1. NAME OF THE MEDICINAL PRODUCT

AKELOX- Cefpodoxime & Potassium Clavulanate Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains

Potassium Clavulanate Diluted BP

Eq.to. Clavulanic Acid…….125 mg

Cefpodoxime Proxetil BP

Eq.to. Cefpodoxime……200 mg

Excipients……q.s.

Colour- Titanium Dioxide BP

3. PHARMACEUTICAL FORM

Film coated tablets

An off white coloured, oblong shaped, biconvex, film coated tablet, plain on both sides.

4. Clinical particulars

4.1 Therapeutic indications

It is a medication that contains two medicines: Cefpodoxime Proxetil (cephalosporin antibiotic) and Potassium Clavulanate (beta-lactamase inhibitors). The medication is indicated if suffering from respiratory tract infections even if they have developed resistance.

4.2 Posology and method of administration

This may be continued for up to 14 days if required. Adults and Children over 10 Years: The recommended adult dosage is 200-400 mg daily according to the severity of infection, given either as a single dose or in two divided doses The Elderly: 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 (See "Dosage in Renal Impairment").

Children weighing more than 50 kg or older than 10 years should be treated with the recommended adult dose (200 - 400 mg daily depending on the severity of infection).

The safety and efficacy of Cefpodoxime has not been established in children less than 6 months.

Dosage in Renal Impairment: Cefpodoxime with potassium Clavulanate Tablets 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 or haemodialysis should follow the same recommendation as that for patients with creatinine clearances of less than 20 ml/min.

4.3 Contraindications

• Hypersensitivity to the active substances, to any of the Cephalosporin or to any of the excipients.

• History of a severe immediate hypersensitivity reaction (e.g. anaphylaxis) to another beta-lactam agent (e.g. cephalosporin, carbapenem or monobactam).

4.4 Special warnings and precautions for use

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 Cefpodoxime. When severe cutaneous adverse reactions occur, Cefpodoxime should be discontinued and appropriate therapy and/or measures should betaken.

Cefpodoxime with potassium Clavulanate Tablets should be given with caution to patients who have shown hypersensitivity to other drugs.

Hypersensitivity to penicillins

As with other cephalosporins, Cefpodoxime 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 Cefpodoxime with potassium Clavulanate Tablets, 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 Cefpodoxime) –associated haemolytic anaemia has also been reported.

Renal failure acute

As with other cephalosporins, Cefpodoxime may cause acute renal failure including tubulointerstitial nephritis as an underlying pathological condition. When acute renal failure occurs, Cefpodoxime should be discontinued and appropriate therapy and/or measures should be taken.

Renal impairment

Cefpodoxime with potassium Clavulanate Tablets should be administered with caution in patients with markedly impaired renal function.

Paediatric use

Safety of Cefpodoxime 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

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.

Cefpodoxime should be administered with caution to patients receiving coumarin-type anticoagulants, e.g. warfarin potassium. Since Cefpodoxime may enhance effects of the anticoagulants, prolonged prothrombin time with or without bleeding may occur.

4.5 Interaction with other medicinal products and other forms of interaction

Carbamazepine: Elevated carbamazepine levels have been reported when Cefpodoxime is administered concomitantly.

Warfarin and Anticoagulants: Increased prothrombin time, with or without clinical bleeding, has been reported when Cefpodoxime is administered concomitantly.

Oral Contraceptives: Cefpodoxime may interfere with the effectiveness of birth control pills.

Glucose Test: A false positive reaction for glucose in the urine may occur with Benedict's or Fehling's solutions or with copper sulphate test tablets.

Coombs test: A false positive direct Coombs test has been reported during treatment with cephalosporin antibiotics

4.6 Pregnancy and Lactation

There are no adequate and well-controlled studies in pregnant women. The combination 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

None

4.8 Undesirable effects

Cefpodoxime and Clavulanate Potassium Tablets are generally well tolerated. The majority of adverse reactions observed in clinical trials were mild and self-limiting in nature.

Gastrointestinal Disturbances: The most frequent side effects seen with are diarrhoea and stool changes; 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. Cefpodoxime and Clavulanate Potassium Tablets should

be discontinued if marked diarrhoea occurs. Other gastrointestinal side effects seen less frequently are nausea, abdominal pain, dyspepsia, vomiting and flatulence. Pseudo membranous colitis has been reported.

Central Nervous System: Headache and dizziness

Hypersensitivity Reactions: Allergies in the form of rash, pruritus, drug fever and arthralgia have been observed, including rare cases of urticaria or angioedema. These reactions usually subsided upon discontinuation of therapy. Rarely, erythema multiform, Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported.

Haematological and Clinical Chemistry: Thrombocytosis, thrombocytopenia, leucopenia, hyper eosinophilia, neutropenia and agranulocytosis have been reported. These reactions were infrequent and reversible. Mild transient changes in liver and renal function tests have been observed.

Hepatic Disorders: Transient rises in liver transaminase, alkaline phosphates and jaundice can also occur.

Miscellaneous: Other possible reactions include genital pruritus and vaginitis.

4.9 Overdose

Adverse reactions seen at dose levels up to 2 g in normal subjects did not differ from the profile seen in patients treated at the recommended doses. Gastric lavage may be indicated in over dosage. No specific antidote exists. Cefpodoxime is not removed from the circulation in significant quantities by dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

Cefpodoxime Proxetil

Pharmacotherapeutic group: β-lactam antibiotic, 3rd generation cephalosporines,

ATC code: J01DD 13

Mechanism of action

Like other beta-lactam drugs, cefpodoxime exerts antibacterial activity by binding to and inhibiting the action of certain bacterial cell wall synthetic enzymes, namely the penicillin binding proteins. This results in the interruption of cell wall (peptidoglycan) biosynthesis, which leads to bacterial cell lysis and death.

Diluted potassium Clavulanate

Clavulanic acid has poor intrinsic antimicrobial activity and is effective primarily as a 'suicide' inhibitor of β-lactamases containing a nucleophilic serine residue at their active sites. Mass spectrometry studies with the TEM-2β- lactamases suggest a mechanism for the reaction of clavulanate which involves acylation at Ser-70. Subsequent decarboxylation is followed either by cross-linking with Ser-130 to form a vinyl ether or by reformation of unmodified enzyme via a Ser-70 linked aldehyde. However, subinihibitory concentrations of clavulanate alone to cause changes in the composition of the bacterial cell wall which appear to be the consequence of suppressed D,Dcarboxypeptidase activity. Clavulanic acid is active mainly against plasmid-mediated penicillinases and has no useful activity against chromosomal cephalosporinases. It does, however, have some effect against chromosomal penicillinase and against chromosomal cephalosporinases.

5.2 Pharmacokinetic properties

Cefpodoxime Proxetil

Cefpodoxime proxetil is taken up in the intestine and is hydrolysed to the active metabolite cefpodoxime. When cefpodoxime proxetil is administered orally to fasting subjects as a tablet corresponding to 100 mg of cefpodoxime, 51.1% is absorbed and absorption is increased by food intake. The volume of distribution is 32.3 l and peak levels of cefpodoxime occur 2 to 3 hours after dosing. The maximum plasma concentration is 1.2 mg/l and 2.5 mg/l after doses of 100 mg and 200 mg respectively. Following administration of 100 mg and 200 mg twice daily over 14.5 days, the plasma pharmacokinetic parameters of cefpodoxime remain unchanged.

Serum protein binding of cefpodoxime, 40% principally to albumin. This binding is non-saturable in type.

Concentrations of cefpodoxime in excess of the minimum inhibitory levels (MIC) for common pathogens can be achieved in lung parenchyma, bronchial mucosa, pleural fluid, tonsils, interstitial fluid and prostate tissue.

Diluted potassium Clavulanate

Absorption: Clavulanic acid, are fully dissociated in aqueous solution at physiological pH. Both components are rapidly and well absorbed by the oral route of administration.

Absorption of clavulanic acid is optimised when taken at the start of a meal. Following oral administration, clavulanic acid are approximately 70% bioavailable. The plasma profiles of both components are similar and the time to peak plasma concentration (T max) in each case is approximately one hour

Distribution: The apparent volume of distribution is around 0.3-0.4 l/kg for amoxicillin and around 0.2 l/kg for clavulanic acid.

Biotransformation: Clavulanic acid is extensively metabolized in man and eliminated in urine and faeces and as carbon dioxide in expired air.

Elimination: Clavulanic acid it is by both renal and non-renal mechanisms. Clavulanic acid has a mean elimination half-life of approximately one hour and a mean total clearance of approximately 25 l/h in healthy subjects.

5.3 Preclinical safety data

No additional pre-clinical data of relevance to the prescriber is available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Croscarmellose Sodium, Colloidal Anhydrous silica, Magnesium Stearate, Talcum, Microcrystalline cellulose, Coloreazy Coat, Isopropyl Alcohol, Methylene Dichloride

6.2 Incompatibilities

None stated.

6.3 Shelf life

18 months

6.4 Special precautions for storage

Protect from light.

Store below temperature at below 30°C.

6.5 Nature and contents of container

10 tablets in Aluminium- Aluminium blister strip ack. Such 1 blister strips are packed in a monocarton with an insert

6.6 Special precautions for disposal

None stated.

7. <APPLICANT/MANUFACTURER>

AKESTAR PHARMACEUTICAL LTD

House 4, Cliford O. Avenue, Plot 656, Arab Road, Kubwa, Kubwa, FCT, Abuja, Nigeria
CENTURION REMEDIES PVT. LTD., PLOT NO. G/5-6 B.I.D.C, GORWA, VADODARA-390016, GUJARAT, INDIA

8. Marketing Authorization Number

Not Applicable

9. Date of First Authorization /Renewal of the Authorization

Not Applicable

10. Date of Revision of the Text

Not Applicable