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CIN NO: U24231GJ1992PLC018237

Summary of Product Characteristics (SmPC)

1. Name of the medicinal product:

Generic Name/INN Name: Cefixime and Clavulanate Potassium tablets

Trade Name: AFRIXIME CLV

Strength:

Each film coated tablet contains:

Cefixime USP (As Trihydrate) eq. to
Anhydrous Cefixime 200 mg
Potassium Clavulanate Diluted BP
Eq. to Clavulanic acid 125 mg
Colour: Titanium Dioxide BP
Excipients Q.S

2. Qualitative and Quantitative composition:

Sr. No.	Ingredients	Specification	Label Claim (mg)	Overages (%)	Qty./ Tablet (mg)	% w/w	Function
Mixing							
1	Cefixime (Trihydrate)	USP	200	0.00	200.00	30.67	Active
2	Clavulanate Potassium with Avicel in 1:1 Ratio (MCC)	BP	125	5.00	131.25	20.13	Active
3	Sodium Starch Glycollate	BP	--	0.00	262.662	40.29	Disintegrant
Lubrication							
4	Croscarmellose Sodium	BP	--	0.00	20.00	3.07	Disintegrant
5	Purified Talc	BP	--	0.00	9.245	1.42	Lubricant
6	Colloidal Anhydrous Silica	BP	--	0.00	5.598	0.86	Glidant
7	Magnesium Stearate	BP	--	0.00	11.245	1.72	Lubricant
Total weight of uncoated Tablet					640.00		
Coating							
8	Isopropyl Alcohol	BP	--	0.00	160.00	--	Solvent
9	Methylene Chloride (Dichloromethane)	BP	--	0.00	240.00	--	Solvent
10	Col. Opadry White	In-	--	0.00	12.00	1.84	Coating

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	21K58794	House					agent
Total weight of coated Tablet					652.00	100.00	

3. Pharmaceutical form:

Dosage Form: Solid oral dosage form- Tablet

Visual & Physical characteristics of the product:

White coloured, capsule shaped, biconvex, film coated tablet, having "CHCL" on one side and symbol "CHANRAI" other side of the tablet.

4. Clinical particulars

4.1. Therapeutic indications:

Cefixime-Clavulanate Potassium should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. Cefixime-Clavulanate Potassium is indicated for the treatment of:

Uncomplicated Urinary Tract Infections caused by Escherichia coli and Proteus mirabilis.

Otitis Media caused by Haemophi/us influenzae (beta-lactamase positive and negative strains), Moraxella (Branhamella) catarrha/is, (most of which are beta-lactamase positive) and S. pyogenes.

Pharyngitis and Tonsillitis, caused by S. pyogenes.

Acute Bronchitis and Acute Exacerbations of Chronic Bronchitis, caused by Streptococcus pneumoniae and Haemophilus influenzae (beta-lactamase positive and negative strains).

Uncomplicated gonorrhea (cervical/urethral), caused by Neisseria gonorrhoeae (penicillinase- and non-penicillinase- producing strains).

4.2. Posology and method of administration:

Adults and Children over 10 Years of Age

One tablet twice daily.

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

Geriatric Patients

Elderly patients may be given the same dose as recommended for adults. Renal function should be assessed, and dosage should be adjusted in severe renal impairment.

Patients with Renal Impairment

Cefixime may be administered in the presence of impaired renal function. Normal dose and schedule may be given in patients with creatinine clearances of 20 mL/min or greater. In patients whose creatinine clearance is less than 20 mL/min, it is recommended that a dose of

200 mg once daily should not be exceeded. The dose and regimen for patients who are maintained on chronic ambulatory peritoneal dialysis (CAPD) or haemodialysis should follow the same recommendation as that for patients with creatinine clearances of less than 20 mL/min.

4.3. Contraindications:
Cefixime-Clavulanate Potassium is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

4.4. Special warnings and precautions for use:
Hypersensitivity Reactions
Anaphylactic/anaphylactoid reactions (including shock and fatalities) have been reported with the use of cefixime. There is some evidence of partial cross-allergenicity between the penicillins and cephalosporins. Before therapy with cefixime is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to cephalosporins, penicillins or other drugs. If this product is to be given to penicillin-sensitive patients, caution should be exercised because cross-hypersensitivity among beta-lactam antibiotics has been clearly documented and may occur in up to 10% of patients with a history of penicillin allergy. If an allergic reaction to cefixime occurs, discontinue the drug.

Clostridium difficile-associated Diarrhoea
Clostridium difficile-associated diarrhoea (CDAD) has been reported with the use of nearly all antibacterial agents, including cefixime, and may range in severity from mild diarrhoea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon, leading to overgrowth of *C. difficile*.
C. difficile produces toxins A and B, which contribute to the development of CDAD. Hypertoxin-producing isolates of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhoea following antibacterial drug use. Careful medical history is necessary since CDAD has been reported to occur over 2 months after the administration of antibacterial agents.
If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile,* and surgical evaluation should be instituted as clinically indicated.
Dose Adjustment in Renal Impairment
The dose of cefixime should be adjusted in patients with renal impairment as well as those undergoing CAPD and haemodialysis. Patients on dialysis should be monitored carefully.

Coagulation Effects

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Cephalosporins, including cefixime, may be associated with a fall in prothrombin activity. Those at risk include patients with renal or hepatic impairment, or poor nutritional state, as well as patients receiving a protracted course of antimicrobial therapy, and patients previously stabilised on anticoagulant therapy. Prothrombin time should be monitored in patients at risk and exogenous vitamin K administered as indicated.

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.

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

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.

Development of Drug-resistant Bacteria
Prescribing cefixime in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

4.5. Interaction with other medicinal products and other forms of interaction:
The use of the following drugs is strictly contraindicated due to the potential for severe drug interaction effects:
Carbamazepine

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Elevated carbamazepine levels have been reported in postmarketing experience when cefixime is administered concomitantly. Drug monitoring may be of assistance in detecting alterations in carbamazepine plasma concentrations.

Warfarin and Anticoagulants

In common with other cephalosporins, increases in prothrombin times with or without clinical bleeding have been noted in a few patients. Care should, therefore, be taken in patients receiving anticoagulation therapy.

Effects on Laboratory Tests

A false-positive reaction for ketones in the urine may occur with tests using nitroprusside, but not with those using nitroferricyanide.

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 Coomb's test has been reported during treatment with other cephalosporins; therefore, it should be recognised that a positive Coomb's test may be due to the drug.

4.6. Pregnancy and lactation:

Pregnancy

Pregnancy Category B

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.

Lactating Women

It is not known whether cefixime is excreted in human milk. Consideration should be given to discontinuing nursing temporarily during treatment with this drug.

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:

The most frequent adverse reactions seen with Cefixime-Clavulanate Potassium are diarrhoea and stool changes. Events like nausea/vomiting, transient elevation in livertransaminases, alkaline phosphatase and jaundice can also occur.

Thrombocytosis, thrombocytopenia, leucopenia, hypereosinophilia, neutropenia and agranulocytosis may also occur.

Other adverse events that may occur are abdominal pain, abdominal cramps, flatulence, indigestion, headache, vaginitis, vulvar itch, rash, hives, itch, dysuria, chills, chest pain, shortness of breath, mouth ulcers, swollen tongue, sleepiness, thirst, anorexia.

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Rare but very serious adverse reactions of cefixime includes: yellowing eyes/skin, dark urine, unusual tiredness, new signs of infection (e.g., persistent sore throat, fever), easy bruising/bleeding, change in the amount of urine, mental/mood changes (such as confusion).This medication may rarely cause a severe intestinal condition (Clostridium difficile-associated diarrhea) due to a resistant bacteria. This condition may occur weeks to months after treatment has stopped. Following side effects may develop: persistent diarrhea, abdominal or stomach pain/cramping, or blood/mucus in your stool.
Use of this medication for prolonged or repeated periods may result in oral thrush or a new vaginal yeast infection (oral or vaginal fungal infection).
Symptoms of a serious allergic reaction may include: rash, itching/swelling (especially of the face/tongue/throat), severe dizziness, trouble breathing.

4.9 Overdose

There is no experience with overdoses with cefixime. Gastric lavage may be indicated; otherwise, no specific antidote exists. Cefixime is not removed in significant quantities from the circulation by haemodialysis or peritoneal dialysis. Adverse reactions in small numbers of healthy adult volunteers receiving single doses up to 2 g of cefixime did not differ from the profile seen in patients treated at the recommended doses.

5. Pharmacological properties:

5.1. Pharmacodynamic properties:

Pharmacotherapeutic group: third generation cephalosporin, ATC code: J01DD08

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

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Resistance
Resistance to cefixime in isolates of *Haemophilus influenzae* and *Neisseria gonorrhoeae* is most often associated with alterations in penicillin-binding proteins (PBPs). Cefixime may have limited activity against Enterobacteriaceae-producing extended-spectrum beta-lactamases (ESBLs). *Pseudomonas* species, *Enterococcus* species, strains of Group D streptococci, *Listeria monocytogenes,* most strains of staphylococci (including methicillin-resistant strains), most strains of *Enterobacter* species, most strains of *Bacteroides fragilis,* and most strains of *Clostridium* species are resistant to cefixime.

5.2. Pharmacokinetic properties:
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 was evaluated in healthy elderly (age >64 years) and young volunteers (age 11–35 years) by comparing 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.

5.3 Preclinical safety data
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

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micronucleus test. In rats, fertility and reproductive performance were not affected by cefixime at doses up to 25 times the adult therapeutic dose.

6. Pharmaceutical particulars:

6.1. List of Excipients:

Excipients name

Sodium Starch Glycollate
Croscarmellose Sodium
Purified Talc
Colloidal Anhydrous Silica
Magnesium Stearate
Isopropyl Alcohol
Methylene Chloride (Dichloromethane)
Col. Opadry White 21K58794

6.2. Incompatibilities:

Not applicable.

6.3. Shelf life: 24 months

6.4. Special precautions for storage:

Store below 30°C. Protect from light & moisture.

6.5. Nature and contents of container:

1×10 Tablets in Alu-Alu blister pack. Such one blister packed in one monocarton along with pack insert.

6.6. Special precautions for disposal:

No special requirements.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. Applicant:

M/S CHANRAI HEALTH CARE LIMITED
122-132, Oshodi Apapa Expressway,
Isolo, Lagos,
Nigeria

Name and Address of manufacturer:

M/s. Bharat Parenterals Limited
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AFRIXIME CLV - SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

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