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

Pharmacotherapeutic group: third generation cephalosporin, ATC code: J01DD08.

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

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

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

• Keep this leaflet. You may need to read it again.

• If you have any further questions, ask your doctor or pharmacist.

• This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.

• If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 9.4.

What is in this leaflet:

1. What Topcef Clav is and what they are used for
2. What you need to know before you use Topcef Clav
3. How to use Topcef Clav
4. Possible side effects
5. How to store Topcef Clav
6. Contents of the pack and other information

9.1 What Topcef Clav is and what it is used for.

Topcef Clav is an antibiotic and works by killing bacteria that cause infections. It contains two different medicines called cifexime and clavulanic acid. Cifexime belongs to a group of medicines called “cephalosporins” that can sometimes be stopped from working (made inactive). The other active component (clavulanic acid) stops this from happening.

Topcef Clav is used 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.

9.2 What you need to know before you use Topcef Clav.

Do not use Topcef Clav:

- if you are allergic to cefixime, any other cephalosporin antibiotics including penicillin, clavulanic acid or to any of the other ingredients of this medicine.
  Signs of an allergic reaction include: a rash, swallowing or breathing problems, swelling of the lips, face, throat and tongue.

Do not take this medicine if the above applies to you. If you are not sure, talk to your doctor or pharmacist before taking Topcef Clav.

Warnings and precautions

Talk to your doctor or pharmacist before taking Topcef Clav:

- if you have ever had colitis
- if you have kidney problems

If you are not sure if any of the above apply to you, talk to your doctor or pharmacist before taking this medicine.

Other medicines and Topcef Clav

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines. This includes medicines you buy without a prescription, including herbal medicines. This is because Topcef Clav can affect the way some other medicines work. Also some medicines can affect the way Topcef Clav works. In particular, tell your doctor if you are taking the following:

• Medicines to thin the blood such as warfarin

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines

This medicine can cause symptoms including fits (convulsions), feeling confused, feeling less alert or aware of things than usual, unusual muscle movements or stiffness. If you experience any of these effects don't drive or use machinery.

Medical Tests

If you require any tests (such as blood or urine tests) while taking this medicine, please make sure your doctor knows that you are taking Topcef Clav.

9.3 How to use Topcef Clav

Always take Topcef Clav exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

• Take this medicine by mouth
• Swallow tablets whole with a drink of water
• If you feel the effect of the medicine is too weak or too strong, do not change the dose yourself, but ask your doctor.

Carefully read the label from the pharmacist. Ask your pharmacist if you are not sure about the dose to take. The medicine should be taken for the prescribed number of days.

The recommended dose is:

Adults, Elderly and Children over 12 years or weighing more than 50kg

• 1-2 tablets each day given as a single or divided dose

People with kidney problems

• Your doctor may prescribe a lower dose

Children under 12 years old

• Topcef Clav should not be given to children under 12 years old

If you take more Topcef Clav than you should

If you have too much of this medicine, talk to your doctor straight away.

If you forget to take Topcef Clav

If you forget to take a dose, take it as soon as you remember. However, if it is nearly time for the next dose, skip the missed dose. Do not take a double dose to make up for a forgotten dose.

If you stop taking Topcef Clav

Do not stop taking this medicine without talking to your doctor. You should not stop taking Topcef Clav just because you feel better. This is because the infection may come back or get worse again.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

9.4 Possible Side Effects

Like all medicines, these tablets can cause side effects, although not everybody gets them.

Tell your doctor straight away or go to the nearest hospital casualty department if you notice any of the following serious side effects-you may need urgent medical treatment:

• You have an allergic reaction. The signs may include: a rash, joint pain, swallowing or breathing problems, swelling of your lips, face, throat or tongue

• Blistering or bleeding of the skin around the lips, eyes, mouth, nose and genitals. Also flu-like symptoms and fever. This may be something called 'Stevens-Johnson' syndrome.

• Severe blistering rash where layers of the skin may peel off to leave large areas of raw exposed skin over the body. Also a feeling of being generally unwell, fever, chills and aching muscles. This may be something called 'Toxic epidermal necrolysis'

• You have a skin rash or skin lesions with a pink/red ring and a pale centre which may be itchy, scaly or filled with fluid. The rash may appear especially on the palms or soles of your feet. These could be signs of a serious allergy to the medicine called 'erythema multiforme'

• You get infections more easily than usual. This could be because of a blood disorder. This normally gets better after stopping the medicine

• You bruise or bleed more easily than normal. This could be because of a blood disorder.

This normally gets better after stopping the medicine

• If your child gets nose bleeds, bleeding gums, chills, tiredness, pale skin (often with a yellow tinge), shortness of breath. This may be due to haemolytic anaemia.

• Changes in the way the kidneys are working or blood in your child's urine

• Fits (convulsions) - Frequency not known • A brain condition with symptoms including fits (convulsions), feeling confused, feeling less alert or aware of things than usual, unusual muscle movements or stiffness. This may be something called encephalopathy. This side effect is more likely if you have taken an overdose or you already have a problem with your kidneys.

Stop taking this medicine and contact your doctor without delay if you get:

• Severe watery diarrhoea that will not stop and you are feeling weak and have a fever. This may be something called 'Pseudomembranous colitis'

Tell your doctor or pharmacist if any of the following side effects get serious or lasts longer than a few days:
• Feeling sick (nausea), being sick (vomiting)
• Stomach pains, indigestion or wind
• Headaches
• Feeling dizzy
• Feeling itchy in the genital or vaginal area

Tell your doctor if any of the side effects gets serious or lasts longer than a few days, or if you notice any side effects not listed in this leaflet.

Blood Tests
Topcef Clav can cause blood clots or small changes to the way the liver and kidney work. This would be shown up in blood tests. This is not common and goes back to normal after stopping this medicine.

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.
By reporting side effects, you can help provide more information on the safety of this medicine.

9.5 How to store Topcef Clav
Store at a temperature not exceeding 25°C, protected from light and moisture.

Keep out of reach of children.

9.6 Contents of the pack and other information
Available in strip pack of 10 Tablets.

What Topcef Clav contains:

The active substance in this product is Cefixime and Clavulanic acid.

The other 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.

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
Aug 2019

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/TOPCEF Clav 200, 200mg, 125mg/Aug-2019/02/PI