# Summary of Product Characteristics

## 1. Name of The Medicinal Product

Cefuroxime-Clavulanic Acid 250 Tablet (Film coated)

## 2. Qualitative and Quantitative Composition

Each film coated tablet contains Cefuroxime Axetil USP equivalent to Cefuroxime 250 mg & Diluted Potassium Clavulanate BP equivalent to Clavulanic Acid 62.50 mg.

For the full list of excipients, See Section 6.1

## 3. Pharmaceutical Form

Film-coated tablet (tablet)

## 4. Clinical Particulars

### 4.1 Therapeutic indications

Cefuroxime-Clavulanic Acid is indicated for the treatment of patients with mild to moderate infections caused by susceptible strains of the designated microorganisms in the conditions listed below:

- Pharyngitis/tonsillitis
- Acute bacterial otitis media
- Acute bacterial maxillary sinusitis
- Acute bacterial exacerbations of chronic bronchitis and secondary bacterial infections of acute bronchitis
- Uncomplicated skin and skin-structure infections
- Uncomplicated urinary tract infections
- Uncomplicated gonorrhea (urethral and endocervical)
- Early lyme disease (erythema migrans)

## 4.2 Posology and method of administration

Posology

**Adolescents and Adults (13 years and older):** For pharyngitis/tonsillitis, the recommended dosage is 250 mg twice daily for 5–10 days. For acute bacterial maxillary sinusitis, 250 mg twice daily is administered for 10 days. For acute bacterial exacerbations of chronic bronchitis, the recommended dosage is 250–500 mg twice daily for 10 days. For secondary bacterial infections of acute bronchitis, 250–500 mg twice daily is administered for 5–10 days. For uncomplicated skin and skin-structure infections, the recommended dosage is 250–500 mg twice daily for 10 days. For uncomplicated urinary tract infections, 250 mg twice daily is administered for 7–10 days. For uncomplicated gonorrhea, a dose of 1000 mg is administered as a single dose. For community-acquired pneumonia, the recommended dosage is 250–500 mg twice daily for 5–10 days. For MDR typhoid fever, 500 mg twice daily is administered for 10–14 days. For Lyme disease, the recommended dosage is 500 mg twice daily for 20 days.

**Pediatric Patients (3 months to 12 years):** For pharyngitis/tonsillitis, the recommended dosage is 20 mg/kg/day administered in two divided doses for 5–10 days. For acute otitis media, 30 mg/kg/day is administered in two divided doses for 10 days. For acute bacterial maxillary sinusitis, 30 mg/kg/day is administered in two divided doses for 10 days. For uncomplicated skin and skin-structure infections, the recommended dosage is 30 mg/kg/day administered in two divided doses for 10 days. For community-acquired pneumonia, 30 mg/kg/day is administered in two divided doses for 5–10 days. For MDR typhoid fever, 30 mg/kg/day is administered in two divided doses for 10–14 days. For uncomplicated urinary tract infections, 20 mg/kg/day is administered in two divided doses for 7–10 days.

**Method of Administration:** The tablets may be administered without regard to meals.

## 4.3 Contraindications

Cefuroxime-Clavulanic Acid is contraindicated in patients with known allergy to cephalosporin & in patients with *Pseudomembranous Colitis*.

## 4.4. Special warnings and precautions for use

- Tablets are not bioequivalent and are therefore not substitutable on a milligram-per-milligram basis
- Before therapy with Cefuroxime-Clavulanic Acid is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to cephalosporins, penicillins or

other drugs.

- Because Cefuroxime is excreted in human milk, consideration should be given to discontinuing nursing temporarily during treatment with cefuroxime.
- Prescribing Cefuroxime-Clavulanic Acid in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.
- Cephalosporins, including Cefuroxime, should be given with caution to patients receiving concurrent treatment with potent diuretics because these diuretics are suspected of adversely affecting renal function.
- Cefuroxime, as with other broad-spectrum antibiotics, should be prescribed with caution in individuals with a history of colitis.

## 4.5. Interaction with other medicinal products and other forms of interaction

**Probenecid:** Concomitant administration of probenecid with Cefuroxime axetil tablets increases the area under the serum concentration versus time curve by 50%. The peak serum Cefuroxime concentration after a 1.5-g single dose is greater when taken with 1 g of probenecid (mean = 14.8 mcg/mL) than without probenecid (mean = 12.2 mcg/mL).

**Antacids:** Drugs that reduce gastric acidity may result in a lower bioavailability of Cefuroxime - Clavulanic Acid compared with that of fasting state and tend to cancel the effect of postprandial absorption.

**Oral contraceptives:** In common with other antibiotics, cefuroxime axetil may affect the gut flora, leading to lower estrogen reabsorption and reduced efficacy of combined oral estrogen/progesterone.

## 4.6 Fertility, pregnancy and lactation

**Pregnancy**

While all antibiotics should be avoided in the first trimester if possible. However, Cefuroxime-Clavulanic Acid can be safely used in later pregnancy to treat urinary and other infections.

**Lactation**

Cefuroxime-Clavulanic Acid is excreted into the breast milk in small quantities. However, the possibility of sensitizing the infant should be kept in mind.

**Fertility**
No studies on the effect on human fertility have been conducted for Cefuroxime-Clavulanic Acid.

### 4.7 Effects on ability to drive and use machines

Data is not available

### 4.8 Undesirable effects

Adverse reactions to cefuroxime axetil have been generally mild and transient in nature. The following adverse reactions to cefuroxime axetil have been reported. However, the possibility of the occurrence of other adverse reactions, seen with the cephalosporin class of antibiotics, should be borne in mind.

4.8.1 Major adverse reactions which may occur are diarrhea/loose motions, nausea/vomiting, transient elevation in AST, ALT, LDH, Eosinophilia.

4.8.2 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.

**Reporting of suspected adverse reactions**
Healthcare professional are requested to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Reporting System (PvERS) https://pv.pharmacyboardkenya.org.

### 4.9 Overdose

There is no experience with overdose.

## 5. Pharmacological Properties

### 5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Antimicrobial agent & Beta lactamase Inhibitor
ATC code: J01DC02 (WHO) S01AA27 (WHO) QJ51DC02 (WHO); Clavulanic Acid: J01CR (WHO)

Mechanism of action

Cefuroxime has bactericidal activity against a wide range of common

pathogens, including beta-lactamase producing strains. The bactericidal action of cefuroxime results from inhibition of cell wall synthesis by binding to essential target proteins. Cefuroxime has good stability to bacterial beta-lactamases.

Clavulanic acid is a naturally derived beta lactamase inhibitor produced by Streptomyces clavuligerus. Clavulanic acid binds to and inactivates them thus preventing the destruction of cefuroxime that is a substrate for this enzyme. It has poor intrinsic antimicrobial activity, but it is an irreversible binder of ß-lactamases produced by a wide range of gram positive and gram negative microorganism.

**Rationale for combination:** Although Clavulanic acid does have some degree of bacterial activity, its principal role is as a beta-lactamase inhibitor. Beta-lactam antibiotics, such as the

penicillins and cephalosporins, act by disrupting the development of bacterial cells walls thus causing the disintegration of the bacteria. However, some bacteria acquire the genes to produce enzymes which inactivate this mode of action - so called beta-lactamases - drastically reducing the efficacy of this class of antibiotics.

Clavulanic acid has a similar structure to the beta-lactam antibiotics but binds irreversibly to the beta-lactamase enzymes. Used in combination with the beta-lactam antibiotics, it has become one of the most prescribed antibiotics prolonging the effective life of antibiotics. Thus, the combination of cefuroxime and clavulanic acid (ß -lactamase inhibitor) provides a solution for treatment of bacterial infections caused by beta lactam resistant pathogens.

<u>Clinical efficacy and safety</u>

Early Lyme disease:
Two adequate and well-controlled studies were performed in patients with early Lyme disease. In these studies all patients had to present with physician-documented erythema migrans, with or without systemic manifestations of infection. Patients were randomized in a 1:1 ratio to a 20-day course of treatment with cefuroxime axetil 500 mg twice daily or doxycycline 100 mg 3 times daily. Patients were assessed at 1 month posttreatment for success in treating early Lyme disease (Part I) and at 1 year post treatment for success in preventing the progression to the sequelae of late Lyme disease (Part II).

A total of 355 adult patients (181 treated with cefuroxime axetil and 174 treated with doxycycline) were enrolled in the 2 studies. In order to

objectively validate the clinical diagnosis of early Lyme disease in these patients, 2 approaches were used: 1) blinded expert reading of photographs, when available, of the pretreatment erythema migrans skin lesion; and 2) serologic confirmation (using enzyme-linked immunosorbent assay [ELISA] and immunoblot assay ["Western" blot]) of the presence of antibodies specific to Borrelia burgdorferi, the etiologic agent of Lyme disease. By these procedures, it was possible to confirm the physician diagnosis of early Lyme disease in 281 (79%) of the 355 study patients. The efficacy data summarized below are specific to this "validated" patient subset, while the safety data summarized below reflect the entire patient population for the 2 studies.

Secondary Bacterial Infections of Acute Bronchitis:
Four randomized, controlled clinical studies were performed comparing 5 days versus 10 days of CEFUROXIME-CLAV for the treatment of patients with secondary bacterial infections of acute bronchitis. These studies enrolled a total of 1,253 patients (CAE-516 n = 360; CAE-517 n = 177; CAEA4001 n = 362; CAEA4002 n = 354). The protocols for CAE-516 and CAE-517 were identical and compared CEFUROXIME-CLAV 250 mg twice daily for 5 days, CEFUROXIME-CLAV 250 mg twice daily for 10 days, and AUGMENTIN® 500 mg 3 times daily for 10 days. These 2 studies were conducted simultaneously. CAEA4001 and CAEA4002 compared CEFUROXIME-CLAV 250 mg twice daily for 5 days, CEFUROXIME-CLAV 250 mg twice daily for 10 days, and CECLOR® 250 mg 3 times daily for 10 days. They were otherwise identical to CAE-516 and CAE-517 and were conducted over the following 2 years. Patients were required to have polymorphonuclear cells present on the Gram stain of their screening sputum specimen, but isolation of a bacterial pathogen from the sputum culture was not required for inclusion.

## 5.2 Pharmacokinetic Properties

After oral administration cefuroxime axetil is absorbed from the gastrointestinal tract and rapidly hydrolysed in the body to release cefuroxime into the circulation. Approximately 60% of an administered dose is absorbed. Optimum absorption occurs when it is administered after a light meal. Absorption is not decreased by drugs which affect gastrointestinal motility e.g. loperamide, diphenoxylate or castor oil. However, absorption is decreased by concurrent administration of drugs such as ranitidine.

The mean peak serum level of cefuroxime following a 250 mg dose in

normal healthy adults, after food, was 4.1 mg/L and occurred two to three hours after dosing. Serum levels were significantly higher in the elderly, apparently due to slower excretion. Unhydrolysed drug was not detected in the serum but 1-2% of the administered dose is excreted in the urine in a form which indicates that small amounts of the intact ester are absorbed into circulation. The mean serum half life of cefuroxime is approximately 1.2 hours. Protein binding has been variously stated as 33-50% depending on the methodology used. Cefuroxime is not metabolized to any significant extent.

Excretion occurs mainly through the kidney both by glomerular filtration and tubular secretion. Approximately 49% of an administered dose, after food, is recovered in the urine in 24 hours; urinary recovery is significantly reduced if the drug is taken on an empty stomach.

After 250 mg dose urinary concentrations at 0-6 and 6-12 hours were 227 mcg/mL (range 92-
515) and 35.3 mcg/mL (range 7.6-102) respectively.

Concurrent administration of probenecid prolongs the terminal half life of cefuroxime. Serum levels of cefuroxime are reduced by haemodialysis.

### 5.3 Preclinical safety data

No data has been yet available

## 6. Pharmaceutical Particulars

### 6.1 List of excipients Core tablet

- Microcrystalline Cellulose (Avicel PH 112) BP
- Crospovidone USP NF
- Colloidal Anhydrous Silica (Aerocil-200) BP
- Magnesium Stearate BP

Coated Tablet

- Opadry White (OY-C-7000A) Ph. Gr.
- **Methanol BP
- **Methylene Chloride BP
- Carnuba Wax BP

** will not appear in the final product

### 6.2 Incompatibilities

Not applicable

### 6.3 Shelf life

2 years

### 6.4 Special precautions for storage

- Store below 30ºC
- Protect from light.
- Keep out of the reach of children.

### 6.5 Nature and contents of container

Perforated aluminium/aluminium unit dose blisters in cartons containing 12 x 1 film-coated tablets.

### 6.6 Special precautions for disposal and other handling

No special requirements.

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

## 7. Marketing Authorisation Holder

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## 8. Marketing Authorisation Number

H2024/CTD10548/21438

## 9. Date of First Authorisation/Renewal of the Authorisation

Date of first authorisation: 23th August, 2016

## 10. Date of Revision of the Text

To be given after approval of the product