Front side

120 mm

370 mm

For the use of a Registered Medical Practitioner/ Hospital/ Laboratory Only.

Cefuroxime Axetil and Potassium Clavulanate Tablets IP

VIACFRO®- CV 500

Composition:

Each film coated tablet contains:

Cefuroxime Axetil IP

Eq. to Cefuroxime.....500 mg

Potassium Clavulanate Diluted IP

Eq. to Clavulanic Acid.....125 mg

Colour : Titanium Dioxide IP

PHARMACEUTICAL FORM

Film Coated Tablet

THERAPEUTIC INDICATION

For adult patients with infection caused by susceptible microbes, including S. aureus (e.g. urinary tract infections; upper and lower respiratory tract infections; gonococcal urethritis).

DOSAGE AND ADMINISTRATION

The dose or duration of treatment depends upon the severity of infection, clinical response, age of the patients, symptoms and bacteriological findings or as directed by the Physician.

Posology

The recommended adult dose is 1 tablet twice daily depending upon the severity of infection or clinical response or to be given in a dose and duration as directed by the Physician.

The usual course of therapy is seven days (may range from five to ten days).

Special population:

Renal impairment

The safety and efficacy of cefuroxime axetil in patients with renal failure have not been established. Cefuroxime is primarily excreted by the kidneys. In patients with markedly impaired renal function it is recommended that the dosage of cefuroxime should be reduced to compensate for its slower excretion. Cefuroxime is effectively removed by dialysis.

Hepatic impairment

There are no data available for patients with hepatic impairment. Since cefuroxime is primarily eliminated by the kidney, the presence of hepatic dysfunction is expected to have no effect on the pharmacokinetics of cefuroxime.

Method of administration: For oral administration only.

Patients should be advised to swallow the tablet as whole and must not be crushed or chewed.

CONTRAINDICATIONS

It is contraindicated in patients with known hypersensitivity to cefuroxime or clavulanic acid or any other component of this product or to other drugs in the same class, or in patients who have demonstrated anaphylactic reactions to beta-lactams or beta-lactam inhibitors.

- History of severe hypersensitivity (e.g. anaphylactic reaction) to any other type of beta-lactam antibacterial agent (penicillins, monobactams and carbapenems).

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Hypersensitivity reactions

Special care is indicated in patients who have experienced an allergic reaction to penicillins or other beta-lactam antibiotics because there is a risk of cross-sensitivity. As with all beta-lactam antibacterial agents, serious and occasionally fatal hypersensitivity reactions have been reported. In case of severe hypersensitivity reactions, treatment with cefuroxime must be discontinued immediately and adequate emergency measures must be initiated.

Before beginning treatment, it should be established whether the patient has a history of severe hypersensitivity reactions to cefuroxime, to other cephalosporins or to any other type of beta-lactam agent. Caution should be used if cefuroxime is given to patients with a history of non-severe hypersensitivity to other beta-lactam agents.

Jarisch-Herxheimer reaction

The Jarisch-Herxheimer reaction has been seen following cefuroxime axetil treatment of Lyme disease. It results directly from the bactericidal activity of cefuroxime axetil on the causative bacteria of Lyme disease, the spirochaete Borrelia burgdorferi. Patients should be reassured that this is a common and usually self-limiting consequence of antibiotic treatment of Lyme disease.

Overgrowth of non-susceptible microorganisms

As with other antibiotics, use of cefuroxime axetil may result in the overgrowth of Candida. Prolonged use may also result in the overgrowth of other non-susceptible microorganisms (e.g. enterococci and Clostridium difficile), which may require interruption of treatment.

Antibacterial agent–associated pseudomembranous colitis have been reported with nearly all antibacterial agents, including cefuroxime and may range in severity from mild to life threatening. This diagnosis should be considered in patients with diarrhoea during or subsequent to the administration of cefuroxime. Discontinuation of therapy with cefuroxime and the administration of specific treatment for Clostridium difficile should be considered. Medicinal products that inhibit peristalsis should not be given.

Interference with diagnostic tests

The development of a positive Coombs' Test associated with the use of cefuroxime may interfere with cross matching of blood.

As a false negative result may occur in the ferricyanide test, it is recommended that either the glucose oxidase or hexokinase methods are used to determine blood/plasma glucose levels in patients receiving cefuroxime axetil.

DRUG INTERACTIONS

Oral Contraceptives

Cefuroxime axetil may affect the gut flora, leading to lower estrogen reabsorption and reduced efficacy of combined oral estrogen/progesterone contraceptives. Counsel the patients to consider alternate supplementary (non-hormonal) contraceptive measures during treatment.

Drugs that Reduce Gastric Acidity

Drugs that reduce gastric acidity may result in a lower bioavailability of Cefuroxime compared with administration in the fasting state. Administration of drugs that reduce gastric acidity may negate the food effect of increased absorption of Cefuroxime when administered in the postprandial state. Administer Cefuroxime at least 1 hour before or 2 hours after administration of short-acting antacids. Histamine-2 (H2) antagonists and proton pump inhibitors should be avoided.

Probenecid

Cefuroxime is excreted by glomerular filtration and tubular secretion. Concomitant use of probenecid is not recommended. Concurrent administration of probenecid significantly increases the peak concentration, area under the serum concentration time curve and elimination half-life of cefuroxime.

Concomitant use with oral anticoagulants may give rise to increased INR.

Drug/Laboratory Test Interactions

A false-positive reaction for glucose in the urine may occur with copper reduction tests (e.g., Benedict's or Fehling's solution), but not with enzyme-based tests for glycosuria. As a false-negative result may occur in the ferricyanide test, it is recommended that either the glucose oxidase or hexokinase method be used to determine blood/plasma glucose levels in patients receiving cefuroxime axetil. The presence of cefuroxime does not interfere with the assay of serum and urine creatinine by the alkaline picrate method.

USE IN SPECIFIC POPULATION

Pregnancy

Pregnancy Category B. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, Cefuroxime should be used during pregnancy only if clearly needed. Reproduction studies have been performed in mice at doses up to 3,200 mg/kg/day (14 times the recommended maximum human dose based on body surface area) and in rats at doses up to 1,000 mg/kg/day (9 times the recommended maximum human dose based on body surface area) and have revealed no evidence of impaired fertility or harm to the fetus due to cefuroxime axetil.

There are limited data from the use of cefuroxime in pregnant women. Studies in animals have shown no harmful effects on pregnancy, embryonal or foetal development, parturition or postnatal development. Cefuroxime axetil should be prescribed to pregnant women only if the benefit outweighs the risk.

Lactation

Cefuroxime is excreted in human milk in small quantities. Adverse effects at therapeutic doses are not expected, although a risk of diarrhoea and fungus infection of the mucous membranes cannot be excluded. Breastfeeding might have to be discontinued due to these effects. The possibility of sensitisation should be taken into account. Cefuroxime should only be used during breastfeeding after benefit/risk assessment by the physician in charge.

In studies, excretion of clavulanate potassium in milk occurs to a limited extent, the concentrations being lower than those detected in the serum. Because of the potential for serious reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

The safety and effectiveness of Cefuroxime have been established for pediatric patients aged 3 months to 12 years for acute bacterial maxillary sinusitis based upon its approval in adults. Use of Cefuroxime in pediatric patients is supported by pharmacokinetic and safety data in adults and paediatric patients, and by clinical and microbiological data from adequate and well-controlled trials of the treatment of acute bacterial maxillary sinusitis in adults and of acute otitis media with effusion in pediatric patients. It is also supported by postmarketing adverse events surveillance.

Geriatric Use

Of the total number of subjects who received Cefuroxime in 20 clinical trials, 375 were aged 65 and older while 151 were aged 75 and older. No overall differences in safety or effectiveness were observed between these subjects and younger adult subjects. Reported clinical experience has not identified differences in responses between the elderly and younger adult patients, but greater sensitivity of some older individuals cannot be ruled out.

Cefuroxime is substantially excreted by the kidney, and the risk of adverse reactions may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Renal Impairment

Reducing the dosage of Cefuroxime is recommended for adult patients with severe renal impairment (creatinine clearance <30 mL/min).

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects on the ability to drive and use machines have been performed. However, as this medicine may cause dizziness, patients should be warned to be cautious when driving or operating machinery.

UNDESIRABLE EFFECTS

Fixed drug eruption (FDE) has been reported with cephalosporin class formulations.

The most common adverse reactions are Candida overgrowth, eosinophilia, headache, dizziness, gastrointestinal disturbances and transient rise in liver enzymes. The frequency categories assigned to the adverse reactions below are estimates, as for most reactions suitable data (for example from placebo-controlled studies) for calculating incidence were not available. In addition the incidence of adverse reactions associated with cefuroxime axetil may vary according to the indication.

Data from large clinical studies were used to determine the frequency of very common to rare undesirable effects. The frequencies assigned to all other undesirable effects (i.e. those occurring at <1/10,000) were mainly determined using post-marketing data and refer to a reporting rate rather than true frequency. Placebo-controlled trial data were not

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Design & Style	NA					
Size	OS: 120 (L) X 370 (H) mm F/S: 120 (L) X 23.125 (H) mm (4 Horizontal Fold as equal distance)					
Material Code	20233439					
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Printing Pantone No's	1 BLACK	2 NA	3 NA			
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	7 NA	8 NA	9 NA			
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available. Where incidences have been calculated from clinical trial data, these were based on drug-related (investigator assessed) data. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.
Treatment related adverse reactions, all grades, are listed below by MedDRA body system organ class, frequency and grade of severity. The following convention has been utilised for the classification of frequency: very common ≥1/10; common ≥1/100 to <1/10, uncommon ≥1/1,000 to < 1/100; rare ≥1/10,000 to <1/1,000; very rare < 1/10,000 and not known (cannot be estimated from the available data).
Infections and infestations: Common: Candida overgrowth. Not known: Clostridium difficile overgrowth.
Blood and lymphatic system disorders: Common: Eosinophilia. Uncommon: Positive Coombs' test, thrombocytopenia, leukopenia (sometimes profound). Not known: Haemolytic anaemia.
Immune system disorders: Not known: Drug fever, serum sickness, anaphylaxis, Jarisch-Herxheimer reaction.
Nervous system disorders: Common: Headache, dizziness.
Gastrointestinal disorders: Common: Diarrhoea, nausea, abdominal pain. Uncommon: Vomiting. Not known: Pseudomembranous colitis.
Hepatobiliary disorders: Common: Transient increases of hepatic enzyme levels. Not known: Jaundice (predominantly cholestatic), hepatitis.
Skin and subcutaneous tissue disorders: Uncommon: Skin rashes. Not known: Urticaria, pruritus, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (exanthematic necrolysis) (see Immune system disorders), angioneurotic oedema.
Description of selected adverse reactions: Cephalosporins as a class tend to be absorbed onto the surface of red cells membranes and react with antibodies directed against the drug to produce a positive Coombs' test (which can interfere with cross-matching of blood) and very rarely haemolytic anaemia. Transient rises in serum liver enzymes have been observed which are usually reversible.
Paediatric population: The safety profile for cefuroxime axetil in children is consistent with the profile in adults.
Post-marketing Experience with Cefuroxime
The following adverse reactions have been identified during post-approval use of Cefuroxime. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.
Blood and Lymphatic System Disorders: Hemolytic anemia, leukopenia, pancytopenia, and thrombocytopenia.
Gastrointestinal Disorders: Pseudomembranous colitis.
Hepatobiliary Disorders: Hepatic impairment including hepatitis and cholestasis, jaundice.
Immune System Disorders: Anaphylaxis, serum sickness-like reaction.
Investigations: Increased prothrombin time.
Nervous System Disorders: Seizure, encephalopathy.
Renal and Urinary Disorders: Renal dysfunction.
Skin and Subcutaneous Tissue Disorders: Angioedema, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, and urticaria.
Cephalosporin-Class Adverse Reactions
In addition to the adverse reactions listed above that have been observed in patients treated with cefuroxime axetil, the following adverse reactions and altered laboratory tests have been reported for cephalosporin-class antibiotics: toxic nephropathy, aplastic anemia, hemorrhage, increased BUN, increased creatinine, false-positive test for urinary glucose, increased alkaline phosphatase, neutropenia, elevated bilirubin, and agranulocytosis.
Several cephalosporins have been implicated in triggering seizures, particularly in patients with renal impairment when the dosage was not reduced. If seizures associated with drug therapy occur, the drug should be discontinued. Anticonvulsant therapy can be given if clinically indicated.

OVERDOSE
Overdose can lead to neurological sequelae including encephalopathy, convulsions and coma. Symptoms of overdose can occur if the dose is not reduced appropriately in patients with renal impairment. Serum levels of cefuroxime can be reduced by haemodialysis and peritoneal dialysis.
Clavulanic acid can be removed from the circulation by haemodialysis.

PHARMACOLOGICAL PROPERTIES
Pharmacodynamic properties
Cefuroxime/Clavulanic acid is an oral antibacterial combination consisting of the oral cephalosporin antibiotic, and the β-lactamase inhibitor, clavulanic acid.
Cefuroxime
Cefuroxime axetil is a semisynthetic, broad-spectrum cephalosporin antibiotic for oral administration. Cefuroxime inhibits bacterial cell wall synthesis following attachment to penicillin binding proteins (PBPs). This results in the interruption of cell wall (peptidoglycan) biosynthesis, which leads to bacterial cell lysis and death. Cefuroxime is bactericidal against a wide range of common pathogens, including many beta-lactamase–producing strains. It is stable to many bacterial beta-lactamases, especially plasmid-mediated enzymes that are commonly found in Enterobacteriaceae.
Clavulanic acid
Clavulanic acid is an irreversible 'suicide' inhibitor of intracellular and extracellular beta-lactamases, demonstrating concentration-dependent and competitive inhibition. Clavulanic acid is produced by the fermentation of Streptomyces clavuligerus. It is a β-lactam structurally related to the penicillins and possesses the ability to inactivate a wide variety of β-lactamases by blocking the active sites of these enzymes. Clavulanic acid is particularly active against the clinically important plasmid-mediated β-lactamases frequently responsible for transferred drug resistance to penicillins and cephalosporins.

Pharmacokinetic properties
Absorption
After oral administration cefuroxime axetil is absorbed from the gastrointestinal tract and rapidly hydrolysed in the intestinal mucosa and blood to release cefuroxime into the circulation. Optimum absorption occurs when it is administered shortly after a meal. Following administration of cefuroxime axetil tablets peak serum levels (2.9 µg/mL for a 125 mg dose, 4.4 µg/mL for a 250 mg dose; 7.7 µg/mL for a 500 mg dose and 13.6 µg/mL for a 1000 mg dose) occur approximately 2.4 hours after dosing when taken with food. The pharmacokinetics of cefuroxime is linear over the oral dosage range of 125 to 1000 mg. No accumulation of cefuroxime occurred following repeat oral doses of 250 to 500 mg.
Clavulanic acid is well absorbed after oral administration.
Distribution
Protein binding has been stated as 33 to 50% depending on the methodology used. Following a single dose of cefuroxime axetil 500 mg tablet to 12 healthy volunteers, the apparent volume of distribution was 50 L (CV%=28%). Concentrations of cefuroxime in excess of the minimum inhibitory levels for common pathogens can be achieved in the tonsilla, sinus tissues, bronchial mucosa, bone, pleural fluid, joint fluid, synovial fluid, interstitial fluid, bile, sputum and aqueous humor. Cefuroxime passes the blood-brain barrier when the meninges are inflamed.
About 25% of total plasma clavulanic acid is bound to protein. The apparent volume of distribution is around 0.2 l/kg for clavulanic acid. Well distributed after oral administration. Clavulanic acid has been shown to cross the placental barrier.
Metabolism and Excretion
Cefuroxime is not metabolised. The serum half-life is between 1 and 1.5 hours. Cefuroxime is excreted by glomerular filtration and tubular secretion. The renal clearance is in the region of 125 to 148 mL/min/1.73 m2.
Clavulanic acid is extensively metabolized in man and eliminated in urine and faeces, and as carbon dioxide in expired air. The major route of elimination for clavulanic acid is by both renal and non-renal mechanisms. Approximately 40 to 65% of the clavulanic acid is excreted unchanged in urine during the first 6 h after administration. In the case of clavulanic acid, the largest amount of drug is excreted during the first 2 hours after administration.
PK/PD relationship
For cephalosporins, the most important pharmacokinetic-pharmacodynamic index correlating with in vivo efficacy has been shown to be the percentage of the dosing interval (%T) that the unbound concentration remains above the minimum inhibitory concentration (MIC) of cefuroxime for individual target species (i.e. %T>MIC).

INCOMPATIBILITY
Not applicable.

SHELF LIFE
24 months

PACKAGING INFORMATION
6 Tablets packed in a Alu-Alu Blister, 1 Alu-Alu Blister packed in a mono carton and such 10 mono cartons packed in a outer carton along with package insert.

STORAGE INSTRUCTIONS
Store protected from light & moisture, at a temperature not exceeding 25°C.

Keep all medicines out of reach of children.

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VIA**CFRO®- CV 500**

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