

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

TOPCEF-O 200
(Cefixime & Ofloxacin Tablets)

COMPOSITION

Each film coated tablet contains :
Cefixime I.P. as Trihydrate equivalent to
Anhydrous Cefixime 200 mg
Ofloxacin I.P. 200 mg
Colours : Lake of Tartrazine & Titanium Dioxide I.P.

INDICATIONS

For the treatment in adults with-

- Urinary Tract infections
- Typhoid fever

DOSAGE AND ADMINISTRATION

1 or 2 tablets given twice daily or as directed by physician.

CONTRAINDICATIONS

Ofloxacin

Ofloxacin should not be used in patients with known hypersensitivity to 4-quinolone antibacterials or any of the tablet excipients. Ofloxacin should not be used in patients with a past history of tendonitis. Ofloxacin, like other 4-quinolones, is contra-indicated in patients with a history of epilepsy or with a lowered seizure threshold. Ofloxacin is contra-indicated in children or growing adolescents, and in pregnant or breast-feeding women, since animal experiments do not entirely exclude the risk of damage to the cartilage of joints in the growing subject. Patients with latent or actual defects in glucose-6-phosphate dehydrogenase activity may be prone to haemolytic reactions when treated with quinolone antibacterial agents.

Cefixime

Patients with known hypersensitivity to cephalosporin or Penicillin antibiotics

WARNINGS AND PRECAUTION

Ofloxacin

Ofloxacin is not the drug of first choice for pneumonia caused by Pneumococci or Mycoplasma, or angina tonsillaris caused by β -haemolytic Streptococci. Hypersensitivity and allergic reactions have been reported for fluoroquinolones after first administration. Anaphylactic and anaphylactoid reactions can progress to life-threatening shock, even after the first administration. In these cases ofloxacin should be discontinued and suitable treatment (e.g treatment for shock) should be initiated.

Clostridium difficile-associated disease

Diarrhoea, particularly if severe, persistent and/or bloody, during or after treatment with ofloxacin, may be symptomatic of pseudo-membranous colitis. If pseudo-membranous colitis is

suspected, ofloxacin must be stopped immediately. Appropriate specific antibiotic therapy must be started without delay (e.g. oral vancomycin, oral teicoplanin or metronidazole). Products inhibiting the peristalsis are contraindicated in this clinical situation.

Patients predisposed to seizures

In case of convulsive seizures, treatment with ofloxacin should be discontinued.

Cardiac Disorders

Very rare cases of QT interval prolongation have been reported in patients taking fluoroquinolones. Caution should be taken when using fluoroquinolones, including ofloxacin, in patients with known risk factors for prolongation of the QT interval such as, for example :

- Congenital long QT syndrome
- Concomitant use of drugs that are known to prolong the QT interval (e.g. Class IA and III anti-arrhythmics, tricyclic antidepressants, macrolides, antipsychotics)
- uncorrected electrolyte imbalance (e.g. hypokalaemia, hypomagnesaemia)
- Elderly
- Cardiac disease (e.g. heart failure, myocardial infarction, bradycardia) . Patients being treated with ofloxacin should not expose themselves unnecessarily to strong sunlight and should avoid UV rays (sun lamps, solaria).

Patients with history of psychotic disorder

Psychotic reactions have been reported in patients receiving fluoroquinolones. In some cases these have progressed to suicidal thoughts or self-endangering behavior including suicide attempt, sometimes after a single dose. In the event that a patient develops these reactions, ofloxacin should be discontinued and appropriate measures instituted. Ofloxacin should be used with caution in patients with a history of psychotic disorder or in patients with psychiatric disease.

Patients with impaired liver function

Ofloxacin should be used with caution in patients with impaired liver function, as liver damage may occur. Cases of fulminant hepatitis potentially leading to liver failure (including fatal cases) have been reported with fluoroquinolones. Patients should be advised to stop treatment and contact their doctor if signs and symptoms of hepatic disease develop such as anorexia, jaundice, dark urine, pruritis or tender abdomen.

Patients treated with vitamin K antagonists

Due to possible increase in coagulation tests (PT/INR) and/or bleeding in patients treated with fluoroquinolones, including ofloxacin, in combination with a vitamin K antagonist (e.g. warfarin), coagulation tests should be monitored when these drugs are given concomitantly.

Myasthenia gravis

Ofloxacin should be used with caution in patients with a history of myasthenia gravis. Administration of antibiotics, especially of prolonged, may lead to proliferation of resistant micro-organisms. The patient's condition must therefore be checked at regular intervals. If a secondary infection occurs, appropriate measures must be taken.

Peripheral neuropathy

Sensory or sensorimotor peripheral neuropathy has been reported in patients receiving fluoroquinolones, including ofloxacin. Ofloxacin should be discontinued if the patient experiences symptoms of neuropathy in order to prevent the development of an irreversible condition.

Hypoglycaemia

As with all quinolones, hypoglycaemia has been reported, usually in diabetic patients receiving concomitant treatment with an oral hypoglycaemic agent (e.g. glibenclamide) or with insulin. In these diabetic patients, careful monitoring of blood glucose is recommended.

Patients with glucose-6-phosphate-dehydrogenase deficiency

Patients with latent or diagnosed glucose-6-phosphate-dehydrogenase deficiency may be predisposed to haemolytic reactions if they are treated with quinolones. Ofloxacin should therefore be administered with caution in such patients.

Patients with rare hereditary disorders

Patients with rare hereditary disorders of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Cefixime

Cefixime should be given with caution to patients who have shown hypersensitivity to other drugs. Cephalosporins should be given with caution to penicillin-sensitive patients, 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. Cefixime should be administered with caution in patients with markedly impaired renal function. 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.

DRUG INTERACTIONS*Cefixime*

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 recognised that a positive Coombs test may be

due to the drug. In common with other cephalosporins, increases in prothrombin times have been noted in a few patients. Care should therefore be taken in patients receiving anticoagulation therapy.

Ofloxacin

Drugs known to prolong QT interval

Ofloxacin, like other fluoroquinolones, should be used with caution in patients receiving drugs known to prolong the QT interval (e.g. Class IA and III anti-arrhythmics, tricyclic antidepressants, macrolides, antipsychotics).

Antacids, Sucralfate, Metal Cations

Co-administered magnesium/aluminium antacids, sucralfate, zinc or iron preparations can reduce absorption. Therefore, ofloxacin should be taken 2 hours before such preparations. Prolongation of bleeding time has been reported during concomitant administration of Tarivid and anticoagulants. There may be a further lowering of the cerebral seizure threshold when quinolones are given concurrently with other drugs which lower the seizure threshold, e.g. theophylline. However ofloxacin is not thought to cause a pharmacokinetic interaction with theophylline, unlike some other fluoroquinolones.

Further lowering of the cerebral seizure threshold may also occur with certain nonsteroidal anti-inflammatory drugs. In case of convulsive seizures, treatment with ofloxacin should be discontinued. Ofloxacin may cause a slight increase in serum concentrations of glibenclamide administered concurrently; patients treated with this combination should be closely monitored.

With high doses of quinolones, impairment of excretion and an increase in serum levels may occur when co-administered with other drugs that undergo renal tubular secretion (e.g. probenecid, cimetidine, frusemide and methotrexate).

Interaction with laboratory tests:

Determination of opiates or porphyrins in urine may give false-positive results during treatment with ofloxacin. It may be necessary to confirm positive opiate or porphyrin screens by more specific methods.

Vitamin K antagonists

Coagulation tests should be monitored in patients treated with vitamin K antagonists because of a possible increase in the effect of coumarin derivatives.

FERTILITY, PREGNANCY AND LACTATION

Ofloxacin

Pregnancy

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 outcome. Animal studies have shown damage to the joint cartilage in immature animals but no teratogenic effects. Therefore ofloxacin should not be used during pregnancy.

Lactation

Ofloxacin is excreted into human breast milk in small amounts. Because of the potential for

arthropathy and other serious toxicity in the nursing infant, breast feeding should be discontinued during treatment with ofloxacin.

Cefixime

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 foetus due to cefixime. In the rabbit, at doses up to 4 times the human dose, there was no evidence of a teratogenic effect; there was a high incidence of abortion and maternal death which is an expected consequence of the known sensitivity of rabbits to antibiotic-induced changes in the population of the microflora of the intestine. There are no adequate and well-controlled studies in pregnant women. Cefixime should therefore not be used in pregnancy or in nursing mothers unless considered essential by the physician.w

UNDESIRABLE EFFECTS

Ofloxacin

System organ class	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)	Very rare (< 1/10,000)	Not known (cannot be estimated from available data)*
Infections and infestations	Fungal infection, Pathogen resistance			
Blood and lymphatic system disorders			Anaemia, Haemolytic anaemia, Leucopenia, Eosinophilia, Thrombocytopenia	Agranulocytosis, Bone marrow failure, Pancytopenia
Immune system disorders		Anaphylactic reaction*, Anaphylactoid reaction*, Angioedema*	Anaphylactic shock*, Anaphylactoid shock*	
Metabolism and Nutrition disorders		Anorexia		Hypoglycaemia in diabetics treated with hypoglycaemic agents, Hyperglycaemia, Hypoglycaemic coma
Psychiatric disorders	Agitation, Sleep disorder, Insomnia	Psychotic disorder (for e.g. hallucination), Anxiety, Confusional state, Nightmares, Depression		Psychotic disorder and depression with self-endangering behaviour including suicidal ideation or suicide attempt Nervousness,

Nervous system disorders	Dizziness, Headache	Somnolence, Paraesthesia, Dysgeusia, Parosmia	Peripheral sensory neuropathy*, Peripheral sensory motor neuropathy*, Convulsion*, Extra-pyramidal symptoms or other disorders of muscular coordination	Tremor, Dykinesia, Ageusia, Syncope
Eye disorders	Eye irritation	Visual disturbance		Uveitis
Ear and labyrinth disorders	Vertigo		Tinnitus, Hearing loss	Hearing impaired
Cardiac disorders		Tachycardia		Ventricular arrhythmias and torsades de pointes (reported predominantly in patients with risk factors for QT prolongation), ECG QT prolonged
Vascular disorders		Hypotension		
Respiratory, thoracic and mediastinal disorders	Cough, Nasopharyngitis	Dyspnoea, Bronchospasm		Allergic pneumonitis, Severe dyspnoea
Gastrointestinal disorders	Abdominal pain, Diarrhoea, Nausea, Vomiting	Enterocolitis, sometimes haemorrhagic	Pseudomembranous colitis*	Dyspepsia, Flatulence, Constipation, Pancreatitis
Hepatobiliary disorders		Hepatic enzymes increased (ALAT, ASAT, LDH, gamma-GT and/or alkaline phosphatase), Blood bilirubin increased	Jaundice cholestatic	Hepatitis, which may be severe* Severe liver injury, including cases with acute liver failure, sometimes fatal, have been reported with ofloxacin, primarily in patients with underlying liver disorders.
Skin and subcutaneous tissue disorders	Pruritus, Rash	Urticaria, Hot flushes, Hyperhidrosis	Erythema multiforme, Toxic epidermal	Stevens-Johnson syndrome, Acute generalised

		Pustular rash	necrosis, Photo-sensitivity reaction* , Drug eruption, Vascular purpura, Vasculitis, which can lead in exceptional cases to skin necrosis	exanthemous pustulosis, Drug rash, Stomatitis Exfoliative dermatitis
Musculoskeletal and connective tissue disorders		Tendonitis	Arthralgia, Myalgia, Tendon rupture (e.g. Achilles tendon) which may occur within 48 hours of treatment start and may be bilateral	Rhabdomyolysis and/or Myopathy, Muscular weakness, Muscle tear, Muscle rupture, Ligament rupture, Arthritis
Renal and urinary disorders		Serum creatinine increased	Acute renal failure	Acute interstitial nephritis
Congenital, familial and genetic disorders				Attacks of porphyria in patients with porphyria

* postmarketing experience

Other adverse effects reported with ofloxacin are asthenia, chills, malaise, epistaxis, cardiac arrest, oedema, hypertension, palpitation, vasodilation, dyspepsia, burning, irritation, dysmenorrhea, menorrhagia, metrorrhagia, cognitive changes, abnormal dream, euphoria, syncope, tremor, confusion, thirst, weight loss, respiratory arrest, rhinorrhea, diaphoresis, decreased hearing acuity, dysuria, urinary frequency, urinary retention, Leukocytosis, Neutrophilia, increased band forms, lymphocytopenia, lymphocytosis, elevated ESR, Hyperglycaemia, Hypoglycaemia, blood urea nitrogen increased, glucosuria, proteinuria, alkaluria, hyposthenuria, hematuria, pyuria, cerebral thrombosis, pulmonary oedema, hepatic necrosis, jaundice (cholestatic or hepatocellular), intestinal perforation, hepatic failure (including fatal cases), pseudomembranous colitis, GI haemorrhage, hiccough, painful oral mucosa, pyrosis, vaginal candidiasis, reversible bone marrow depression, thrombotic thrombocytopenic purpura, petechiae, ecchymosis, bruising, tendinitis, rupture, suicidal thought or acts, disorientation, paranoia, phobia, restlessness, aggressiveness, hostility, manic reaction, emotional liability, ataxia, incoordination, dysphasia, lightheadedness, stridor, serum sickness, erythema nodosum, exfoliative dermatitis, hyperpigmentation, conjunctivitis, phototoxicity or photosensitivity reaction, vesicubullous eruption, diplopia, nystagmus, blurred vision, disturbances in smell, taste, hearing and equilibrium (reversible following discontinuation), anuria, renal calculi, haematuria, prothrombin time prolongation, acidosis, elevation of serum triglyceride level, cholesterol, potassium, liver function test, albuminuria, candiduria, crystaluria, cylinderuria have been reported with the use of ofloxacin.

The drug may cause low blood sugar and mental health related side effects. Low blood sugar levels, also called hypoglycaemia, can lead to coma. The mental health side effects more prominent and more consistent across the systemic fluoroquinolone drug class. The mental health side effects to be added to or updated across all the fluoroquinolones are:

- disturbances in attention
- disorientation
- agitation
- nervousness
- memory impairment
- Serious disturbances in mental abilities called delirium.

Cefixime

Cefixime is generally well tolerated. The majority of adverse reactions observed in clinical trials were mild and self-limiting in nature.

Gastrointestinal Disturbances: The most frequent side effects seen with Cefixime are diarrhoea and stool changes; diarrhoea has been more commonly associated with higher doses. Some cases of moderate to severe diarrhoea have been reported; this has occasionally warranted cessation of therapy. Cefixime should be discontinued if marked diarrhoea occurs. Other gastrointestinal side effects seen less frequently are nausea, abdominal pain, dyspepsia, vomiting and flatulence. Pseudomembranous colitis has been reported.

Central Nervous System: Headache and dizziness.

Hypersensitivity Reactions: Allergies in the form of rash, pruritus, drug fever and arthralgia have been observed, including rare cases of urticaria or angioedema. These reactions usually subsided upon discontinuation of therapy. Rarely, erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported.

Haematological and Clinical Chemistry: Thrombocytosis, thrombocytopenia, leucopenia, hypereosinophilia, neutropenia and agranulocytosis have been reported. These reactions were infrequent and reversible. Mild transient changes in liver and renal function tests have been observed.

Hepatic Disorders: Transient rises in liver transaminases, alkaline phosphatase and jaundice can also occur.

Miscellaneous: Other possible reactions include genital pruritus and vaginitis.

OVERDOSE

Cefixime

There is no experience with overdose of cefixime. Adverse reactions reported 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. Gastric lavage may be indicated in overdosage. No specific antidote exists. Cefixime is not removed from the circulation in significant quantities by dialysis.

Ofloxacin

The most important signs to be expected following acute overdosage 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 eg 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.

CLINICAL PHARMACOLOGY

PHARMACODYNAMIC PROPERTIES

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. Clinical efficacy has been demonstrated in infections caused by commonly occurring pathogens including *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Escherichia coli*, *Proteus mirabilis*, *Klebsiella* species, *Haemophilus influenzae* (beta-lactamase positive and negative), *Branhamella catarrhalis* (beta-lactamase positive and negative) and *Enterobacter* species. It is highly stable in the presence of beta-lactamase enzymes. Most strains of Enterococci (*Streptococcus faecalis*, group D Streptococci) and Staphylococci (including coagulase positive and negative strains and methicillin-resistant strains) are resistant to cefixime. In addition, most strains of *Pseudomonas*, *Bacteroides fragilis*, *Listeria monocytogenes* and *Clostridia* are resistant to cefixime.

Ofloxacin

Ofloxacin is bactericidal and acts by inhibiting DNA gyrase and topoisomerase IV, which are essential enzymes in the reproduction of bacterial DNA. It has a broader spectrum of activity and is more potent in vitro than the non-fluorinated quinolone nalidixic acid although resistance to many species or strains previously sensitive is emerging. Activity may be reduced in acid media and in the presence of urine but not of serum.

Spectrum of activity. Among Gram-negative aerobic bacteria, Ofloxacin may be active in vitro against Enterobacteriaceae, including *Escherichia coli* and *Citrobacter*, *Enterobacter*, *Klebsiella*, *Proteus*, *Providencia*, *Salmonella*, *Serratia*, *Shigella*, and *Yersinia* spp. It may also exhibit activity against *Pseudomonas aeruginosa* and *Neisseria gonorrhoeae*. *H. influenzae*, *Moraxella catarrhalis* (*Branhamella catarrhalis*), and *N. meningitidis* are all sensitive. Other Gram-negative aerobic bacteria reported to be sensitive to Ofloxacin have included *Gardnerella vaginalis*, *Helicobacter pylori*, *Legionella* spp., *Pasteurella multocida*, and *Vibrio* spp. Variable activity has been reported against *Acinetobacter* spp., *Brucella melitensis*, and *Campylobacter* spp.

Among Gram-positive aerobic bacteria, Ofloxacin is active against staphylococci, including penicillinase-producing and penicillinase - nonproducing strains, and against some MRSA. Streptococci, in particular *Streptococcus pneumoniae* and enterococci, are less susceptible. Other Gram-positive bacteria sensitive to Ofloxacin in vitro are *Bacillus* spp.; variable activity has been noted for *Corynebacterium* spp.

Most anaerobic bacteria, including *Bacteroides fragilis* and *Clostridium difficile*, are resistant to Ofloxacin, although some other *Clostridium* spp. may be susceptible. Ofloxacin has some activity against mycobacteria, mycoplasmas, rickettsias, *Chlamydia trachomatis*, and *Ureaplasma urealyticum*. It is also active against *Mycobacterium leprae* as well as *M. tuberculosis* and some other *Mycobacterium* spp. Synergistic activity against *M. leprae* has been reported between ofloxacin and rifabutin.

PHARMACOKINETIC PROPERTIES

Cefixime

Only 40 to 50% of an oral dose of cefixime is absorbed from the gastrointestinal tract, whether taken before or after meals, although the rate of absorption may be decreased in the presence of food. Absorption is fairly slow; peak plasma concentrations of 2 to 3 micrograms/mL and 3.7 to 4.6 micrograms/mL have been reported between 2 and 6 hours after single doses of 200 and 400 mg, respectively. The plasma half-life is usually about 3 to 4 hours and may be prolonged when there is renal impairment. About 65% of cefixime is bound to plasma proteins. Information on the distribution of cefixime in body tissues and fluids is limited. It crosses the placenta. Relatively high concentrations may be achieved in bile and urine. About 20% of an oral dose (or 50% of an absorbed dose) is excreted unchanged in the urine within 24 hours. Up to 60% may be eliminated by nonrenal mechanisms; there is no evidence of metabolism but some is probably excreted into the faeces from bile. It is not substantially removed by dialysis.

Ofloxacin

Ofloxacin is rapidly and well absorbed from the gastrointestinal tract. Oral bioavailability is almost 100% and a peak plasma concentration of about 3 to 5 micrograms/mL occurs 1 to 2 hours after an oral dose of 400 mg. Absorption may be delayed by the presence of food, but the extent of absorption is not substantially affected. About 25% is bound to plasma proteins. Ofloxacin is widely distributed in body fluids, including the CSF, and tissue penetration is good. It crosses the placenta and is distributed into breast milk. It also appears in the bile. The elimination of ofloxacin is biphasic; half-lives of about 4 to 5 and 20 to 25 hours have been reported for the 2 phases, respectively. In renal impairment values of 15 to 60 hours have been reported. There is limited metabolism to desmethyl and N-oxide metabolites; desmethyl ofloxacin has moderate antibacterial activity. Ofloxacin is eliminated mainly by the kidneys.

Excretion is by tubular secretion and glomerular filtration and 65 to 80% of a dose is excreted unchanged in the urine over 24 to 48 hours, resulting in high urinary concentrations. Less than 5% is excreted in the urine as metabolites. From 4 to 8% of a dose may be excreted in the faeces. Only small amounts of ofloxacin are removed by haemodialysis or peritoneal dialysis.

EXPIRY DATE:

Do not use later than date of expiry.

STORAGE

Store below 30°C, protected from light and moisture.
Keep out of reach of children

PRESENTATION

Topcef O - 200 is available as blister strip of 10 tablets.

MARKETED BY



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IN/TOPCEF-O 200,200 mg/JAN-19/02/PI