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

Cefixime & Ofloxacin Tablets

(**Brand Name: EXTACEF®-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:

Cefixime IP as Trihydrate equivalent to Anhydrous Cefixime …… 200 mg.

Ofloxacin IP ……. 200 mg.

Excipients …….. q.s.

Colours: Tartrazine

3. Dosage Form and Strength

Dosage Form: Tablets.

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

4. Clinical Particulars

4.1 Therapeutic Indication

EXTACEF-PLUS Tablets are indicated for the treatment of typhoid fever and urinary tract infections in adults.

4.2 Posology and Method of Administration

For oral administration in adults.

Adults: One tablet of EXTACEF-PLUS to be administered twice daily.

EXTACEF-PLUS Tablets may be taken regardless of food. The tablet should be swallowed whole with water and not to be cut, crushed or chewed.

Duration of therapy in typhoid is 7 to 14 days.

Or, as prescribed by the physician.

4.3 Contraindications

EXTACEF-PLUS Tablets are contraindicated in the following:

- Patients with known hypersensitivity to cefixime/cephalosporin antibiotics or to ofloxacin/quinolone group of antimicrobial agents or to any component of the formulation.
- Patients with epilepsy.
- Patients with history of tendon disorders (tendinitis) related to use of fluoroquinolones.
- In patients with latent or actual defects in glucose-6-phosphate dehydrogenese (G6PD) activity.
- Children or growing adolescents.
- Pregnancy and lactation.

4.4 Special Warnings and Precautions for Use

Cefixime

Hypersensitivity to penicillins: As with other cephalosporins, cefixime should be given with caution to patients with a history of hypersensitivity to penicillin, as there is some evidence of partial cross-allergenicity between the penicillins and cephalosporins. Patients have had severe reactions (including anaphylaxis) to both classes of drugs. If an allergic effect occurs with cefixime, the drug should be discontinued and the patient treated with appropriate agents if necessary.

Severe cutaneous adverse reactions: Severe cutaneous adverse reactions such as toxic epidermal necrolysis, Stevens-Johnson syndrome and drug rash with eosinophilia and systemic symptoms (DRESS) have been reported in some patients on cefixime. When severe cutaneous adverse reactions occur, cefixime should be discontinued and appropriate therapy and/or measures should be taken. Cefixime should be given with caution to patients who have shown hypersensitivity to other drugs.

Hemolytic anemia: Drug-induced hemolytic anemia, including severe cases with a fatal outcome, has been described for cephalosporins (as a class). The recurrence of hemolytic anemia after re-administration of cephalosporins in a patient with a history of cephalosporin (including cefixime)-associated hemolytic anemia has also been reported.

Acute renal failure: As with other cephalosporins, cefixime may cause acute renal failure including tubulointerstitial nephritis as an underlying pathological condition. When acute renal failure occurs, cefixime should be discontinued and appropriate therapy and/or measures should be taken.

Antibiotic-associated diarrhoea: Treatment with broad spectrum antibiotics alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of antibiotic-associated diarrhoea. Pseudomembranous colitis is associated with the use of broad-spectrum antibiotics (including macrolides, semi-synthetic penicillins, lincosamides and cephalosporins); it is therefore important to consider its diagnosis in patients who develop diarrhoea in association with the use of antibiotics.

Symptoms of pseudomembranous colitis may occur during or after antibiotic treatment. Management of pseudomembranous colitis should include sigmoidoscopy, appropriate bacteriologic studies, fluids, electrolytes and protein supplementation. If the colitis does not improve after the drug has been discontinued, or if the symptoms are severe, oral vancomycin is the drug of choice for antibiotic-associated pseudomembranous colitis produced by *C. difficile*. Other causes of colitis should be excluded.

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 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:** 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.

4.5 Drug Interactions

Cefixime

Anticoagulants: As with other cephalosporins, increase in prothrombin time has been noted in a few patients. Care should therefore be taken in patients receiving anticoagulation therapy. Cefixime should be administered with caution to patients receiving coumarin-type anticoagulants, e.g., warfarin potassium. Since cefixime may enhance effects of the anticoagulants, prolonged prothrombin time with or without bleeding may occur.

Other forms of interaction: 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.

A false positive direct Coombs test has been reported during treatment with cephalosporin antibiotics, therefore it should be recognized that a positive Coombs test may be due to the drug.

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 aluminium, 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., 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.

4.6 Use in Special Populations

Pregnant Women

Cefixime: Pregnancy Category B; Ofloxacin: Pregnancy Category C. Reproduction studies have been performed in mice and rats at doses up to 400 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to cefixime. In rabbits, with cefixime doses up to 4 times the human dose, there was no evidence of a teratogenic effect.

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. 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, EXTACEF-PLUS Tablets must not be used during pregnancy.

Lactating Women
It is not known whether cefixime is excreted in human milk. 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 EXTACEF-PLUS Tablets.

Paediatric Patients
Cefixime can be administered in children above 6 months of age. Ofloxacin and other fluoroquinolones have been reported to cause degenerative changes/arthropathy in weight bearing joints of young animals (beagle dogs). Thus, EXTACEF-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. Dosage adjustment is necessary only in patients with impaired renal function due to reduced clearance of cefixime and ofloxacin.

Renal Impairment Patients
In patients whose creatinine clearance is less than 20 ml/min or patients on peritoneal dialysis or haemodialysis, it is recommended that cefixime dose of 200 mg once daily should not be exceeded. 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, it is recommended to adjust the dosage according to degree of renal impairment and monitor the renal function periodically.

Hepatic Impairment Patients
The excretion of ofloxacin may be reduced in patients with severe hepatic dysfunction (e.g., liver cirrhosis). In such cases, it is recommended that ofloxacin dose should not exceed 400 mg daily, because of possible reduction of excretion.

4.7 Effect on Ability to Drive and Use Machines
Cefixime may cause side effect such as encephalopathy (which may include convulsion, confusion, impairment of consciousness, movement disorders). Further, ofloxacin may cause neurological adverse effects (e.g., dizziness, lightheadedness). If any of these side effects reported, the patient should not operate machines or drive a vehicle.

4.8 Undesirable Effects

Cefixime

The most commonly reported adverse reactions are gastrointestinal events such as diarrhea, loose or frequent stools, abdominal pain, nausea, dyspepsia, and flatulence.

Additional adverse reactions reported include:
Central Nervous System: Headaches, dizziness, seizures.
Gastrointestinal: Pseudomembranous colitis
Hypersensitivity Reactions: Anaphylactic/anaphylactoid reactions (including shock and fatalities), skin rashes, urticaria, drug fever, pruritus, angioedema, and facial edema. Erythema multiforme, Stevens-Johnson syndrome (SJS), Acute Generalized Exanthematous Pustulosis (AGEP) and serum sickness-like reactions.
Hepatic: Transient elevations in SGPT, SGOT, alkaline phosphatase, hepatitis, jaundice.Renal: Transient elevations in BUN or creatinine, acute renal failure.
Hematologic System: Transient thrombocytopenia, leukopenia, neutropenia, prolongation in prothrombin time, elevated LDH, pancytopenia, agranulocytosis, and eosinophilia.
Other Adverse Reactions: Genital pruritus, vaginitis, candidiasis, toxic epidermal necrolysis.
Abnormal Laboratory Tests: Hyperbilirubinemia.
Adverse Reactions Reported for Cephalosporin-Class Drugs: Allergic reactions, superinfection, renal dysfunction, toxic nephropathy, hepatic dysfunction including cholestasis, aplastic anemia, hemolytic anemia, hemorrhage, colitis 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.

Ofloxacin

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

Additional adverse reactions reported include:
Body as a Whole: Asthenia, chills, malaise, extremity pain, pain, epistaxis, fatigue, trunk pain
Cardiovascular System: Cardiac arrest, edema, hypertension, hypotension, palpitations, vasodilation, chest pain, cerebral thrombosis, pulmonary edema, tachycardia, hypotension/shock, syncope, torsades de pointes.
Gastrointestinal System: Dyspepsia, abdominal pain and cramps, flatulence, gastrointestinal distress, constipation, hepatic necrosis, jaundice, hepatitis; intestinal perforation; hepatic failure, pseudomembranous colitis, GI hemorrhage; hiccough, painful oral mucosa, pyrosis.
Genital/Reproductive System: Burning, irritation, pain and rash of the female genitalia; dysmenorrhea; menorrhagia; metrorrhagia; vaginal candidiasis, vaginal discharge
Musculoskeletal System: Arthralgia, myalgia, tendinitis/rupture; weakness, rhabdomyolysis.

Hematopoietic: Anemia, including hemolytic and aplastic; hemorrhage, pancytopenia, agranulocytosis, leukopenia, reversible bone marrow depression, thrombocytopenia, thrombotic thrombocytopenic purpura, petechiae, ecchymosis/bruising.
Nervous System: Seizures, anxiety, cognitive change, depression, dream abnormality, euphoria, hallucinations, paresthesia, syncope, vertigo, tremor, confusion, nervousness, sleep disorders, somnolence, 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.
Nutritional/Metabolic: Thirst, weight loss, decreased appetite, hyper-or hypoglycemia, especially in diabetic patients on insulin or oral hypoglycemic agents.
Respiratory System: Respiratory arrest, cough, rhinorrhea, pharyngitis, dyspnea, bronchospasm, allergic pneumonitis, stridor.
Skin/Hypersensitivity: Angioedema, diaphoresis, urticaria, vasculitis, fever, erythema multiforme/Stevens-Johnson Syndrome (SJS) / Toxic Epidermal Necrolysis (TEN), anaphylactic reactions/shock; purpura, serum sickness, erythema nodosum, exfoliative dermatitis, hyperpigmentation, conjunctivitis, photosensitivity/phototoxicity reaction, vesiculobullous eruption.
Special Senses: Decreased hearing acuity, tinnitus, photophobia, visual disturbances, diplopia, nystagmus, disturbances of taste, smell, hearing and equilibrium, usually reversible following discontinuation.
Urinary System: Dysuria, urinary frequency, urinary retention, anuria, polyuria, renal calculi, renal failure, interstitial nephritis, hematuria, albuminuria, candiduria.z
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.

4.9 Overdose

Cefixime

There is no experience regarding overdose with cefixime. Adverse reactions seen at dose levels up to 2 g cefixime in normal subjects did not differ from the profile seen in patients treated at the recommended doses. Cefixime is not removed from the circulation in significant quantities by dialysis. No specific antidote exists. General supportive measures are recommended.

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 reactions such as nausea and mucosal erosions. In the case of overdose, steps to remove any unabsorbed ofloxacin e.g., gastric lavage, administration of adsorbants 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.

5. Pharmacological Properties

5.1 Mechanism of Action

Cefixime

Cefixime is an oral third generation cephalosporin which has marked *in vitro* bactericidal activity against a wide variety of Gram-positive and Gram-negative organisms.

Cefixime inhibits bacterial cell wall synthesis during cell multiplication and produces bactericidal 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. 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.

5.2 Pharmacodynamic Properties

Cefixime

Cefixime has been shown to be active against most isolates of the following bacteria both *in vitro* and in clinical infections:

Gram-positive bacteria

- *Streptococcus pneumoniae*
- *Streptococcus pyogenes*

Gram-negative bacteria

- *Haemophilus influenzae*
- *Moraxella catarrhalis*
- *Escherichia coli*
- *Proteus mirabilis*
- *Neisseria gonorrhoeae*

The following *in vitro* data are available, but their clinical significance is unknown. Cefixime exhibits *in vitro* MICs of 1 mcg/ml or less against most (≥ 90%) isolates of the following bacteria; however, the safety and effectiveness of cefixime in treating clinical infections due to these bacteria have not been established in adequate and well-controlled clinical trials.

Gram-positive bacteria

- *Streptococcus agalactiae*

Gram-negative bacteria

- *Haemophilus parainfluenzae*
- *Proteus vulgaris*
- *Klebsiella pneumoniae*

- *Klebsiella oxytoca*
- *Pasteurella multocida*
- *Providencia species*
- *Salmonella species*
- *Shigella species*
- *Citrobacter amalonaticus*
- *Citrobacter diversus*
- *Serratia marcescens*

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 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.

5.3 Pharmacokinetic Properties

Cefixime

Absorption and Distribution: The absolute oral bioavailability of cefixime is in the range of 22 to 54%. Absorption is not significantly modified by the presence of food. Cefixime may therefore be given without regard to meals. Typically, the peak serum levels following the recommended adult or pediatric doses are between 1.5 and 3 mcg/ml. Little or no accumulation of cefixime occurs following multiple dosing. Serum protein binding is concentration-independent with a bound fraction of approximately 65%. Cefixime is almost exclusively bound to the albumin fraction. Protein binding of cefixime is only concentration-dependent in human serum at very high concentrations which are not seen following clinical dosing.

Metabolism and Excretion: There is no evidence of metabolism of cefixime *in vivo*. Approximately 50% of the absorbed dose is excreted unchanged in the urine in 24 hours. In animal studies, it was noted that cefixime is also excreted in the bile in excess of 10% of the administered dose. The serum half-life of cefixime in healthy subjects is independent of dosage form and averages 3 to 4 hours, but may range up to 9 hours in some volunteers.

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

Cefixime

Lifetime studies in animals to evaluate carcinogenic potential have not been conducted. Cefixime did not cause point mutations in bacteria or mammalian cells, DNA damage, or chromosome damage in vitro and did not exhibit clastogenic potential in vivo in the mouse micronucleus test. In rats, fertility and reproductive performance were not affected by cefixime at doses up to 25 times the adult therapeutic dose.

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.

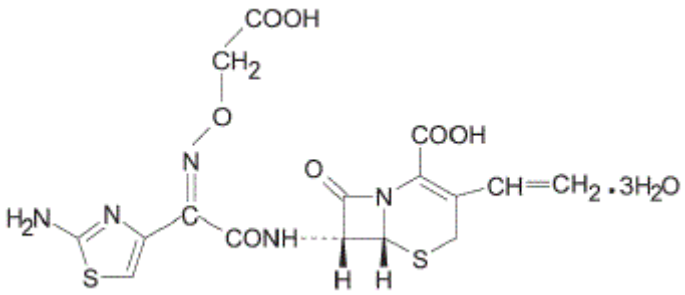
7. Description

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

EXTACEF-PLUS Tablets contain 200 mg of cefixime and 200 mg of ofloxacin for oral administration in adults.

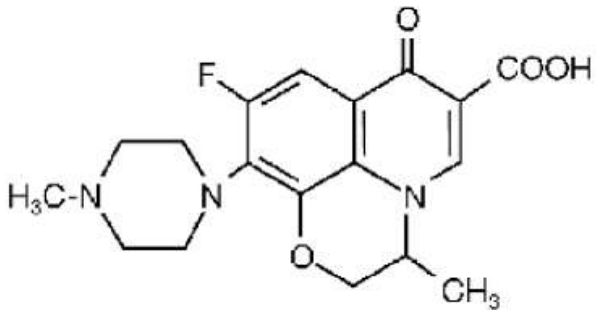
Cefixime

Cefixime is a broad-spectrum, third-generation cephalosporin class of beta-lactam antibiotic.
Molecular Weight: 507.5 g/mol.
Molecular Formula: $C_{16}H_{21}N_5O_{10}S_2$.
Chemical Name: (6R,7R)-7-[[(2Z)-2-(2-amino-1,3-thiazol-4-yl)-2-(carboxymethoxyimino)acetyl]amino]-3-ethenyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid; trihydrate.
Structural Formula:



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:



Inactive ingredients (excipients) of EXTACEF-PLUS Tablet contain Filleraa – A, Magnesium Stearate, Talcum, Colloidal Silicon Dioxide, Sodium Starch Glycolate, H.P.M.C E15, PEG 6000, Titanium Dioxide, Colour Tartrazine Lake, Isoproyl Alcohol & Methylene Chloride.

8. Pharmaceutical Particulars

8.1 Incompatibilities

None known.

8.2 Shelf-life

24 months

8.3 Packaging Information

Strip of 10 tablets.

8.4 Storage and Handling Instructions

Store protected from light and moisture, at a temperature not exceeding 30°C.
Keep out of reach of the 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.
- 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 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.
- 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 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 product permission: 03/11/2014

12. Date of Revision

January 2024.

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.