

Cefixime & Potassium Clavulanate Tablet

Taxim-O CV 200



1. NAME OF THE MEDICINAL PRODUCT

Taxim-O CV 200

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains:

Cefixime IP (as Trihydrate) equivalent to anhydrous Cefixime200 mg

Potassium Clavulanate Diluted IP equivalent to Clavulanic acid.....125 mg

3. PHARMACEUTICAL FORM

Film coated tablet for oral administration

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Cefixime & Clavulanic acid tablets can be applied for the treatment of the following infections, when caused by microorganisms sensitive to cefixime:

- Urinary tract infection
- Upper respiratory tract infection
- Lower respiratory tract infection

4.2 Posology and Method of Administration

One tablet twice daily

4.3 Contraindications

Cefixime is contraindicated in patients with known hypersensitivity to cephalosporin antibiotics or any of the other components of the product.

History of a severe immediate hypersensitivity reaction (e.g. anaphylaxis) to another beta-lactam agent.

4.4 Special Warnings and Special Precautions for Use

FDC of Cefixime and Clavulanic acid 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 crossallergenicity between the penicillins and cephalosporins. Patients have had severe reactions (including anaphylaxis) to both classes of drugs. If an allergic effect occurs with, the drug should be discontinued and the patient treated with appropriate agents if necessary. 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.

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.

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.

Renal failure acute

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

Cefixime should be administered with caution in patients with markedly impaired renal function (See section 4.2 under Dosage in Renal Impairment).

Paediatric use

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

This presentation of cefixime and clavulanic acid is not suitable for use when there is a high risk that the presumptive pathogens have reduced susceptibility or resistance to beta-lactam agents that is not mediated by beta-lactamases susceptible to inhibition by clavulanic acid. This presentation should not be used to treat penicillin-resistant *S. pneumoniae*.

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

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 Fertility, Pregnancy and Lactation

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.

Clavulanic acid:

Data is not available for cefixime or combination of cefixime and clavulanic acid

4.7 Effects on Ability to Drive and Use Machines

Cefixime

None.

Clavulanic acid:

Data is not available for cefixime or combination of cefixime and clavulanic acid

4.8 Undesirable Effects

Cefixime

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

Table 1. Adverse Reactions Reported in Clinical Trials

Blood and lymphatic system disorders:	Eosinophilia Hypereosinophilia Agranulocytosis Leucopenia Neutropenia Granulocytopenia Haemolytic anaemia Thrombocytopenia Thrombocytosis
Gastrointestinal:	Abdominal pain Diarrhoea* Dyspepsia Nausea Vomiting Flatulence
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
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 eosinophilia and systemic symptoms (DRESS) Pruritus Rash Drug Fever Arthralgia Erythema multiforme 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.

*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

Clavulanic acid:

Gastro-intestinal tolerance is poorer-especially in children. Other side effects are Candida stomatitis/vaginitis and rashes. Some cases of hepatic injury have been reported with the combination.

4.9 Overdose

Cefixime

There is no experience with overdoses 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

Clavulanic acid:

Data is not available for cefixime or combination of cefixime and clavulanic acid

5. PHARMACOLOGICAL PROPERTIES

5.1 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.

Clavulanic acid:

It has a β -lactam ring but no antibacterial activity of its own. It inhibits a wide variety (class II to class V) of B-lactamases (but not class I cephalosporinase) produced by both gram-positive and gram-negative bacteria. Clavulanic acid is a 'progressive' inhibitor: binding with B-lactamase is reversible initially, but becomes covalent later-inhibition increasing with time. Called a 'suicide, inhibitor, it gets inactivated after binding to the enzyme. It permeates the outer layers of the cell wall of gram negative bacteria and inhibits the periplasmically located B-lactamase.

5.2 Pharmacokinetic Properties

Cefixime

The absolute oral bioavailability of cefixime is in the range of 22-54%. Absorption is not significantly modified by the presence of food. Cefixime may therefore be given without regard to meals.

From *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.

Transfer of ^{14}C -labelled cefixime from lactating rats to their nursing offspring through breast milk was quantitatively small (approximately 1.5% of the mothers' body content of cefixime in the pup). No data are available on secretion of cefixime in human breast milk. Placental transfer of cefixime was small in pregnant rats dosed with labelled cefixime.

Clavulanic acid:

Clavulanic acid has rapid absorption and a bioavailability of 60%; can also be injected. Its elimination half-life is 1 hr and tissue distribution matches amoxicillin. However, it is eliminated mainly by glomerular filtration and its excretion is not affected by probenecid. Also, it is largely hydrolysed and decarboxylated before excretion, while amoxicillin is primarily excreted unchanged by tubular secretion.

5.3 Preclinical Safety Data

Cefixime

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of this document.

Clavulanic acid:

Data is not available for cefixime or combination of cefixime and clavulanic acid

6. PHARMACEUTICAL PARTICULARS

6.1 Shelf-life

18 Months

6.2 Special Precautions for Storage

Store in a cool place, Protected from light

7. MARKETING BY



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