN-OZ Tablet contain Microcrystalline Cellulose, Pregelatinised Starch, Hydroxy Propyl Cellulose, Talcum, Magnesium Stearate, Croscarmellose Sodium.

8. Pharmaceutical Particulars

8.1 Incompatibilities

None known.

8.2 Shelf-life

24 months.

8.3 Packaging Information

10 tablets per strip.

8.4 Storage and Handling Instructions

Store at a temperature not exceeding 30°C. Protected from moisture.

Keep out of reach of children.

9. Patient Counseling Information

Administration Instructions

- Patients should be counseled that antibacterial drugs should only be used to treat bacterial infections. Not to use this medicine to treat infections caused by viruses.
- 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 decrease the effectiveness of the treatment and increase the likelihood that bacteria will develop resistance to the antibiotic.
- Instruct patient to drink plenty of fluids while taking this medicine to prevent the formation of highly concentrated urine.
- In case of serious allergic reaction or signs of tendon damage/rupture, discontinue therapy and consult Doctor immediately.
- Dizziness is possible after taking this medicine. Instruct patients not to drive or operate machinery, or do other activities that require mental alertness or coordination until they know how this medicine affects them.
- Instruct patients to avoid sunlight exposure. Therapy should be discontinued if photosensitivity/phototoxicity (sunburn, blisters or swelling of skin, skin eruption) occurs.
- This medicine should not be used during pregnancy and lactation.
- This drug therapy may cause low blood sugar and mental health related side effects. If affected, patient should immediately discontinue therapy and consult Doctor.

10.Details of Manufacturer

M/s. Pure & Cure Healthcare Pvt. Ltd.
Plot No. 26A, 27-30, Sector-8A, I.I.E., SIDCUL, Haridwar – 249 403, Uttarakhand.

11.Details of Permission or License Number with Date

DCG (I) Approval Date: 20/01/2005.
Manufacturing License No.: 31/UA/2013. Date of Product Permission: 03/11/2014.

12. Date of Revision

January 2021.

Marketed by:
BLUE CROSS LABORATORIES PVT LTD.
A-12, M.I.D.C., NASHIK-422 010.
Regd. Off.: Peninsula Chambers, G. K. Marg, Mumbai-400 013.