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

TOPCEF CLAV 200

1. Generic Name

Cefixime and Potassium Clavulanate Tablets

2. Qualitative and quantitative composition

Each film coated tablet contains:

Cefixime I.P. (as Trihydrate) equivalent to

Cefixime Anhydrous …….200mg

Potassium Clavulanate Diluted I.P. equivalent to

Clavulanic acid …….125mg

Colour: Titanium Dioxide I.P.

Other inactive ingredients are Mannitol, Starch Dried, Crospovidone, Colloidal, Silicon Dioxide, Magnesium Stearate, Hydroxy Propyl Methyl Celulose, Ethyl Cellulose, Diethyl Phthalate, Titanium Dioxide, Methanol and Methylene Chloride.

3. Dosage form and strength

Film coated tablets

Cefixime Anhydrous 200mg, Clavulanic acid 125mg

4. Clinical particulars

4.1 Therapeutic indication

For the treatment of adult patients with infections caused by susceptible microorganism, viz, Urinary tract infection, Upper and lower respiratory tract infections, and gonococcal urethritis.

4.2 Posology and method of administration

Adults and Children over 12 Years: One tablet twice daily.

The usual course of treatment is 7 days. This may be continued for up to 14 days if required.

4.3 Contraindications

Topcef Clav is contraindicated in the patients with known hypersensitivity to cephalosporin antibiotics or to any of the excipients.

4.4 Special warnings and precautions for use

Encephalopathy

Beta-lactams, including cefixime, predispose the patient to encephalopathy risk (which may include convulsions, confusion, impairment of consciousness, movement disorders), particularly in case of overdose or renal impairment.

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.

Topcef Clav should be given with caution to patients who have shown hypersensitivity to other drugs.

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 Topcef Clav, the drug should be discontinued and the patient treated with appropriate agents if necessary.

Haemolytic anaemia

Drug-induced haemolytic anaemia, including severe cases with a fatal outcome, has been described for cephalosporins (as a class). The recurrence of haemolytic anaemia after re-administration of cephalosporins in a patient with a history of cephalosporin (including cefixime) –associated haemolytic anaemia 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.

Renal impairment

Topcef Clav should be administered with caution in patients with markedly impaired renal function.

Paediatric use

Safety of cefixime in premature or newborn infant has not been established.

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.

4.5 Drugs interactions

Anticoagulants

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.

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 recognised that a positive Coombs test may be due to the drug.

4.6 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

As per reported data, 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. Topcef Clav should therefore not be used in pregnancy or in nursing mothers unless considered essential by the physician.

4.7 Effects on ability to drive and use machines

In the case of side effects such as encephalopathy (which may include convulsion, confusion, impairment of consciousness, movement disorders), the patient should not operate machines or drive a vehicle.

4.8 Undesirable effects

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

The following adverse reaction (Preferred term# or equivalent) will be considered listed:

Blood and lymphatic system disorders:	Eosinophilia Hypereosinophilia Agranulocytosis Leucopenia Neutropenia Granulocytopenia Haemolytic anaemia Thrombocytopenia Thrombocytosis
Gastrointestinal disorders:	Abdominal pain Diarrhoea* Dyspepsia Nausea Vomiting Flatulance
Hepatobiliary disorders:	Jaundice

Infections and infestations:	Pseudomembranous colitis
Investigations:	Aspartate aminotransferase increased Alanine aminotransferase increased Blood bilirubin increased Blood urea increased Blood creatinine increased
Nervous system disorders:	Dizziness Headache Cases of convulsions have been reported with cephalosporins including cefixime (frequency not known)[**] Beta-lactams, including cefixime, predispose the patient to encephalopathy risk (which may include convulsions, confusion, impairment of consciousness, movement disorders), particularly in case of overdose or renal impairment (frequency not known)[**]
Respiratory, thoracic and mediastinal disorders:	Dyspnoea
Renal and urinary disorders:	Renal failure acute including tubulointerstitial nephritis as an underlying pathological condition
Immune system disorders, administrative site conditions, skin and subcutaneous tissue disorders:	Anaphylactic reaction Serum sickness-like reaction Drug rash with eaosinophilia and systemic symptoms (DRESS) Pruritus Rash Drug Fever Arthralgia Erythema multiforme Acute generalized exanthematous pustulosis (AGEP) Stevens-Johnson syndrome Toxic epidermal necrolysis Angio-oedema Urticaria Pyrexia Face oedema Genital pruritus Vaginitis

The above mentioned listed adverse reactions have been observed during clinical studies and/or during marketed use.

Preferred term in MedDRA (v.14.0)

*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. Topcef Clav should be discontinued if marked diarrhoea occurs

** Cannot be estimated from available data.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/Index.php/site/info/adverse_event_reporting.

4.9 Overdose

There is a risk of encephalopathy in cases of administration of beta-lactam antibiotics, including cefixime, particularly in case of overdose or renal impairment.

Adverse reactions seen at dose levels up to 2 g Topcef Clav 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.

5. Pharmacological properties

5.1 Mechanism of Action

The bactericidal action of cefixim is due to the inhibition of cell wall synthesis. It binds to one of the penicillin binding proteins (PBPs) which inhibits the final transpeptidation step of the peptidoglycan synthesis in the bacterial cell wall, thus inhibiting biosynthesis and arresting cell wall assembly resulting in bacterial cell death.

Clavulanic acid is a beta-lactam structurally related to penicillins. It inactivates some beta-lactamase enzymes thereby preventing inactivation of cefixim. Clavulanic acid alone does not exert a clinically useful antibacterial effect.

5.2 Pharmacodynamic properties

Cefixime is an orally active third generation bactericidal cephalosporin (beta lactam antibiotic) with broad spectrum of coverage. Cefixime has been shown to be active against most strains of the following organisms both in vitro and in clinical infections.

Gram-positive Organisms:

Streptococcus pneumoniae,

Streptococcus pyogenes.

Gram-negative Organisms:

Haemophilus influenza (beta-lactamase positive and negative strains),
Moraxella (Branhamella) catarrhalis (most of which are beta-lactamase positive),
Escherichia coli,
Proteus mirabilis,
Neisseria gonorrhoeae (including penicillinase - and non-penicillinase- producing strains).

Cefixime has been shown to be active in vitro against most strains of the following organisms; however, clinical efficacy has not been established.

Gram-positive Organisms:

Streptococcus agalactiae.

Gram-negative Organisms:

Haemophilus parainfluenzae (beta-lactamase positive and negative strains),

Proteus vulgaris,

Klebsiella pneumoniae,

Klebsiella oxytoca,

Pasteurella multocida,

Providencia species,

Salmonella species,

Shigella species,

Citrobacter amalonaticus,

Citrobacter diversus,

Serratia marcescens.

Note: *Pseudomonas* species, strains of group D streptococci (including enterococci), Listeria monocytogenes, most strains of staphylococci (including methicillin-resistant strains) and most strains of Enterobacter are resistant to cefixime. In addition, most strains of Bacteroides fragilis and Clostridia are resistant to cefixime.

Cefixime is highly stable in the presence of betalactamase enzymes. As a result, many organisms resistant to penicillins and some cephalosporins due to the presence of beta-lactamases, may be susceptible to cefixime. However, cefixime was found to be ineffective against bacteria which produces Extended Spectrum β-Lactamase enzyme and resistance is seen in such types of bacteria.

Clavulanic acid is an irreversible 'suicide' inhibitor of intracellular and extracellular β-lactamases, demonstrating concentration-dependent and competitive inhibition. It has a high affinity for the class A β-lactamases. This wide range of β-lactamases, which includes the plasmid-mediated TEM and SHV enzymes, is found frequently in members of the Enterobacteriaceae, *Haemophilus influenzae* and *Neisseria gonorrhoeae*. The chromosomally mediated β-lactamases of Klebsiella pneumoniae, Proteus mirabilis, *Proteus vulgaris, Bacteroides fragilis* and *Moraxella catarrhalis* are also inhibited, as are the extended-spectrum β-lactamases. The frequency of β-lactamase mediated resistance has continued to rise over the years, but the majority of clinically significant β-lactamases are inhibited by clavulanate.

5.3 Pharmacokinetic properties

Combining clavulanic acid with beta lactam antibiotic causes no appreciable alteration of the pharmacokinetics of either drug compared with their separate administration.

About 40-50% of cefixime is absorbed slowly following oral administration from the GIT. Absorption is not significantly modified by the presence of food.

From reported *in vitro* studies, serum or urine concentrations of 1 mcg/mL or greater were considered to be adequate for most common pathogens against which cefixime is active. Typically, the peak serum levels following the recommended adult or paediatric doses are between 1.5 and 3 mcg/mL. Little or no accumulation of cefixime occurs following multiple dosing.

The pharmacokinetics of cefixime in healthy elderly (age >64 years) and young volunteers (11-35) compared the administration of 400 mg doses once daily for 5 days. Mean C_{max} and

AUC values were slightly greater in the elderly. Elderly patients may be given the same dose as the general population.

Cefixime is predominantly eliminated as unchanged drug in the urine. Glomerular filtration is considered the predominant mechanism. Metabolites of Cefixime have not been isolated from human serum or urine. Serum protein binding is well characterised for human and animal sera; cefixime is almost exclusively bound to the albumin fraction, the mean free fraction being approximately 30%. Protein binding of cefixime is only concentration dependent in human serum at very high concentrations which are not seen following clinical dosing.

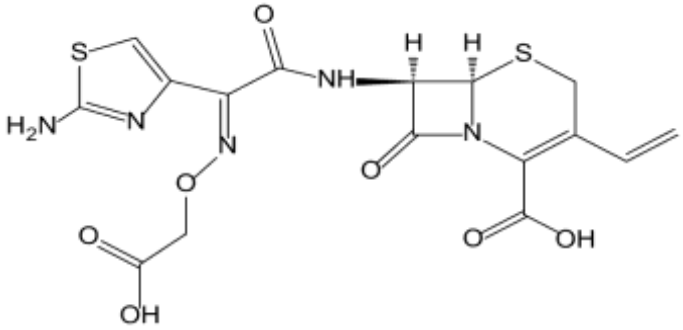
6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

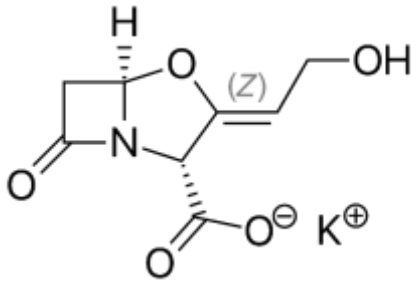
Lifetime studies in animals to evaluate carcinogenic potential have not been conducted. Cefixime did not cause point mutations in bacteria or mammalian cells, DNA damage, or chromosome damage in vitro and did not exhibit clastogenic potential in vivo in the mouse micronucleus test. In rats, fertility and reproductive performance were not affected by cefixime at doses up to 125 times the adult therapeutic dose.

7. Description

Cefixime is a semisynthetic, cephalosporin antibacterial for oral administration. Chemically, it is (6R,7R)-7-[2-(2-Amino-4-thiazolyl) glyoxylamido]-8-oxo-3-vinyl-5-thia1-azabicyclo [4.2.0] oct-2-ene-2-carboxylic acid, 72-(Z)-[O-(carboxy methyl) oxime] rihydrate. The molecular weight is 507.50 as the trihydrate and chemical formula is C16H15N5O7S2.3H2O. The structural formula for cefixime is:



Potassium clavulanate is the potassium salt of clavulanic acid, a β-lactamase inhibitor used in combination with β-lactam antibiotics for oral or parenteral administration. Chemically, it is (2R,3Z,5R)-3-(2-Hydroxyethylidene)-7-oxo-4-oxa-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, potassium salt.



White to off white capsule shape, biconvex, film coated tablets, plain on both sides.

8. Pharmaceutical particulars

8.1 Incompatibilities

None Stated

8.2 Shelf-life

Do not use later than date of expiry

8.3 Packaging information

Available in strip pack of 10 Tablets

8.4 Storage and handing instructions

Store at a temperature not exceeding 25°C, protected from light and moisture.

Keep out of reach of children.

9. Patient Counselling Information

Ask the patients to inform the treating physicians in case of any of the below:

- Have any allergies
- Have kidney or liver problems
- Are pregnant or plan to become pregnant
- Are breastfeeding or plan to breastfeed
- Have any serious illness
- Are taking any medicines (prescription, over-the-counter, vitamins, or herbal products)

10. Details of manufacturer

Manufactured by:

Torrent Pharmaceuticals Ltd.

Indrad-382 721 Dist. Mehsana, INDIA

At : Block No. 10-13 , Nr.M.N. Desai Petrol Pump,

Sarkhej-Bavla Road, Village-Changodar, Dist.Ahmedabad 382 213

11. Details of permission or licence number with date

Mfg.Lic.No : G/28A/4897-A dated 21.12.10

12. Date of revision

JAN 2025

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/TOPCEF ClAV 200, 200mg, 125mg/JAN-2025/02/PI