National Agency for Food & Drug Administration & Control (NAFDAC)

Registration & Regulatory Affairs (R & R) Directorate

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC) TEMPLATE

1. NAME OF THE MEDICINAL PRODUCT

KALCEP-200 mg dispersible tablets

2. QUALITATIVE AND QUANTITATIVECOMPOSITION

Each uncoated dispersible tablet contains:

Cefpodoxime Proxetil USP

Equivalent to Cefpodoxime: 200 mg

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Off white oval shaped uncoated tablet with break line on one side.

4. Clinical particulars

4.1 Therapeutic indications

KALCEP-200 tablets are indicated for the treatment of:

• Upper respiratory tract infections

- Acute bacterial sinusitis

- Tonsillitis

• Lower respiratory tract infections

- Bacterial pneumonia

- Cefpodoxime might not be suitable option depending on the pathogen involved. Consideration should be given to the official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

The tablets should be taken with food for optimum absorption.

Adults and adolescents with normal renal function:

Upper respiratory tract infections: Acute bacterial sinusitis: 200 mg twice daily.
Tonsillitis: 100 mg twice daily.
Lower respiratory tract infections:
Acute exacerbation of chronic bronchitis: 200mg twice daily
Bacterial pneumonia: 200mg twice daily

Elderly:
It is not necessary to modify the dose in elderly patients with normal renal function.

Children:
Pediatric formulation of cefpodoxime is available for infants and children.

Hepatic Impairment:
The dosage does not require modification in cases of hepatic impairment.

Renal Impairment:
The dosage of cefpodoxime does not require modification if creatinine clearance exceeds 40 ml/min. Below this value, pharmacokinetic studies indicate an increase in plasma elimination half-life and the maximum plasma concentrations, and hence the dosage should be adjusted appropriately.

CREATININE CLEARANCE (ml/min)
39-10 : Single dose administered every 24 hours instead of twice a day (i.e half of the usual adult dose).
<10 : Single dose administered every 48 hours (i.e quarter of the usual adult dose).
Haemodialysis Patients: Single dose administered after each dialysis session 1.

Method of administration: Oral

4.3 Contraindications
KALCEP-200 is contra-indicated in:
• Hypersensitivity to cefpodoxime, any other cephalosporins or to any of the excipients.
• Previous history of immediate and or severe hypersensitivity reaction (anaphylaxis) to penicillin or other betalactam antibiotic.

4.4 Special warnings and precautions for use
- Cefpodoxime is not a preferred antibiotic for the treatment of staphylococcal pneumonia and should not be used in the treatment of atypical pneumonia caused by organisms such as Legionella, Mycoplasma and Chlamydia. Cefpodoxime is not recommended for the treatment of pneumonia due to S. pneumonia.
- As with all beta-lactam antibacterial agents, serious and occasionally fatal hypersensitivity reactions have been reported. In case of severe hypersensitivity reactions, treatment with cefpodoxime 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 cefpodoxime, to other cephalosporins or to any other type of beta-lactam agent. Caution should be used if cefpodoxime is given to patients with a history of non-severe hypersensitivity to other beta-lactam agents.
- In cases of severe renal insufficiency it may be necessary to reduce the dosage regimen dependent on the creatinine Clearance.

4.5 Interaction with other medicinal products and other forms of interaction

- No clinically significant drug interactions have been reported during the course of clinical studies.
- Histamine H -antagonists and antacids reduce the bioavailability of cefpodoxime. Probenecid reduces the excretion of cephalosporins. Cephalosporins potentially enhance the anticoagulant effect of coumarins and reduce the contraceptive effect of oestrogens.
- Oral anticoagulants: Simultaneous administration of cefpodoxime with warfarin may augment its anti-coagulant effects. There have been many reports of increases in oral anti-coagulant activity in patients receiving antibacterial agents, including cephalosporins. The risk may vary with the underlying infection, age and general status of the patient so that the contribution of the cephalosporins to the increase in INR (international normalised ratio) is difficult to assess. It is recommended that the INR should be monitored frequently during and shortly after coadministration of cefpodoxime with an oral anti-coagulant agent. Studies have shown that bioavailability is decreased by approximately 30% when cefpodoxime is administered with drugs which neutralise gastric pH or inhibit acid secretions. Therefore, such drugs as antacids of the mineral type and H blockers such as ranitidine, which can cause an increase in gastric pH, should be taken 2 to 3 hours after Cefpodoxime administration.

4.6 Pregnancy and Lactation

Pregnancy:
There are no or limited amount of data from the use of cefpodoxime in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. Due to the benefit of antibiotic treatment, the use of cefpodoxime may be considered during pregnancy if necessary. Caution should be exercised when prescribing to pregnant women.

Lactation:
Cefpodoxime is excreted in breast milk in small amounts. Cefpodoxime may be used during breast-

feeding. Continuation of breast-feeding should be questioned in case of diarrhoea or mucosal fungus infection in the Breast fed infant. The possibility of sensitisation should be borne in mind.

Fertility: No data available

4.7 Effects on ability to drive and use machines

Attention should be drawn to the risk of dizzy sensations.

4.8 Undesirable effects

Adverse drug reactions are listed below by system organ class and frequency. Frequencies are defined as:
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), not known (cannot be estimated from the available data)

Blood and lymphatic system disorders
Rare: Haematological disorders such as reduction in haemoglobin, thrombocytosis, thrombocytopenia,
leucopenia and eosinophilia.
Very rare: Haemolytic anaemia.
Nervous system disorders
Uncommon: Headache, paraesthesia, dizziness
Ear and labyrinth disorders
Uncommon: Tinnitus
Gastrointestinal disorders
Common: Gastric pressure, nausea, vomiting, abdominal pain, flatulence, diarrhoea.
Bloody diarrhoea can occur as a symptom of enterocolitis.
The possibility of pseudomembranous enterocolitis should be considered if severe or persistent diarrhoea occurs during or after treatment.
Metabolism and nutrition disorders
Common: Loss of appetite
Immune system disorders
Hypersensitivity reactions of all degrees of severity have been observed.
Very rare: anaphylactic reactions, bronchospasm, purpura and angioedema.
Renal and urinary disorders
Very rare: Slight increases in blood urea and creatinine
Hepato-biliary disorders
Rare: Transient moderate elevations of ASAT, ALAT and alkaline phosphatase and/or bilirubin. These laboratory abnormalities which may be explained by the infection,
may rarely exceed twice the upper limit of the named range and elicit a pattern of liver injury, usually cholestatic and most often asymptomatic.
Very rare: liver damage
Skin and subcutaneous tissue disorders
Uncommon: Hypersensitivity mucocutaneous reactions, rash, urticaria, pruritus
Very rare: Stevens- Johnson syndrome, toxic epidermal necrolysis and erythema multiforme
Infections and infestations
There can be multiplication of non-sensitive micro-organisms (see section 4.4)

4.9 Overdose

In the event of overdosage with cefpodoxime, supportive and symptomatic therapy is indicated.
In cases of overdosage, particularly in patients with renal insufficiency, encephalopathy may occur. The encephalopathy is usually reversible once cefpodoxime plasma levels have fallen.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

Pharmacotherapeutic group: Beta-lactam antibacterial, a 3rd generation cephalosporin.
ATC Code: J01DD13

Mechanism of Action:
Cefpodoxime 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.

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 that the unbound concentration remains above the minimum inhibitory concentration (MIC) of cefpodoxime for individual target species (i.e. %T>MIC).

Mechanism(s) of resistance:
Resistance to cephalosporins results from a variety of mechanisms:
1) alteration of the cell-wall permeability of gram-negative bacteria.
2) alteration of the penicillin binding proteins (PBPs)
3) β-lactamase production
4) bacterial efflux pumps

Break points:
European Committee on Antimicrobial Susceptibility Testing (EUCAST) clinical breakpoints for MIC testing is presented below. EUCAST clinical MIC breakpoints for cefpodoxime (2011-01-05, v 1.3)

Organism	Susceptible (S) (mg/l)	Resistant (R) (mg/l)
Enterobacteriaceae (uncomplicated UTI only)	≤ 1	>1
Staphylococcus spp.	Note[1]	Note[1]
Streptococcus groups A, B, C and G	Note[2]	Note[2]
Streptococcus pneumonia	≤ 0.25	>0.5
Haemophilus influenza	≤ 0.25 Note[3]	>0.5
Moraxella catarrhalis	≤ 0.25 Note[3]	>0.5
Neisseria gonorrhoeae	IE	IE
Non-species related breakpoint	IE	IE

1. Susceptibility of staphylococci to cephalosporins is inferred from the cefoxitin susceptibility.
2. The beta-lactam susceptibility of beta-haemolytic streptococcus groups A, B, C and G is inferred from the penicillin susceptibility.
3. Strains with MIC values above the susceptible breakpoint are very rare or not yet reported. The identification and antimicrobial susceptibility tests on any such isolate must be repeated and if the result is confirmed the isolate must be sent to a reference laboratory.
*Insufficient evidence

5.2 Pharmacokinetic properties

Absorption and Bioavailability: Cefpodoxime 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, 51.5% is absorbed and absorption is increased by food intake.

Distribution: The volume of distribution is 32.3 L and peak levels of cefpodoxime occur 2 to 3 hrs 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.

Metabolism & Elimination: As the majority of cefpodoxime is eliminated in the urine, the concentration is high. (Concentrations in 0-4, 4-8, 8-12 hr fractions after a single dose exceed MIC90 of common urinary pathogens). Good diffusion of cefpodoxime is also seen into renal tissue, with concentrations above MIC90 of the common urinary pathogens, 3-12 hrs after an administration of a single 200 mg dose (1.6-3.1µg/g). Concentrations of cefpodoxime in the medullary and cortical tissues is similar.

Special Population: Studies in healthy volunteers show median concentrations of cefpodoxime in the total ejaculate 6-12 hrs following administration of a single 200 mg dose to be above the MIC90 of N. gonorrhoeae. The main route of excretion is renal, 80% is excreted unchanged in the urine, with an elimination half-life of approx 2.4 hours.

5.3 Preclinical safety data

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Beta Cyclodextrin	USP
Lactose	BP
Mannitol	BP
Soluble Starch	BP
Sodium chloride	BP
Sodium Lauryl Sulphate	BP
Magnesium Stearate	BP
Purified Talc	BP
Colloidal anhydrous Silica	BP
Polacrilin Potassium (Kyron T 314)	USP-NF
Flavour Pineapple Dry	IHS
Aspartame	BP
Sodium benzoate	BP

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Do not store above 30°C.
KEEP OUT OF REACH OF CHILDREN

6.5 Nature and contents of container<and special equipment for use, administration or implantation>

1 X 10 Tablets Alu-Alu is packed in a carton with package insert.

6.6 Special precautions for disposal <and other handling>

No special requirements.

7. APPLICANT/MANUFACTURER

SAGA
LIFESCIENCES LIMITED

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