Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:

Axim CV 500 Tablet
Axim CV 250 Tablets

2. Qualitative and quantitative composition

Axim CV 500 Tablet: Each film coated tablet contains Cefuroxime Axetil USP equivalent to Cefuroxime 500 mg & Diluted Potassium Clavulanate BP equivalent to Clavulanic Acid 125 mg.
Axim CV 250 Tablets: 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 excipients see section 6.1.

3. Pharmaceutical form

Film-coated tablet

4. Clinical particulars

4.1 Therapeutic indications

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.
- Early Lyme disease (erythema migrans)
- Cystitis.
- Pyelonephritis.

4.2 Posology and method of administration

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

Table 1. Adults and children (≥ 40 kg)

Indication	Dosage
Acute tonsillitis and pharyngitis, acute bacterial sinusitis	250/62.5 mg twice daily
Acute otitis media	500/125 mg twice daily
Acute exacerbations of chronic bronchitis	500/125 mg twice daily
Cystitis	250/62.5 mg twice daily
Pyelonephritis	250/62.5 mg twice daily
Uncomplicated skin and soft tissue infections	250/62.5 mg twice daily
Lyme disease	500/125 mg twice daily for 14 days (range of 10 to 21 days)

Table 2. Children (<40 kg)

Indication	**Dosage**
Acute tonsillitis and pharyngitis, acute bacterial sinusitis	10 mg/kg twice daily to a maximum of 125 mg twice daily
Children aged two years or older with otitis media or, where appropriate, with more severe infections	15 mg/kg twice daily to a maximum of 250 mg twice daily
Cystitis	15 mg/kg twice daily to a maximum of 250 mg twice daily
Pyelonephritis	15 mg/kg twice daily to a maximum of 250 mg twice daily for 10 to 14 days
Uncomplicated skin and soft tissue infections	15 mg/kg twice daily to a maximum of 250 mg twice daily
Lyme disease	15 mg/kg twice daily to a maximum of 250 mg twice daily for 14 days (10 to 21 days)

There is no experience of using Cefuroxime-Clavulanic in children under the age of 3 months.

Renal impairment

The safety and efficacy of Cefuroxime-Clavulanic in patients with renal failure have not been established.

Cefuroxime-Clavulanic is primarily excreted by the kidneys. In patients with markedly impaired renal function, it is recommended that the dosage of Cefuroxime-Clavulanic should be reduced to compensate for its slower excretion. Cefuroxime-Clavulanic is effectively removed by dialysis.

Table 3. Recommended doses for Axim CV *in renal impairment*

Creatinine clearance	$T_{1/2}$ (hrs)	Recommended dosage
≥ 30 mL/min/1.73 m^2	1.4– 2.4	no dose adjustment necessary (standard dose of 125/62.5 mg to 500/125 mg given twice daily)
10-29 mL/min/1.73 m^2	4.6	standard individual dose given every 24 hours
<10 mL/min/1.73 m^2	16.8	standard individual dose given every 48 hours
Patients on haemodialysis	2– 4	a further standard individual dose should be given at the end of each dialysis

Hepatic impairment

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

Method of administration

Oral use

Cefuroxime-Clavulanic acid tablets should be taken after food for optimum absorption.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Patients with known hypersensitivity to cephalosporin antibiotics.

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

4.4 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. There have been reports of hypersensitivity reactions which progressed to Kounis syndrome (acute allergic coronary arteriospasm that can result in myocardial infarction, see section 4.8). In case of severe hypersensitivity reactions, treatment with Cefuroxime-Clavulanic must be discontinued immediately and adequate emergency measures must be initiated.

Severe cutaneous adverse reactions (SCARS)

Severe cutaneous adverse reactions including: Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS), which can be life-threatening or fatal, have been reported in association with Cefuroxime-Clavulanic treatment.

At the time of prescription patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of these reactions appear, Cefuroxime-Clavulanic should be withdrawn immediately and an alternative treatment considered. If the patient has developed a serious reaction such as SJS, TEN or DRESS with the use of Cefuroxime-Clavulanic, treatment must not be restarted in this patient at any time.
Before beginning treatment, it should be established whether the patient has a history of severe hypersensitivity reactions to Cefuroxime-Clavulanic, to other cephalosporins or to any other type of beta-lactam agent. Caution should be exercised if Cefuroxime-Clavulanic 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-Clavulanic treatment of Lyme disease. It results directly from the bactericidal activity of Cefuroxime-Clavulanic 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-Clavulanic 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-Clavulanic 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-Clavulanic. Discontinuation of therapy with Cefuroxime-Clavulanic 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 Coomb's Test associated with the use of Cefuroxime-Clavulanic 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-Clavulanic.

4.5 Interaction with other medicinal products and other forms of interaction

Drugs which reduce gastric acidity may result in a lower bioavailability of Cefuroxime-Clavulanic with that of the fasting state and tend to cancel the effect of enhanced absorption after food.

Cefuroxime-Clavulanic 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-Clavulanic.

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

4.6 Pregnancy and Lactation

Pregnancy

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

Breastfeeding

Cefuroxime-Clavulanic acid 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-Clavulanic acid should only be used during breastfeeding after benefit/risk assessment by the physician in charge.

Fertility

There are no data on the effects of Cefuroxime-Clavulanic acid on fertility in humans. Reproductive studies in animals have shown no effects on fertility.

4.7 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.

4.8 Undesirable effects

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 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).

System organ class	Common	Uncommon	Not known
Infections and infestations	Candida overgrowth		Clostridium difficile overgrowth
Blood and lymphatic system disorders	eosinophilia	positive Coombs' test, thrombocytopenia, leukopenia (sometimes profound)	haemolytic anaemia
Immune system disorders			drug fever, serum sickness, anaphylaxis, Jarisch-Herxheimer reaction
Cardiac disorders			Kounis syndrome
Nervous system disorders	headache, dizziness		
Gastrointestinal disorders	diarrhoea, nausea, abdominal pain	vomiting	pseudomembranous colitis
Hepatobiliary disorders	transient increases of hepatic enzyme levels		jaundice (predominantly cholestatic), hepatitis
Skin and subcutaneous tissue disorders		skin rashes	urticaria, pruritus, severe cutaneous adverse reactions (SCARs), including erythema multiforme (EM), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (exanthematic necrolysis) (TEN) , drug reaction with eosinophilia and systemic symptoms (DRESS), and angioneurotic oedema

Paediatric population

The safety profile for Cefuroxime-Clavulanic acid in children is consistent with the profile in adults.

Reporting of suspected adverse reactions: Healthcare professionals are asked to report any suspected adverse reactions via pharmacy and poisons

board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org

4.9 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-Clavulanic acid can be reduced by haemodialysis and peritoneal dialysis.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antibacterials for systemic use, second-generation cephalosporins, ATC-Code: J01DC02

Mechanism of action

Cefuroxime-Clavulanic acid undergoes hydrolysis by esterase enzymes to the active antibiotic, cefuroxime.

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.

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 any degree of bacterial activity, its principal role is as a beta-lactamase inhibitor. Beta-lactam antibiotics, such as 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.

Mechanism of resistance

Bacterial resistance to cefuroxime may be due to one or more of the following mechanisms:

• reduced affinity of penicillin-binding proteins for cefuroxime;
• outer membrane impermeability, which restricts access of cefuroxime to penicillin binding proteins in Gram-negative bacteria;
• bacterial efflux pumps.

Organisms that have acquired resistance to other injectable cephalosporins are expected to be resistant to cefuroxime.

Depending on the mechanism of resistance, organisms with acquired resistance to penicillins may demonstrate reduced susceptibility or resistance to cefuroxime.

Commonly susceptible species
Gram-positive aerobes: *Staphylococcus aureus* (methicillin-susceptible) * *Coagulase negative staphylococcus* (methicillin susceptible) *Streptococcus pyogenes* *Streptococcus agalactiae*
Gram-negative aerobes: *Haemophilus influenzae* *Haemophilus parainfluenzae* *Moraxella catarrhalis*
Spirochaetes: *Borrelia burgdorferi*
Microorganisms for which acquired resistance may be a problem
Gram-positive aerobes: *Streptococcus pneumoniae*
Gram-negative aerobes: *Citrobacter freundii* *Enterobacter aerogenes* *Enterobacter cloacae* *Escherichia coli* *Klebsiella pneumoniae* *Proteus mirabilis* *Proteus* spp. (other than *P. vulgaris)* *Providencia* spp.
Gram-positive anaerobes: *Peptostreptococcus* spp. *Propionibacterium* spp.
Gram-negative anaerobes: *Fusobacterium* spp. *Bacteroides* spp.
Inherently resistant microorganisms
Gram-positive aerobes: *Enterococcus faecalis* *Enterococcus faecium*
Gram-negative aerobes: *Acinetobacter* spp. *Campylobacter* spp. *Morganella morganii* *Proteus vulgaris* *Pseudomonas aeruginosa* *Serratia marcescens*

Gram-negative anaerobes: *Bacteroides fragilis*
Others: *Chlamydia* spp. *Mycoplasma* spp. *Legionella* spp.

* All methicillin-resistant *S. aureus* are resistant to cefuroxime.

5.2 Pharmacokinetic properties

Cefuroxime Axetil is 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. Unhydrolyzed 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.

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.

Biotransformation

Cefuroxime is not metabolised.

Excretion

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.

Special patient populations

Gender

No differences in the pharmacokinetics of cefuroxime were observed between males and females.

Elderly

No special precaution is necessary in the elderly patients with normal renal function at dosages up to the normal maximum of 1 g per day. Elderly patients are more likely to have decreased renal function; therefore, the dose should be adjusted in accordance with the renal function in the elderly (see section 4.2).

Paediatric population

In older infants (aged >3 months) and in children, the pharmacokinetics of cefuroxime are similar to that observed in adults.

There is no clinical trial data available on the use of cefuroxime axetil in children under the age of 3 months.

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. Therefore, as with all such antibiotics, in patients with markedly impaired renal function (i.e. C1cr <30 mL/minute) it is recommended that the dosage of cefuroxime should be reduced to compensate for its slower excretion (see section 4.2). 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.

5.3 Preclinical safety data

- Non-clinical data reveal no special hazard for humans based on studies of safety pharmacology, repeated dose toxicity, genotoxicity and toxicity to reproduction and development. No carcinogenicity studies have been performed; however, there is no evidence to suggest carcinogenic potential.

- Gamma glutamyl transpeptidase activity in rat urine is inhibited by various cephalosporins, however the level of inhibition is less with cefuroxime. This may have significance in the interference in clinical laboratory tests in humans.

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 30°C
Protect from light.
Keep out of the reach of children.

6.5 Nature and Content of container

Perforated aluminium/aluminium unit dose blisters in cartons containing 8 x 1 film-coated tablets.

6.6 Special precautions for disposal and other handling

No special requirements.

7. Marketing Authorization Holder

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8. Marketing Authorization Number

Axim CV 250: CTD10548
Axim CV 500: CTD10547

9. Date of first authorization/renewal of the authorization

18/4/2024

10. Date of revision of the text

5/5/2025