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

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

Prescribing Information

1. Generic Name

Cefpodoxime & Ofloxacin Tablets

(Brand Name: CEDON-Plus 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:

Cefpodoxime Proxetil IP equivalent to Cefpodoxime ……..…..… 200 mg.

Ofloxacin IP …….. 200 mg.

Excipients …….. q.s.

Colours: Quinoline Yellow WS & Titanium Dioxide IP

3. Dosage Form and Strength

Dosage Form: Tablets.

Dosage Strength: Cefpodoxime 200 mg with Ofloxacin 200 mg per tablet.

4. Clinical Particulars

4.1 Therapeutic Indication

CEDON-Plus Tablets are indicated for the treatment of typhoid fever and respiratory tract infections in adults only. This combination therapy is useful when such infections are caused by susceptible species of bacteria.

4.2Posology and Method of Administration

For oral administration in adults only.

Usual Recommended Dose of CEDON-Plus Tablets: 1 tablet to be administered twice daily (i.e., every 12 hours).

Usual duration of therapy is 5 to 10 days. CEDON-Plus Tablets may be administered with or without food; however, administration with food results in increased absorption of cefpodoxime. The tablet should be swallowed whole with water.
Or, as prescribed by the physician.

4.3Contraindications

CEDON-Plus Tablets are contraindicated in the following:

- Patients with known hypersensitivity to cefpodoxime or to ofloxacin or to other cephalosporin/quinolone antibiotics or to any component of the formulation.
- Previous history of immediate and/or severe hypersensitivity reactions (anaphylaxis) to penicillin or other beta-lactam antibiotic.
- Patients with epilepsy.
- Patients with history of tendon disorders related to fluoroquinolone use.
- Children or growing adolescents.
- Pregnancy and lactation.

4.4Special Warnings and Precautions for Use

Cefpodoxime

Hypersensitivity: Before therapy with cefpodoxime proxetil is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to cefpodoxime, other cephalosporins, penicillins, or other drugs. If an allergic reaction to cefpodoxime proxetil occurs, discontinue the drug. Serious acute hypersensitivity reactions may require treatment with epinephrine and other emergency measures, including oxygen, intravenous fluids, intravenous antihistamine, and airway management, as clinically indicated.

***Clostridium difficile*-associated diarrhea:** *Clostridium difficile*-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including cefpodoxime proxetil, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*. *Clostridium 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 diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two 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.

A concerted effort to monitor for *C. difficile* in cefpodoxime-treated patients with diarrhea was undertaken because of an increased incidence of diarrhea associated with *C. difficile* in early trials in normal subjects. *Clostridium difficile* organisms or toxin was reported in 10% of the

cefpodoxime-treated adult patients with diarrhea; however, no specific diagnosis of pseudomembranous colitis was made in these patients. Cefpodoxime proxetil should always be prescribed with caution in patients with a history of gastrointestinal (GI) disease, particularly colitis.

Superinfection: As with other antibiotics, prolonged use of cefpodoxime proxetil may result in overgrowth of non-susceptible organisms. Repeated evaluation of the patient's condition is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Antibiotic resistance: Prescribing cefpodoxime in the absence of a proven or strongly suspected bacterial infection or as a prophylaxis therapy is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria. To reduce the development of drug-resistant bacteria and maintain the effectiveness of cefpodoxime and other antibacterial drugs, cefpodoxime should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

Neutropenia: As with all beta-lactam antibiotics, neutropenia and more rarely agranulocytosis may develop particularly during extended treatment. For cases of treatment lasting longer than 10 days, the blood count should be monitored and treatment discontinued if neutropenia is found.

Renal dysfunction: In patients with transient or persistent reduction in urinary output due to renal insufficiency, the total daily dose of cefpodoxime proxetil should be reduced because high and prolonged serum antibiotic concentrations can occur in such individuals following usual doses. Changes in renal function have been observed with cephalosporin antibiotics, particularly when given concurrently with potentially nephrotoxic drugs such as aminoglycosides and/or potent diuretics. In such cases, cefpodoxime proxetil should be used with caution and renal function should be monitored as and when required.

Ofloxacin

Caution - safety issues with fluoroquinolone antibiotics: The drug may cause low blood sugar and mental health related 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 are:

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

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: 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:** 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 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 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.

4.5Drug Interactions

Cefpodoxime

Antacids/H_2-antagonists: Studies have shown that the bioavailability is decreased by approximately 30% when cefpodoxime is administered with drugs which neutralize gastric pH or inhibit acid secretions. Therefore, antacids (such as aluminum hydroxide and sodium bicarbonate) and H_2 blockers (such as ranitidine), which can cause an increase in gastric pH, should be taken 2 to 3 hours after cefpodoxime administration.

Propantheline: Oral anti-cholinergics (e.g., propantheline) delay peak plasma levels (47% increase in T_{max}), but do not affect the extent of absorption (AUC).

Probenecid: As with other beta-lactam antibiotics, renal excretion of cefpodoxime was inhibited by probenecid and resulted in an approximately 31% increase in AUC and 20% increase in peak cefpodoxime plasma levels. Thus, co-administration of probenecid with cefpodoxime proxetil is not recommended.

Nephrotoxic drugs: Although nephrotoxicity has not been reported when cefpodoxime proxetil was given alone, close monitoring of renal function is advised when cefpodoxime is administered concomitantly with drugs having nephrotoxic potential.

Oral anticoagulants: Simultaneous administration of cefpodoxime with warfarin may augment its anti-coagulant effects. There have been many reports of increases in oral anti-coagulant activity in patients receiving antibacterial agents, including cephalosporins. The risk may vary with the underlying infection, age and general status of the patient so that the contribution of the cephalosporins to the increase in international normalised ratio (INR) is difficult to assess. It is recommended that the INR should be monitored frequently during and shortly after co-administration of cefpodoxime with an oral anti-coagulant agent.

Oral contraceptives: Cephalosporins reduces the contraceptive effect of estrogen derivatives. It is advised that patients to consider alternative supplementary (non-hormonal) contraceptive measures during treatment with cefpodoxime proxetil.

Drug/laboratory test interactions: Cephalosporins, including cefpodoxime proxetil, are known to occasionally induce a positive direct Coombs' test. A false positive reaction for glucose in the urine may occur with Benedict's or Fehling's solutions or with copper sulphate test tablets, but not with tests based on enzymatic glucose oxidase reactions.

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.

Ciclosporin: Elevated serum levels of ciclosporin have been reported with concomitant use of ciclosporin with some other quinolones. The potential for interaction between ofloxacin and ciclosporin 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., ciclosporin, 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.

4.6Use in Special Populations

Pregnant Women

Cefpodoxime: Pregnancy Category B; Ofloxacin: Pregnancy Category C. Cefpodoxime proxetil was neither teratogenic nor embryocidal when administered to rats during organogenesis at doses up to 100 mg/kg/day (2 times the human dose based on mg/m^2) or to rabbits at doses up to 30 mg/kg/day (1 to 2 times the human dose based on mg/m^2). There are, however, no adequate and well-controlled studies of cefpodoxime proxetil use in pregnant women.

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 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. Based on a limited amount of human data, the use of fluoroquinolones in the first trimester of pregnancy has not been associated with an increased risk of major malformations or other adverse effects on pregnancy outcomes. There are, however, no adequate and well-controlled studies in pregnant women. As ofloxacin use in animal studies has shown damage to the joint cartilage in immature animals, CEDON-Plus Tablets must not be used during pregnancy.

Lactating Women

Cefpodoxime is excreted in human milk. Ofloxacin is also 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 CEDON-Plus Tablets. Accordingly, a decision should be made whether to discontinue nursing or to discontinue the drug therapy, taking into account the importance of the drug to the mother.

Paediatric Patients

Cefpodoxime proxetil can be administered in infants above 2 months of age. However, ofloxacin and other fluoroquinolones have been reported to cause degenerative changes/ arthropathy in weight bearing joints of young animals (beagle dogs). Thus, CEDON-Plus Tablets are contraindicated for use in children and growing adolescents.

Geriatric Patients

Elderly patients with normal renal function may be given the same dose as recommended for adults. No overall differences in effectiveness or safety were observed between the elderly and younger patients. Clearance of both, cefpodoxime and ofloxacin is reduced in patients with renal impairment. As elderly patients are more likely to have renal impairment, dosage adjustment is necessary in such patients with compromised renal function.

Renal Impairment Patients

Elimination of cefpodoxime is reduced in patients with moderate to severe renal impairment (creatinine clearance < 50 ml/min). For patients with severe renal impairment (creatinine clearance < 30 ml/min), the dosing intervals should be increased to every 24 hours. In patients with creatinine clearance < 10 ml/min, cefpodoxime to be administered every 48 hours. In patients maintained on hemodialysis, the dosing frequency of cefpodoxime is 3 times/week or one single dose after each dialysis session.

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.

Thus, in patients with moderate to severe renal impairment, alteration of dosage regimen is necessary. Also, periodic assessment of renal function is advisable during long-tern therapy.

Hepatic Impairment Patients (Liver Cirrhosis)

Absorption of cefpodoxime was found to be decreased while excretion becomes unchanged in patients with liver cirrhosis. The mean cefpodoxime t½ and renal clearance in cirrhotic patients were similar to those of healthy subjects; ascites did not appear to affect values in cirrhotic subjects. However, excretion of ofloxacin may be reduced in patients with severe hepatic dysfunction. In such cases, it is recommended that ofloxacin dose should not exceed 400 mg daily. Thus, in patient with liver cirrhosis or severe hepatic impairment, CEDON-Plus Tablets should be used with caution and if necessary, dosage regimen to be altered.

4.7Effect on Ability to Drive and Use Machines

Dizziness has been reported during treatment with cefpodoxime. Ofloxacin may also cause neurological adverse effects such as dizziness and lightheadedness. Patients should know how they react to this drug therapy before they drive or operate machinery. If affected, patient should not engage in mental alertness related activities such as driving a vehicle or operating machineries.

4.8Undesirable Effects

Cefpodoxime

1) Clinical Trials Experience

Cefpodoxime proxetil is generally well tolerated. Adverse events possibly or probably related to cefpodoxime proxetil in multiple-dose clinical trials were:

A. Incidence Greater Than 1%

- Diarrhea (7.0%) - Diarrhea or loose stools were dose-related decreasing from 10.4% of patients receiving 800 mg per day to 5.7% for those receiving 200 mg per day.
- Nausea (3.3%).
- Vaginal fungal infections (1.0%).
- Vulvovaginal infections (1.3%).
- Abdominal pain (1.2%).
- Headache (1.0%).

B. Incidence Less Than 1%

Body as a Whole: Fungal infections, abdominal distention, malaise, fatigue, asthenia, fever, chest pain, back pain, chills, generalized pain, abnormal microbiological tests, moniliasis, abscess, allergic reaction, facial edema, bacterial infections, parasitic infections, localized edema, localized pain.

Cardiovascular: Congestive heart failure, migraine, palpitations, vasodilation, hematoma, hypertension, hypotension.

Digestive: Vomiting, dyspepsia, dry mouth, flatulence, decreased appetite, constipation, oral moniliasis, anorexia, eructation, gastritis, mouth ulcers, gastrointestinal disorders, rectal disorders, tongue disorders, tooth disorders, increased thirst, oral lesions, tenesmus, dry throat, toothache.
Hemic and Lymphatic: Anemia.
Metabolic and Nutritional: Dehydration, gout, peripheral edema, weight gain.
Musculo-Skeletal: Myalgia.
Nervous: Dizziness, insomnia, somnolence, anxiety, shakiness, nervousness, cerebral infarction, change in dreams, impaired concentration, confusion, nightmares, paresthesia, vertigo.
Respiratory: Asthma, cough, epistaxis, rhinitis, wheezing, bronchitis, dyspnea, pleural effusion, pneumonia, sinusitis.
Skin: Urticaria, rash, pruritus, diaphoresis, maculopapular rash, fungal dermatitis, desquamation, dry skin, hair loss, vesiculobullous rash, sunburn.
Special Senses: Taste alterations, eye irritation, taste loss, tinnitus.
Urogenital: Hematuria, urinary tract infections, metrorrhagia, dysuria, urinary frequency, nocturia, penile infection, proteinuria, vaginal pain.

2) Post-Marketing Experience

The following serious adverse experiences have been reported: Allergic reactions including Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme and serum sickness-like reactions, pseudomembranous colitis, bloody diarrhea with abdominal pain, ulcerative colitis, rectorrhagia with hypotension, anaphylactic shock, acute liver injury, in utero exposure with miscarriage, purpuric nephritis, pulmonary infiltrate with eosinophilia, and eyelid dermatitis. One death was attributed to pseudomembranous colitis and disseminated intravascular coagulation.

3) Adverse Reactions of Cephalosporin-Cass Antibiotics

The following adverse reactions and altered laboratory tests have been reported for cephalosporin class antibiotics: Renal dysfunction, toxic nephropathy, hepatic dysfunction including cholestasis, aplastic anemia, hemolytic anemia, serum sickness-like reaction, hemorrhage, agranulocytosis, pancytopenia and fixed drug eruption (FDE). Several cephalosporins have been implicated in triggering seizures, particularly in patients with renal impairment when the dosage was not reduced. If seizures associated with drug therapy occur, the drug should be discontinued. Anticonvulsant therapy can be given if clinically indicated.

4) Laboratory Abnormalities

Most of the altered laboratory values are transient and not clinically significant. Significant laboratory changes that have been reported in adult and paediatric patients in clinical trials of cefpodoxime proxetil, without regard to drug relationship were:

Hepatic: Transient increases in alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), alkaline phosphatase, bilirubin, and lactate dehydrogenase (LDH).
Hematologic: Eosinophilia, leukocytosis, lymphocytosis, granulocytosis, basophilia, monocytosis, thrombocytosis, decreased hemoglobin, decreased hematocrit, leukopenia, neutropenia, lymphocytopenia, thrombocytopenia, thrombocythemia, positive Coombs' test, prolonged prothrombin time (PT), and partial thromboplastin time (PTT).
Serum Chemistry: Hyperglycemia, hypoglycemia, hypoalbuminemia, hypoproteinemia, hyperkalemia, and hyponatremia.
Renal: Increase in blood urea nitrogen (BUN) and creatinine.

Ofloxacin

1) 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.

2) 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, torsades 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/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, 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.

4.9Overdose

Cefpodoxime

Symptoms: The toxic symptoms following an overdose of beta-lactam antibiotics may include nausea, vomiting, epigastric distress, and diarrhea. In cases of overdose, particularly in patients with renal insufficiency, encephalopathy may occur. The encephalopathy is usually reversible once cefpodoxime plasma levels have fall down.

Treatment: In the event of overdose with cefpodoxime, supportive and symptomatic therapy is indicated. If serious toxic reaction from overdose occurs, hemodialysis or peritoneal dialysis may aid in the removal of cefpodoxime from the body, particularly if renal function is compromised.

Ofloxacin

Symptoms: 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 reactions such as nausea and mucosal erosions.

Treatment: In the event of ofloxacin overdose, supportive and symptomatic treatment should be implemented. It is recommended to remove any unabsorbed ofloxacin by gastric lavage, administration of adsorbents and sodium sulphate, if possible, during the first 30 minutes. Also, antacids are recommended for protection of the gastric mucosa. Elimination of ofloxacin may be increased by forced diuresis. ECG monitoring should be undertaken, because of the possibility of QT interval prolongation.

5. Pharmacological Properties

5.1 Mechanism of Action

Cefpodoxime Proxetil

Cefpodoxime proxetil is a prodrug; its active metabolite is cefpodoxime. Cefpodoxime is 3rd generation oral cephalosporin class of beta-lactam antibiotic.

Cefpodoxime inhibits bacterial cell wall synthesis following attachment to penicillin binding proteins (PBPs). This results in the interruption of cell wall (peptidoglycan) biosynthesis, which leads to bacterial cell lysis and death (bactericidal effect). Cefpodoxime has activity in the presence of some beta-lactamases, both penicillinases and cephalosporinases, of gram-negative and gram-positive bacteria.

Ofloxacin

Ofloxacin is a quinolone antimicrobial agent. The mechanism of action of ofloxacin and other fluoroquinolone antimicrobials involves inhibition of bacterial topoisomerase IV and DNA gyrase (both of which are type II topoisomerases), enzymes required for DNA replication, transcription, repair and recombination. Ofloxacin has *in vitro* activity against a wide range of gram-negative and gram-positive microorganisms. Ofloxacin is often bactericidal at concentrations equal to or slightly greater than inhibitory concentrations.

5.2Pharmacodynamic Properties

Cefpodoxime Proxetil

Cefpodoxime produces antibacterial effect. Cefpodoxime has been shown to be active against most isolates of the following bacteria, both *in vitro* and in clinical infections:

Gram-Positive Bacteria

- *Staphylococcus aureus* (methicillin-susceptible strains).

- *Staphylococcus saprophyticus.*
- *Streptococcus pneumoniae* (excluding penicillin-resistant isolates).
- *Streptococcus pyogenes.*

Gram-Negative Bacteria

- *Escherichia coli.*
- *Klebsiella pneumonia.*
- *Proteus mirabilis.*
- *Haemophilus influenzae* (including beta-lactamase producing isolates).
- *Moraxella catarrhalis.*
- *Neisseria gonorrhoeae* (including penicillinase-producing isolates).

The following *in vitro* data are available, but their clinical significance is unknown. At least 90% of the following microorganisms exhibit an *in vitro* minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for cefpodoxime. However, the efficacy of cefpodoxime in treating clinical infections due to these microorganisms has not been established in adequate and well-controlled clinical trials.

Gram-Positive Bacteria

- *Streptococcus agalactiae.*
- Streptococcus species (Groups C, F, G).

Gram-Negative Bacteria

- *Citrobacter diversus.*
- *Klebsiella oxytoca.*
- *Proteus vulgaris.*
- *Providencia rettgeri.*
- *Haemophilus parainfluenzae.*

Anaerobic Gram-Positive Bacteria

- *Peptostreptococcus magnus.*

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 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 influenza.*
- *Klebsiella pneumonia.*
- *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 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 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.

5.3Pharmacokinetic Properties

Cefpodoxime

Over the recommended dosing range (100 to 400 mg), the rate and extent of cefpodoxime absorption is dose-dependent. In patients with normal renal function, neither accumulation nor significant changes in other pharmacokinetic parameters were noted following multiple oral dosage of up to 400 mg every 12 hours.

Absorption: Cefpodoxime proxetil is a prodrug that is absorbed from the gastrointestinal tract and de-esterified to its active metabolite, cefpodoxime. Following oral administration of 100 mg of cefpodoxime proxetil to fasting subjects, approximately 50% of the administered cefpodoxime dose was absorbed systemically. The extent of absorption (mean AUC) and the mean peak plasma concentration increased when cefpodoxime proxetil were administered with food. Over the recommended dosing range, the T_{max} was approximately 2 to 3 hours. Mean C_{max} was 1.4 mcg/ml for the 100 mg dose, 2.3 mcg/ml for the 200 mg dose, and 3.9 mcg/ml for the 400 mg dose.

Distribution: The volume of distribution of cefpodoxime is 32.3 liters. Plasma protein binding of cefpodoxime ranges from 21 to 29%. Concentrations of cefpodoxime in excess of the minimum inhibitory concentration (MIC) for common pathogens can be achieved in lung parenchyma, bronchial mucosa, pleural fluid, tonsils, interstitial fluid and prostate tissue.

Metabolism: There is minimal metabolism of cefpodoxime *in vivo*.

Excretion: Cefpodoxime is primarily excreted by renal route; 80% is excreted unchanged in the urine, with an elimination half-life of approximately 2.4 hours.

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. Absorption of ofloxacin after single or multiple doses of 200 to 400 mg is predictable, and the amount of drug absorbed increases proportionately with the 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: Elimination is mainly by renal excretion. 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.

6. Nonclinical Properties

6.1 Animal Toxicology

Cefpodoxime Proxetil

Acute toxicity: The median lethal dose in mice and rats was above 8 g/kg and 4 g/kg bodyweight, respectively. In Fisher rats doses of 1 g/kg body weight and higher influenced stool consistency and weight gain. Single doses of 800 mg/kg body weight were non-toxic in dogs.

Repeat-dose toxicity: Chronic toxicity studies were carried out over 12 months in rats and 6 months in dogs. Maximum daily doses (1000 mg/kg body weight orally in rats and 400 mg/kg orally in dogs) were considerably higher than recommended therapeutic doses (3-8 mg/kg body weight). No mortality was observed in rats receiving 250, 500 or 1000 mg/kg for 12 months. Only at 1000 mg/kg, effects on the GI-tract, softened stools and dilatation of the caecum were observed. Intestinal side effects, which were more pronounced in Fisher rats, are due to the change in intestinal flora caused by the pronounced antibacterial effect of cefpodoxime. Daily administration of 0, 25, 100, and 400 mg/kg body weight to dogs did not reveal mortality. Unchanged cefpodoxime was detected in faeces.

Carcinogenesis: Long-term animal carcinogenesis studies of cefpodoxime proxetil have not been performed.

Mutagenesis: Mutagenesis studies of cefpodoxime, including the Ames test both with and without metabolic activation, the chromosome aberration test, the unscheduled DNA synthesis assay, mitotic recombination and gene conversion, the forward gene mutation assay and the in vivo micronucleus test, were all negative.

Impairment of fertility: No untoward effects on fertility or reproduction were noted when 100 mg/kg/day or less (2 times the human dose based on mg/m^2) was administered orally to rats.

Teratogenicity: Cefpodoxime proxetil was neither teratogenic nor embryocidal when administered to rats during organogenesis at doses up to 100 mg/kg/day (2 times the human dose based on mg/m^2) or to rabbits at doses up to 30 mg/kg/day (1-2 times the human dose based on mg/m^2).

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.

7. Description

CEDON-Plus Tablets are are yellow coloured, elongated, biconvex, one side scored & film coated tablets.

CEDON-Plus Tablets contain 200 mg of cefpodoxime and 200 mg of ofloxacin for oral administration in adults.

Cefpodoxime Proxetil

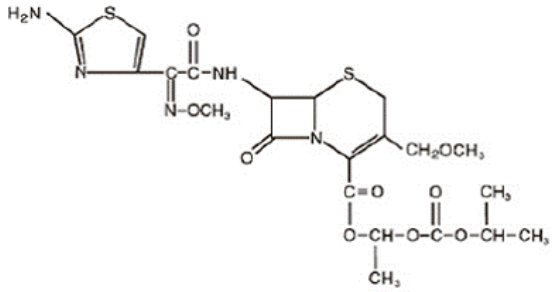
Cefpodoxime proxetil is a prodrug; its active metabolite is cefpodoxime. Cefpodoxime proxetil is an orally administered, extended spectrum, semi-synthetic, 3rd generation cephalosporin class of beta-lactam antibiotic.

Cefpodoxime proxetil appears as almost white to pale yellow coloured powder.

Molecular Weight: 557.6 g/mol.

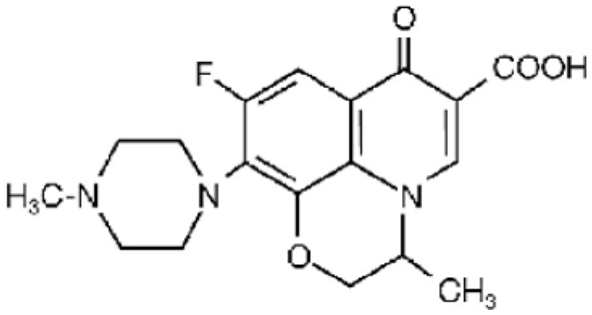
Molecular Formula: C21H27N5O9S2.

Chemical Name: (RS)-1(isopropoxycarbonyloxy) ethyl (+)-(6R,7R)-7-[2-(2-amino-4-thiazolyl)-2-{(Z)methoxyimino}acetamido]-3-methoxymethyl-8-oxo-5-thia-1-azabicyclo [4.2.0]oct-2-ene-2-carboxylate.
Structural Formula:



Ofloxacin

Ofloxacin is a synthetic broad-spectrum antimicrobial agent. Ofloxacin is off-white to pale yellow crystalline powder.
Molecular Weight: 361.4 g/mol.
Molecular Formula: C18H20FN3O4.
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:



Inactive ingredients (excipients) of CEDON-Plus Tablet contain Microcrystalline Cellulose, Lactose, Croscarmellose Sodium, Sodium Lauryl Sulphate, Magnesium Stearate, Sodium Starch Glycolate, Talcum, Colloidal Silicon Dioxide, H.P.M.C E15, PEG 6000, Titanium Dioxide, Colour Quinoline Yellow Lake, Isoproyl Alcohol & Methylene Chloride.

8. Pharmaceutical Particulars

8.1 Incompatibilities

None known.

8.2Shelf-life

18 months

8.3Packaging Information

10 tablets per strip.

8.4Storage and Handling Instructions

Store protected from light & moisture, at a temperature not exceeding 30°C.
Keep out of reach of children.

9. Patient Counseling Information

Administration Instructions to Patients

- 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 (such as common cold).
- 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.
- Advise patients that diarrhea is a common problem caused by antibacterial drugs which usually ends when the antibacterial drug is discontinued. Sometimes after starting treatment with antibacterial drugs, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibacterial drug. If this occurs, patients should contact their physician as soon as possible.
- 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 your Doctor immediately.
- Dizziness and/or lightheadedness are 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.
- Advise patients to strictly avoid this medicine 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 their Doctor.

10. Details of Manufacturer

Malik Lifesciences Pvt. Ltd.
(A subsidiary of Akums Drugs & Pharmaceutical)
Plot No. – 16, Vardhman Industrial Estate, N.H. 58,
Haridwar – 247 667, Uttarakhand.

11. Details of Permission or License Number with Date

Mfg. Lic No. : 48/UA/SC/P- 2013. Date of FDA product permission: 03/11/2014

12. Date of Revision

September 2022.