PRESCRIBING INFORMATION : For the use of a Registered Medical Practitioner or Hospital or Laboratory only.

CEFTAS 0

Cefixime & Ofloxacin Tablets

COMPOSITION:
Each film coated tablet contains:
Cefixime Trihydrate IP
Equivalent to Anhydrous Cefixime …….. 200mg
Ofloxacin IP …….. 200mg
Excipients…….. q.s.

INDICATION:
Multi-Drug Resistant Typhoid Fever, Uncomplicated Urinary Tract Infections, Uncomplicated Gonorrhea, Otitis Media, Pharyngitis, Tonsillitis, Acute Bronchitis, Acute Excerebations Of Chronic Bronchitis

DOSAGE AND ADMINISTRATION:
Each tablet contains cefixime 200 mg and ofloxacin 200mg and is recommended twice daily.

CONTRAINDICATIONS:
- **Cefixime**

Cefixime is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.
- **Ofloxacin**

Ofloxacin tablets are contraindicated in persons with a history of hypersensitivity associated with the use of Ofloxacin or any member of the quinolone group of antimicrobial agents.

WARNINGS AND PRECAUTIONS:
- **Cefixime**

1) Before therapy with cefixime is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to cephalosporins, penicillins, or other drugs. If this product is to be given to penicillin-sensitive patients, caution should be exercised because cross hypersensitivity among beta-lactam antibiotics has been clearly documented and may occur in up to 10% of patients with a history of penicillin allergy. If an allergic reaction to cefixime occurs, discontinue the drug. Serious acute hypersensitivity reactions may require treatment with epinephrine and other emergency measures, including oxygen, intravenous fluids, intravenous antihistamines, corticosteroids, pressor amines and airway management, as clinically indicated.
2) Anaphylactic/anaphylactoid reactions (including shock and fatalities) have been reported with the use of cefixime.
3) Treatment with broad spectrum antibiotics, including Cefixime, 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 severe antibiotic-associated diarrhea including pseudomembranous colitis.
- **Ofloxacin**

1) **Tendinopathy and Tendon Rupture**

Ofloxacin is associated with an increased risk of tendinitis and tendon rupture in all ages. This adverse reaction most frequently involves the Achilles tendon, and rupture of the Achilles tendon may require surgical repair. Tendinitis and tendon rupture in the rotator cuff (the shoulder), the hand, the biceps, the thumb, and other tendon sites have also been reported. The risk of developing fluoroquinolone-associated tendinitis and tendon rupture is further increased in older patients usually over 60 years of age, in those taking corticosteroid drugs, and in patients with kidney, heart or lung transplants.
Ofloxacin should be discontinued if the patient experiences pain, swelling, inflammation or rupture of a tendon. Patients should be advised to rest at the first sign of tendinitis or tendon rupture, and to contact their healthcare provider regarding changing to a non-quinolone anti-microbial drug.

2) **Exacerbation of myasthenia gravis**

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

3) 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.

4) **Hypersensitivity Reactions**

Serious and occasionally fatal hypersensitivity and/or anaphylactic reactions have been reported in patients receiving therapy with quinolones, including Ofloxacin. These reactions often occur following the first dose. Some reactions have been accompanied by cardiovascular collapse, hypotension/shock, seizure, loss of consciousness, tingling, angioedema (including tongue, laryngeal, throat, or facial edema/swelling), airway obstruction (including bronchospasm, shortness of breath, and acute respiratory distress), dyspnea, urticaria, itching, and other serious skin reactions.

5) **Torsade de Pointes**

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

SPECIAL POPULATIONS:
- **Cefixime**

Pregnancy
Pregnancy Category B. Reproduction studies have been performed in mice and rats at doses up to 400 times the human dose and has revealed no evidence of harm to the fetus due to cefixime. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.
Labor and Delivery
Cefixime has not been studied for use during labor and delivery. Treatment should only be given if clearly needed.
Nursing Mothers
It is not known whether cefixime is excreted in human milk. Consideration should be given to discontinuing nursing temporarily during treatment with this drug.
Pediatric Use
Safety and effectiveness of cefixime in children aged less than six months old have not been established.
The incidence of gastrointestinal adverse reactions, including diarrhea and loose stools, in the pediatric patients receiving the suspension, was comparable to the incidence seen in adult patients receiving tablets.
- **Ofloxacin**

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

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

CARCINOGENESIS, MUTAGENESIS AND TERATOGENECITY:
- **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 125 times the adult therapeutic dose.
- **Ofloxacin**

Long-term studies to determine the carcinogenic potential of ofloxacin have not been conducted.
Ofloxacin was not mutagenic in the Ames bacterial test, in vitro and in vivocytogenetic 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.

DRUG INTERACTIONS:
- **Cefixime**

Carbamazepine: Elevated carbamazepine levels have been reported in postmarketing experience when cefixime is administered concomitantly. Drug monitoring may be of assistance in detecting alterations in carbamazepine plasma concentrations.
Warfarin and Anticoagulants: Increased prothrombin time, with or without clinical bleeding, has been reported when cefixime is administered concomitantly.
Drug/Laboratory Test Interactions
A false-positive reaction for ketones in the urine may occur with tests using nitroprusside but not with those using nitroferricyanide.
The administration of cefixime may result in a false-positive reaction for glucose in the urine using Clinitest***, Benedict's solution, or Fehling's solution. It is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix*** or TesTape***) be used.
A false-positive direct Coombs test has been reported during treatment with other cephalosporin antibiotics; therefore, it should be recognized that a positive Coombs test may be due to the drug.
- **Ofloxacin**

Antacids, Sucralfate, Metal Cations, Multivitamins
Quinolones form chelates with alkaline earth and transition metal cations. Administration of quinolones with antacids containing calcium, magnesium, or 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.
Non-steroidal anti-inflammatory drugs
The concomitant administration of a non-steroidal anti-inflammatory drug with a quinolone, including ofloxacin, may increase the risk of CNS stimulation and convulsive seizures.
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.
Interaction with Laboratory or Diagnostic Testing
Some quinolones, including ofloxacin, may produce false-positive urine screening results for opiates using commercially available immunoassay kits. Confirmation of positive opiate screens by more specific methods may be necessary.

ADVERSE EFFECTS
- **Cefixime**

The most commonly seen adverse reactions are gastrointestinal events, such as diarrhea, loose or frequent stools, abdominal pain, nausea , dyspepsia and flatulence.
Below are the less commonly observed adverse events associated with cefixime.
Gastrointestinal: Diarrhea, loose stools, abdominal pain, dyspepsia, nausea, and vomiting. Several cases of documented pseudomembranous colitis were identified during the studies.
Hypersensitivity Reactions: Anaphylactic/anaphylactoid reactions (including shock and fatalities), skin rashes, urticaria, drug fever, pruritus, angioedema, and facial edema. Erythema multiforme, Stevens-Johnson syndrome, and serum sickness-like reactions have been reported.
Hepatic: Transient elevations in SGPT, SGOT, alkaline phosphatase, hepatitis, jaundice.
Renal: Transient elevations in BUN or creatinine, acute renal failure.
Central Nervous System: Headaches, dizziness, seizures.
Hemic and Lymphatic Systems: Transient thrombocytopenia, leukopenia, neutropenia, and eosinophilia. Prolongation in prothrombin time was seen rarely.
- **Ofloxacin**

In clinical trials, the following events such as nausea, insomnia, headacsshe, dizziness, diarrhea, vomiting, rash pruritus, external genital pruritus in women, vaginitis, dysgeusia were considered likely to be drug-related in patients receiving multiple doses of ofloxacin.
Below are the less commonly observed adverse events associated with ofloxacin.

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
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

OVERDOSAGE:
- **Cefixime**

Adverse reactions in small numbers of healthy adult volunteers receiving single doses up to 2 g of cefixime did not differ from the profile seen in patients treated at the recommended doses.
- **Ofloxacin**

Information on overdosage with Ofloxacin is limited. One incident of accidental overdosage has been reported. In this case, an adult female received 3 grams of Ofloxacin intravenously over 45 minutes. During the infusion, the patient developed drowsiness, nausea, dizziness, hot and cold flushes, subjective facial swelling and numbness, slurring of speech, and mild to moderate disorientation. All complaints except the dizziness subsided within 1 h after discontinuation of the infusion.
In the event of an acute overdose, the stomach should be emptied. The patient should be observed and appropriate hydration maintained. Ofloxacin is not efficiently removed by hemodialysis or peritoneal dialysis.

DESCRIPTION
- **Cefixime**

Cefixime for Oral Suspension is a semisynthetic, cephalosporin antibiotic for oral administration. Chemically, it is (6R,7R)-7-[2-(2-Amino-4-thia-zolyl)glyoxylamido]-8-oxo-3-vinyl-5-thia-1-azabicyclo[4.2.0] oct-2-ene-2-carboxylic acid, 7²-(Z)-[O-(carboxymethyl) oxime] trihydrate. Molecular weight = 507.50 as the trihydrate. Chemical Formula is $C_{16}H_{15}N_5O_7S_2 \cdot 3H_2O$
- **Ofloxacin**

Ofloxacin tablets Tablets is a synthetic broad-spectrum antimicrobial agent for oral administration. Chemically, ofloxacin, a fluorinated carboxyquinolone, is the racemate, (±)-9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7oxo-7H-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid.

CLINICAL PHARMACOLOGY
- **Cefixime**

Cefixime, given orally, is about 40-50% % absorbed whether administered with or without food; however, time to maximal absorption is increased approximately 0.8 hours when administered with food. A single 200 mg tablet of cefixime produces an average peak serum concentration of approximately 2 Microg/mL (range 1 to 4 Micro g/mL). Peak serum concentrations occur between 2 and 6 hours following oral administration of a single 200 mg tablet.
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. Serum protein binding is concentration independent with a bound fraction of approximately 65%%. The serum half-life of cefixime averages 3.0-4.0 hours.
In subjects with moderate impairment of renal function (20 to 40 mL/min creatinine clearance), the average serum half-life of cefixime is prolonged to 6.4 hours. In severe renal impairment (5 to 20 mL/min creatinine clearance), the half-life increased to an average of 11.5 hours. The drug is not cleared significantly from the blood by hemodialysis or peritoneal dialysis.
- **Ofloxacin**

Following oral administration, the bioavailability of ofloxacin in the tablet formulation is approximately 98%. Maximum serum concentrations are achieved one to two 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. Ofloxacin has biphasic elimination. Following multiple oral doses at steady-state administration, the half-lives are approximately 4-5 hours and 20-25 hours. However, the longer half-life represents less than 5% of the total AUC. Accumulation at steady-state can be estimated using a half-life of 9 hours. The total clearance and volume of distribution are approximately similar after single or multiple doses. Elimination is mainly by renal excretion. In vitro, approximately 32% of the drug in plasma is protein bound.
Following oral administration of recommended therapeutic doses, ofloxacin has been detected in blister fluid, cervix, lung tissue, ovary, prostatic fluid, prostatic tissue, skin, and sputum. The mean concentration of ofloxacin in each of these various body fluids and tissues after one or more doses was 0.8 to 1.5 times the concurrent plasma level. Inadequate data are presently available on the distribution or levels of ofloxacin in the cerebrospinal fluid or brain tissue.
Ofloxacin has a pyridobenzoxazine ring that appears to decrease the extent of parent compound metabolism. Between 65% and 80% of an administered oral dose of ofloxacin is excreted unchanged via the kidneys within 48 hours of dosing. Studies indicate that less than 5% of an administered dose is recovered in the urine as the desmethyl or N-oxide metabolites. Four to eight percent of an ofloxacin dose is excreted in the feces. This indicates a small degree of biliary excretion of ofloxacin.
The administration of ofloxacin with food does not affect the Cmax and AUC of the drug, but Tmax is prolonged.Clearance of ofloxacin is reduced in patients with impaired renal function (creatinine clearance rate ≤ 50 mL/min), and dosage adjustment is necessary.
After the normal initial dose, the dose should be adjusted as follows:

Creatinine Clearance	Maintenance Dose	Frequency
20-50 mL/min	the usual recommended unit dose	24h
<20 mL/min	1/2 the usual recommended unit dose	24

MECHANISM OF ACTION
- **Cefixime**

It is an oral third generation cephalosporin antibiotic. cefixime binds to specific penicillin-binding proteins (PBPs) located inside the bacterial cell wall, causing the inhibition of the third and last stage of bacterial cell wall synthesis. Cell lysis is then mediated by bacterial cell wall autolytic enzymes such as autolysins.
Cefixime is highly stable in the presence of beta-lactamase enzymes. As a result, many organisms resistant to penicillins and some cephalosporins due to the presence of beta-lactamases, may be susceptible to cefixime. The antibacterial effect of cefixime results from inhibition of mucopeptide synthesis in the bacterial cell wall.
- **Ofloxacin**

Ofloxacin is a quinolone/fluoroquinolone antibiotic. Ofloxacin is bactericidal and its mode of action depends on blocking of bacterial DNA replication by binding itself to an enzyme called DNA gyrase and topoisomerase IV which is an enzyme necessary to separate replicated DNA, thereby inhibiting cell division.which allows the untwisting required to replicate one DNA double helix into two. Notably the drug has 100 times higher affinity for bacterial DNA gyrase than for mammalian. Ofloxacin is a broad-spectrum antibiotic that is active against both Gram-positive and Gram-negative bacteria.

STORAGE:
Keep out of reach of children
Manufactured by : Vapi Care Pharma Pvt. Ltd.
Unit No. 2, Village: Belikhol, Nalagarh Road, Dist. Solan, Pin -174 101 (H.P.)

Marketed by :
INTAS
INTAS PHARMACEUTICALS LTD.
Matoda-382 210, Dist. Ahmedabad. INDIA

Product Name : Ceftas O
Size : 210 x 140 (mm)
Pantone Black
Dt. : 19/05/2011