1.3.1 Summary of Product Characteristics (SmPC)

1. Name of the medicinal product

1.1 (Invented) name of the medicinal product

ZANEF– 125

INN (GENERIC NAME)

Cefuroxime Axetil for Oral Suspension USP 125 mg/5ml

1.2 Strength:- 125 mg/5 ml

1.3 Pharmaceutical form:- Oral Suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ZANEF - 125 (Cefuroxime Axetil for Oral Suspension USP 125 mg/5ml)
Each 5 ml after reconstitution contains :
- Cefuroxime Axetil USP Equivalent to Cefuroxime (125 mg)
- Approved colour and flavour used. (-)
- Excipients: (-QS)

Batch Size: 1000 X 70 ml Bottles

Sr. No.	Ingredients	Quality standard	Overages (%)	Unit composition (Qty/Bottle) gm	Quantity/ Batch (kg)
Active					
1.	Cefuroxime Axetil#	USP	2.50%	2.260	2.26
Excipients					
2.	Sucrose	BP	--	15.806	15.806
3.	Sodium Benzoate	BP	--	0.062	0.062
4.	Colloidal Silicon Dioxide	BP	--	0.200	0.200
5.	Ess. Banana Dry Mix	IH	--	0.560	0.560
6.	Sodium Saccharine	BP	--	0.220	0.220
7.	Purified Talc	BP	--	0.052	0.052
8.	Aspartame	BP	--	0.220	0.220
9.	Sucralose	BP	--	0.600	0.600
10.	Col. Tartrazine Yellow Supra	IH	--	0.040	0.040
	Content Per Bottle			**20.00 gm**	**20.00 kg**

USP = United States of Pharmacopoeia
BP = British Pharmacopoeia
IH = In-house Specification
# Cefuroxime Axetil USP 157.5mg Eq. to Cefuroxime 125mg/5ml

3. PHARMACEUTICAL FORM. :
White coloured powder, when reconstitution with water gives yellow coloured Suspension

4. CLINICAL PARTICULARS

4.1 Therapeutic indications:

ZANEF - 125 is indicated for the treatment of paediatric patients 3 months to 12 years of age with mild to moderate infections caused by susceptible strains of the designated microorganisms in the conditions listed below:
1. Pharyngitis/Tonsillitis caused by Streptococcus pyogenes.
2. Acute Bacterial Otitis Media caused by Streptococcus pneumoniae, Haemophilus influenzae (including beta-lactamase-producing strains), Moraxella catarrhalis (including beta-lactamase-producing strains), or Streptococcus pyogenes.
3. Acute Bacterial Maxillary Sinusitis caused by Streptococcus pneumoniae or Haemophilus influenzae (non-beta-lactamase-producing strains only).
4. Impetigo caused by Staphylococcus aureus (including beta-lactamase-producing strains) or Streptococcus pyogenes.

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 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 ZANEF - 125 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.
In infants (from the age of 3 months) and children with a body mass of less than 40 kg, it may be preferable to adjust dosage according to weight or age. The dose in infants and children 3 months to 18 years is 10 mg/kg twice daily for most infections, to a maximum of 250 mg daily. In otitis media or more severe infections the recommended dose is 15 mg/kg twice daily to a maximum of 500 mg daily.
The following two tables, divided by age group, serve as a guideline for simplified administration, e.g measuring spoon (5 ml) for the 125 mg/5 ml or the 250 mg/5 ml multi-dose suspension if provided.

Table 3. 10 mg/kg dosage for most infections

Age	**Dose (mg) twice daily**	**Volume per dose (ml)**	
		125mg	250mg
3 to 6 months	40 to 60	2.5	-
6 months to 2 years	60 to 120	2.5 to 5	-
2 to 18 years	125	5	2.5

Table 4. 15 mg/kg dosage for otitis media and more serious infections

Age	**Dose (mg) twice daily**	**Volume per dose (ml)**	
		125mg	250 mg
3 to 6 months	60 to 90	2.5	-
6 months to 2 years	90 to 180	5 to7.5	2.5
2 to 18 years	180 to 250	7.5 to 10	2.5 to 5

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 5. Recommended doses for ZANEF - 125 powder for oral suspension 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
<10ml/min/1.73m^2	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
For optimal absorption cefuroxime axetil suspension should be taken with food.

4.3 Contraindications:
ZANEF - 125 is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

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-lactum antibiotics because there is a risk of cross-sensitivity. As with all beta-lactum 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-lactum agent. Caution should be used if cefuroxime is given to patients with a history of non-severe hypersensitivity to other betalactum 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.

4.5 Interaction with other medicinal products and other forms of interaction:
Concomitant administration of probenecid with cefuroxime axetil suspension 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).
Drugs that reduce gastric acidity may result in a lower bioavailability of Viktinoxx compared with that of fasting state and tend to cancel the effect of postprandial absorption. 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 contraceptives.

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. ZANEF - 125 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.

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.

4.8 UNDESIRABLE EFFECTS:

The most common adverse reactions that may be associated with cefuroxime axetil include gastro- intestinal events, such as nausea, vomiting, diarrhea, abdominal pain, flatulence. The gastrointestinal adverse events increase with the higher recommended doses.

4.9 OVERDOSE:

Overdosage of cephalosporin can cause cerebral irritation leading to convulsions. Serum levels of cefuroxime can be reduced by hemodialysis 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 betalactamases (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.

5.2 Pharmacokinetic properties:
The preferred analytical Method is by bioassay, using agar diffusion and a Gram-negative organism as indicator, with the usual lower limit of sensitivity around 0.06 mg.1-1. Cefuroxime has a plasma half-life of approximately 75 min in subjects with normal renal function. It is about 33 % bound to serum. The volume of distribution after a 1 g dose is 11.1- 13.71 per 1.73 m2. There were wide variations in absorption of cefuroxime axetil in early studies and some early papers refer to formulations not now used. The final formulation developed gives peak serum concentrations of 7-10 mg.1-1 if taken before food. Cefuroxime axetil is completely hydrolyzed in the intestine to cefuroxime; Its pharmacokinetics are then the same as cefuroxime sodium, but the serum level is much closer to the MIC of important pathogens that the parent form. The drug is primarily eliminated by the kidneys, with urinary recovery about 35% and an elimination half-life of 1.5 h. The drug crosses the placenta and can also be detected in breast milk.

Oral absorption	
Cefuroxime	not relevant
Cefuroxime axetil	good
Presystemic metabolism	
Cefuroxime	not relevant
Cefuroxime axetil	hydrolyzed to Cefuroxime
Plasma half-life	
Cefuroxime	75 min
Volume of distribution	11.-
(both drugs)	13.7I.173 m-2
Plasma protein binding	
(both drugs)	30%

Concentration –effect relationship
The therapeutic effect of cefuroxime sodium, as with all antibiotics, depends on achieving a level of antibiotic in excess of the MIC of the causative organism. This is relatively easily achieved with an infection in urine or blood, but is more difficult at enclosed sites such as abscesses or gallbladder infections. Fewer data are available for cefuroxime axetil. Serum levels are in excess of the MIC of many pathogens, but information on its penetration into sputum and other sites is still needed.

Metabolism
Cefuroxime is rapidly excreted in high concentration through the kidney with over 90 % of the given dose recovered in the urine within 6 h of injection. Renal clearance is equally divided between clearance through tubules and glomerular filtration ; mean drug: creatinine clearance rations were 1:1 to 1:3 suggesting half the drug is filtered and half is actively secreted by the kidney tubules.
Virtually all cefuroxime is excreted in the urine, with no detectable enterohepatic circulation. High pressure liquid chromatography studies of cefuroxime in urine samples showed that over 95% is excreted as unchanged cefuroxime. There are no known pharmacologically active metabolites.

Cefuroxime axetil is better absorbed if taken after food, when 50% can be recovered in the urine. No unhydrolyzed ester is detected in serum.

5.3 Preclinical safety data :

TOXICOLOGICAL DATA Cefuroxime, like many other β-lactam antibiotics shows little evidence of human or animal toxicity. There are no reports of toxicological results in animals that are of human significance. There was no evidence of nephrotoxicity in mice given up to 6 g.kg-1 cefuroxime subcutaneously. There was no evidence of teratological effects in mice or rabbits. Long term carcinogenicity tests have not been carried out. Cefuroxime axetil has a similar toxicology profile to the parent drug

6 Pharmaceutical Particulars

6.1 List of Excipients.

Sr. No.	Ingredients	Quality standard
1.	Sucrose	BP
2.	Sodium Benzoate	BP
3.	Colloidal Silicon Dioxide	BP
4.	Ess. Banana Dry Mix	IH
5.	Sodium Saccharine	BP
6.	Purified Talc	BP
7.	Aspartame	BP
8.	Sucralose	BP
9.	Col. Tartrazine Yellow Supra	IH

6.2 Incompatibilities

A positive Coombs' test has been reported during treatment with cephalosporins - this phenomenon can interfere with cross-matching of blood.

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

100ml & 70 ml Amber Glass Bottle

7.0 Manufacturer name and address

MEDICO REMEDIES LTD.,

5 & 9, Dewan & Sons Udyog Nagar, Palghar, Dist. Thane, Maharashtra, India

7.1 Applicant name and address

Afrigenerics Pharmaceuticals ltd

Iringa Street, Off D Abuja Fct