1.3.1 Summary of Product Characteristics (SmPC)

1. Name of Medicinal Product

EBENAT 250

CEFUROXIME AXETIL TABLETS USP 250MG

2. Qualitative and Quantitative Composition

2.1. Qualitative declaration:

Composition of the Drug product:

Each Film coated tablets Contains:

Cefuroxime 250mg

(As Cefuroxime Axetil USP)

Qualitative & Quantitative Composition Formula:

Batch Size: 100000 Tablets

Sr. No.	Name of raw material	Specification	Label	Overages	Qty. per Tab (mg)	Qty. Per Batch (Kg)	Function
1.	Cefuroxime Axetil *	USP	250.00 mg	-	312.50	31.250	Active
2.	Citric Acid Monohydrate	BP	-	-	11.00	1.10	Antioxidant
3.	Sodium Lauryl Sulphate	BP	-	-	12.00	1.20	Disintegrant
4.	Magnesium Stearate	BP	-	-	12.00	1.20	Lubricant
5.	Purified Talc	BP	-	-	18.30	1.83	Glidant
6.	Sodium Carbonate	BP	-	-	11.00	1.10	Softener
7.	Mannitol	BP	-	-	98.00	9.80	Sweetener
8.	Crospovidone	USP-NF	-	-	104.50	10.45	Binder
9.	Croscarmellose Sodium	USP-NF	-	-	70.00	7.00	Pharmaceutical additives
10.	Colloidal Anhydrous Silica	BP	-	-	3.00	0.30	Absorbent
11.	Propylene Glycol	BP	-	-	1.50	0.15	Preservative

12.	Isopropyl Alcohol **	BP	-	-	Q. S.	Q. S.	Solvent
13.	Dichloromethane**	BP	-	-	Q. S.	Q. S.	Solvent
14.	Titanium Dioxide	BP	-	-	2.70	0.27	Coating agent
15.	Hypromellose	USP	-	-	3.50	0.35	Lubricate
				Total Weight of Tablet	**660.00**	66.00	

*312.50 mg of Cefuroxime Axetil Eq. to 250.00 mg of Cefuroxime

**Gets evaporated during manufacturing process and does not remain in the final product except in traces

3. Pharmaceutical form

Tablets

White colored, caplet shaped film coated tablets having breakline on one side and plain on other side.

4. Clinical particulars:

4.1 Therapeutic indications:

Cefuroxime Axetil Tablets is indicated for the treatment of the infections listed below in adults and children from the age of 3 months.

• Acute streptococcal tonsillitis and pharyngitis.
• Acute bacterial sinusitis.
• Acute otitis media.
• Acute exacerbations of chronic bronchitis.
• Cystitis.
• Pyelonephritis.
• Uncomplicated skin and soft tissue infections.
• Treatment of early Lyme disease.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration:

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

Adults and children (≥40 kg):

Acute tonsillitis and pharyngitis, acute bacterial sinusitis: 250 mg twice daily

Acute otitis media: 500 mg twice daily

Acute exacerbations of chronic bronchitis: 500 mg twice daily

Cystitis: 250 mg twice daily

Pyelonephritis: 250 mg twice daily

Uncomplicated skin and soft tissue infections: 250 mg twice daily

Lyme disease: 500 mg twice daily for 14 days (range of 10 to 21 days)

Children (<40 kg):

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 in children under the age of 3 months.

Cefuroxime axetil tablets and cefuroxime axetil granules for oral suspension are not bioequivalent and are not substitutable on a milligram-per-milligram basis.

Renal impairment

The safety and efficacy of cefuroxime in patients with renal failure have not been established.

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

Recommended doses for Cefuroxime Axetil in renal impairment

Creatinine clearance	**T1/2 (hrs)**	**Recommended dosage**
≥30 ml/min/1.73 m2	1.4–2.4	no dose adjustment necessary (standard dose of 125 mg to 500 mg given twice daily)
10-29 ml/min/1.73 m2	4.6	standard individual dose given every 24 hours
<10 ml/min/1.73 m2	16.8	standard individual dose given every 48 hours
During haemodialysis	2–4	a single additional 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 is primarily eliminated by the kidney, the presence of hepatic dysfunction is expected to have no effect on the pharmacokinetics of cefuroxime.

Method of administration

Oral use administration

Cefuroxime Axetil Tablets should be taken after food for optimum absorption.

4.3 Contraindications:

Cefuroxime Axetilis contraindicated in patients with:

• Hypersensitivity to cefuroxime or any of the excipients of Cefuroxime Axetil Tablet.

• Known hypersensitivity to cephalosporin antibiotics.

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

Hypersensitivity to cefuroxime 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 betalactam antibacterial agent (penicillins, monobactams and carbapenems).

4.4 Special warnings and precautions:

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. In case of severe hypersensitivity reactions, treatment with cefuroxime 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 cefuroxime, to other cephalosporins or to any other type of beta- lactam agent. Caution should be used if cefuroxime 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 axetil treatment of Lyme disease. It results directly from the bactericidal activity of cefuroxime axetil on the causative bacteria of Lyme disease, the spirochaete *Borreliaburgdorferi*. 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 axetil 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 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. Discontinuation of therapy with cefuroxime 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 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 axetil.

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 axetil compared with that of the fasting state and tend to cancel the effect of enhanced absorption after food.

Cefuroxime axetil may affect the gut flora, leading to lower oestrogen reabsorption and reduced efficacy of combined oral contraceptives.

Cefuroxime is excreted by glomerular filtration and tubular secretion. Concomitant use of probenicidis not recommended. Concurrent administration of probenecid significantly increases the peak concentration, area under the serum concentration time curve and elimination half-life of cefuroxime.

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

4.6 Pregnancy and lactation

Pregnancy: Cefuroxime axetilshould be prescribed to pregnant women only if the benefit outweighs the risk.

Lactation: Cefuroxime 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 sensitisationshould be taken into account. Cefuroxime should only be used during breastfeeding after benefit/risk assessment by the physician in charge.

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 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.

Infections and infestations

Common: *Candida* overgrowth

Not known: *Clostridium difficile* overgrowth

Blood and lymphatic system disorders

Common: eosinophilia

Uncommon: positive Coomb's test, thrombocytopenia, leukopenia (sometimes profound)

Not known: haemolyticanaemia

Immune system disorders:

Not known: drug fever, serum sickness, anaphylaxis, Jarisch-Herxheimer reaction

Nervous system disorders

Common: headache, dizziness

Gastrointestinal disorders

Common: diarrhoea, nausea, abdominal pain

Uncommon: vomiting

Not known: pseudomembranous colitis

Hepatobiliary disorders:

Common: transient increases of hepatic enzyme levels

Not known: jaundice (predominantly cholestatic), hepatitis

Skin and subcutaneous tissue disorders

Uncommon: skin rashes

Not known: urticaria, pruritus, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (exanthematic necrolysis), angioneuroticoedema

Description of selected adverse reactions

Cephalosporins as a class tend to be absorbed onto the surface of red cells membranes and react with antibodies directed against the drug to produce a positive Coombs' test (which can interfere with cross-matching of blood) and very rarely haemolyticanaemia.

Transient rises in serum liver enzymes have been observed which are usually reversible.

Paediatric population

The safety profile for cefuroxime axetil in children is consistent with the profile in adults.

4.9 Overdosage:

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 can be reduced by haemodialysis and peritoneal dialysis.

5. Pharmacological properties:

5.1 Pharmacodynamic properties:

Pharmacotherapeutic group: Antibacterials for systemic use, second-generation cephalosporin's

ATC code: J01DC02

Mechanism of action

Cefuroxime axetil 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.

Mechanism of resistance

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

- hydrolysis by beta-lactamases; including (but not limited to) by extended-spectrum beta-lactamases (ESBLs), and AmpC enzymes that may be induced or stably derepressed in certain aerobic Gram-negative bacteria species;
- 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 cephalosporinsare 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.

Microbiological susceptibility

Commonly susceptible species

Gram-positive aerobes: *Staphylococcus aureus* (methicillin susceptible)*, *Coagulase negative staphylococcus (methicillin susceptible), Streptococcus pyogenes, Streptococcus agalactiae*.

Gram-negative aerobes: *Haemophilus influenza, Haemophilusparainfluenzae, Moraxella catarrhalis.*

Spirochaetes: *Borreliaburgdorferi*

Microorganisms for which acquired resistance may be a problem

Gram-positive aerobes: *Streptococcus pneumoniae*

Gram-negative aerobes: *Citrobacterfreundii, Enterobacteraerogenes, Enterobacter cloacae, Escherichia coli, Klebsiella pneumonia, 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., *Morganellamorganii, Proteus vulgaris, Pseudomonas aeruginosa, Serratiamarcescens.*

Gram-negative anaerobes:*Bacteroidesfragilis*

Others: *Chlamydia* spp., *Mycoplasma* spp., *Legionella* spp.

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

5.2 Pharmacokinetic properties:

Absorption: After oral administration cefuroximeaxetil is absorbed from the gastrointestinal tract and rapidly hydrolysed in the intestinal mucosa and blood to release cefuroxime into the circulation. Optimum absorption occurs when it is administered shortly after a meal.

Following administration of cefuroxime axetil tablets peak serum levels (2.1 mcg/ml for a 125 mg dose, 4.1 mcg/ml for a 250 mg dose, 7.0 mcg/ml for a 500 mg dose and 13.6 mcg/ml for a 1000 mg dose) occur approximately 2 to 3 hours after dosing when taken with food. The rate of absorption of cefuroxime from the suspension is reduced compared with the tablets, leading to later, lower peak serum levels and reduced systemic bioavailability (4 to 17% less). Cefuroxime axetil oral suspension was not bioequivalent to cefuroxime axetil tablets when tested in healthy adults and therefore is not substitutable on a milligram-per-milligram basis (see section 4.2).The pharmacokinetics of cefuroxime is linear over the oral dosage range of 125 to 1000 mg. No accumulation of cefuroxime occurred following repeat oral doses of 250 to 500 mg.

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.

Elimination: The serum half-life is between 1 and 1.5 hours. Cefuroxime is excreted by glomerular filtration and tubular secretion. The renal clearance is in the region of 125 to 148 ml/min/1.73 m^2.

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.

Paediatrics

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. 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.

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

5.3 Preclinical safety data

Reported non-clinical data reveals that 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 glutamyltranspeptidase 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

Sr. No.	Ingredients	Specification
1.	Citric Acid Monohydrate	BP
2.	Sodium Lauryl Sulphate	BP
3.	Magnesium Stearate	BP
4.	Purified Talc	BP
5.	Sodium Carbonate	BP
6.	Mannitol	BP
7.	Crospovidone	USP-NF
8.	Croscarmellose Sodium	USP-NF
9.	Colloidal Anhydrous Silica	BP
10.	Propylene Glycol	BP
11.	Isopropyl Alcohol **	BP
12.	Dichloromethane**	BP
13.	Titanium Dioxide	BP
14.	Hypromellose	USP

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at temperature not exceeding 30°C, protect from moisture.

6.5 Nature and contents of container

10X1X10 Tablets in Alu-Alu Blister Pack.

6.6 Special precautions for disposal and other handling

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.

7- Marketing Authorization Holder:

ELBE PHARMA NIG. LTD.

NO.1, African Church Close,

Off.coker Road, Ilupeju, Lagos, Nigeria.

8- Marketing Authorization Number (s):

Product license / registration Number (s)

9- Manufacturer Name:

ZIM LABORATORIES LIMITED.

B-21/22, MIDC AREA, KALMESHWAR-441501,

DIST-NAGPUR-MAHARASHTRA, INDIA.

10- Date of first authorization/renewal of the authorization:

11- Date of revision of the text:
