1.3.1 Summary of Product Characteristics (SmPC)

1. Name of the medicinal product

1.1 (Invented) name of the medicinal product

ZANEF - 250

INN (GENERIC NAME)

CEFUROXIME AXETIL TABLETS USP 250 MG

1.2 Strength :- 250 MG

1.3 Pharmaceutical form :- Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

CEFUROXIME AXETIL TABLETS USP 250 MG

Each film coated tablets contains:

Cefuroxime Axetil USP

Eq. to Cefuroxime 250mg

Excipients q.s.

Approved colour used q.s.

Batch Size: 100,000 Tablets

Sr. No.	Ingredients	Specification	Label amount mg	% Overages	Qty. / Tablet Mg	Reason for Inclusion
ACTIVE						
1.	Cefuroxime Axetil eq to Cefuroxime*	USP	250 mg	5%	315.0	Active
EXCEPIENTS						
2.	Pregelatinised Starch	BP	--	--	100.0	Diluent
3.	Sodium Lauryl Sulphate	BP	--	--	12.00	Diluent
4.	Sodium Starch Glycolate	BP	--	--	20.00	Diluent
5.	Polyplasdone XL 10	USP	--	--	12.50	Disintegrant
6.	PEG 6000	BP	--	--	7.500	Diluent
7.	Methylene Chloride#	BP	--	--	-----	Solvent
8.	Colloidal Silicon Dioxide	BP	--	--	2.500	Diluent
9.	Purified Talc	BP	--	--	12.50	Glidant
LUBRICATION						
10.	Purified Talc	BP	--	--	2.500	Lubricant
11.	Colloidal Silicon Dioxide	BP	--	--	2.500	Lubricant
12.	Polyplasdone XL 10	USP	--	--	38.00	Disintegrant
COATING						
13.	Methylene Chloride#	BP	--	--	----	Solvent
14.	Isopropyl Alcohol#	BP	--	--	----	Solvent
15.	Hydroxy Propyl Methyl Cellulose 15 CPS	BP	--	19%	8.020	Film coat
16.	Titanium Dioxide	BP	--	19%	1.603	Whitener
17.	Purified Talc	BP	--	19%	2.010	Glidant
18.	PEG 4000	USP	--	19%	1.603	Plasticiser
19.	Propylene Glycol	BP	--	19%	1.603	Humactant
20.	Col. Tartrazine Yellow Lake	IH	--	19%	0.161	Colour

*300 mg of Cefuroxime Axetil eq to 250 mg of Cefuroxime

**19% Coating solution extra taken to compensate loss during production

#Not a part of finished product (Methylene Chloride & Isopropyl Alcohol evaporates during the manufacturing process)

BP = British Pharmacopoeia

IHS = In-house Specification

USP = United States Pharmacopoeia

3. PHARMACEUTICAL FORM. :

Light yellow coloured, elongated, biconvex, film coated tablets having a break line on one side of each tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications:

Cefuroxime Axetil 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:

Posology

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 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)

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 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. 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.

Table 3. Recommended doses for Cefuroxime axetil *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 mg to 500 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 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

Cefuroxime axetil tablets should be taken after food for optimum absorption.

Cefuroxime axetil tablets should not be crushed and are therefore unsuitable for treatment of patients who cannot swallow tablets. In children Cefuroxime axetil oral suspension may be used.

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 betalactam 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. 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 Borrelia burgdorferi. Patients should be reassured that this is a common and usually self-limiting consequence of antibiotic treatment of Lyme disease (see section 4.8).
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 (see section 4.8).
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 (see section 4.8). 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 (see section 4.8).
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 (see section 4.8).
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.
Cefuroxime contains aspartame and sodium.
This medicine contains 0.3 mg aspartame in each coated tablet.
Aspartame is a source of phenylalanine. It may be harmful to patients with phenylketonuria (PKU). Neither non-clinical nor clinical data are available to assess aspartame use in infants below 12 weeks of age.
This medicine contains less than 1 mmol sodium (23 mg) per coated tablet, that is to say essentially 'sodium-free'.

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 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.
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 in pregnant women. Studies in animals have shown no harmful effects on pregnancy, embryonal or foetal development, parturition or postnatal development. Cefuroxime Axetil should be prescribed to pregnant women only if the benefit outweighs the risk.

Breastfeeding

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 sensitisation should be taken into account. Cefuroxime 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 axetil 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 Coomb's test, thrombocytopenia, leukopenia (sometimes profound)	haemolytic anaemia
Immune system disorders			drug fever, serum sickness, anaphylaxis, Jarisch-Herxheimer reaction
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, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (exanthematic necrolysis) (see Immune system disorders), angioneurotic oedema
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 haemolytic anaemia. 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 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 (see sections 4.2 and 4.4).
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 cephalosporins, 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 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.
Cefuroxime axetil breakpoints
Minimum inhibitory concentration (MIC) breakpoints established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) are as follows:

Microorganism	Breakpoints (mg/L)	
	S	R
Enterobacteriaceae [1, 2]	≤8	>8
Staphylococcus spp.	Note[3]	Note[3]
Streptococcus A, B, C and G	Note[4]	Note[4]
Streptococcus pneumoniae	≤0.25	>0.5
Moraxella catarrhalis	≤0.125	>4
Haemophilus influenzae	≤0.125	>1

Non-species related breakpoints[1]	IE[5]	IE[5]

[1] The cephalosporin breakpoints for *Enterobacteriaceae* will detect all clinically important resistance mechanisms (including ESBL and plasmid mediated AmpC). Some strains that produce beta-lactamases are susceptible or intermediate to 3rd or 4th generation cephalosporins with these breakpoints and should be reported as found, i.e. the presence or absence of an ESBL does not in itself influence the categorization of susceptibility. In many areas, ESBL detection and characterization is recommended or mandatory for infection control purposes.

[2] Uncomplicated UTI (cystitis) only (see section 4.1).

[3] Susceptibility of staphylococci to cephalosporins is inferred from the methicillin susceptibility except for ceftazidme and cefixime and ceftibuten, which do not have breakpoints and should not be used for staphylococcal infections.

[4] The beta-lactam susceptibility of beta-haemolytic streptococci groups A, B, C and G is inferred from the penicillin susceptibility.

[5] insufficient evidence that the species in question is a good target for therapy with the drug.

An MIC with a comment but without an accompanying S or R-categorization may be reported.

S=susceptible, R=resistant

Microbiological susceptibility

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of cefuroxime axetil in at least some types of infections is questionable.

Cefuroxime is usually active against the following microorganisms *in vitro*.

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:

Absorption

After oral administration cefuroxime Axetil 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 (2.9 µg/mL for a 125 mg dose, 4.4 µg/mL for a 250 mg dose, 7.7 µg/mL for a 500 mg dose and 13.6 µg/mL for a 1000 mg dose) occur approximately 2.4 hours after dosing when taken with food. 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 m2.
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).
Paediatrics 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.
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 (%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 :
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.

Sr. No.	Ingredients	Specifications
1.	Pregelatinised Starch	BP
2.	Sodium Lauryl Sulphate	BP
3.	Sodium Starch Glycolate	BP
4.	Polyplasdone XL 10	USP
5.	PEG 6000	BP
6.	Methylene Chloride	BP
7.	Colloidal Silicon Dioxide	BP
8.	Purified Talc	BP
9.	Isopropyl Alcohol	BP
10.	Hydroxy Propyl Methyl Cellulose 15 CPS	BP
11.	Titanium Dioxide	BP
12.	PEG 4000	USP
13.	Propylene Glycol	BP
14.	Col. Tartrazine Yellow Lake	IH

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 Years

6.4 Special precautions for storage

Store below 30°C in a dry & cool place.
Keep all medicines out of reach of children.

6.5 Nature and contents of container

Alu-Alu Blister pack of 10 Tablets.

7.1 Manufacturer name and address

MEDICO REMEDIES LTD.
8 & 9, Dewan & Sons Udyog Nagar, Lokmanya Nagar,,
Palghar (West), Palghar -401 404, Dist. Thane, Maharashtra, India

7.2 Applicant name and address

Afrigenerics Pharmaceuticals ltd
No 2, Iringa Street, off Dodoma Street, Wuse Zone 6,
Abuja, FCT, Nigeria