1.3 Product Information

1.3.1 Summary of Product Characteristics (SmPC)

- Attached

National Agency for Food & Drug Administration & Control (NAFDAC)

Registration & Regulatory Affairs (R & R) Directorate

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

1. NAME OF THE MEDICINAL PRODUCT

Generic Name or International Non-Proprietary Name (INN)
CEFUROXIME AXETIL FOR ORAL SUSPENSION USP 125MG/5ML

Brand Name
SUPIME

Strength
Cefuroxime Axetil USP 125MG/5ML

Pharmaceutical Dosage Form
Powder for Oral Suspension
An off white colour granular powder.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml of reconstituted suspension contains:
Cefuroxime Axetil USP
Eq. to Cefuroxime. ..... 125 mg
Excipients. ..... q.s

Qty of Cefuroxime Axetil is approx. 3007.139 mg equivalent to Cefuroxime Axetil Oral Suspension USP 125 mg/5 ml.
Batch Size: 10000 Bottles- 100ml

Sr. No.	Ingredients	Grade	Rationale	Label Claim	Quantity (mg/ bottle)	Qty. required/ batch(kg)
Dry Mixing						
1	Cefuroxime Axetil*	USP	API	2500.00	3007.139	30.071
2	Beta-cyclodextrin	USP	Solubility Enhancer	---	6750.000	67.500
3	IPA**	USP-NF	Solvent	---	6000.000	60.000
4	Purified Water**	USP-NF	Solvent	---	11000.00	110.000
5	Sucrose (Pharma grade 40 Mesh) $	USP-NF	Sweetener	---	11408.751	114.088
6	Sucrose (Pharma grade 40 Mesh)	USP-NF	Sweetener	---	11408.750	114.088
7	Xanthan gum	USP-NF	Thickening Agent	---	126.000	1.260
8	Aspartame	USP-NF	Sweetener	---	504.000	5.040
9	Sodium Benzoate	USP-NF	Preservative	---	277.200	2.772
10	Acesulfame - k	USP-NF	calorie-free sweetener	---	420.000	4.200
11	Talc	USP-NF	Lubricant	---	33.600	0.336
12	Citric acid anhydrous	USP-NF	Antioxidant	---	473.760	4.738

13	Tutti Fruity flavour	IHS	Flavour	---	588.000	5.880
14	Colour Erythrosine supra	IHS	Colour	---	2.800	0.028
				Mixed Blend weight	35,000.00	350.00

NOTE:
1. *Mentioned quantity is considering Assay (on anhydrous basis) as 100%, Potency correction to be done while dispensing considering the actual assay on anhydrous basis.
2. $ Sucrose (Pharma grade 40 Mesh) Part-I to be compensate after potency correction of Cefuroxime Axetil.
3. **Will evaporate during manufacturing process.

EQUIVALENCY:
Molecular weight of Cefuroxime Axetil = 510.475 g/mol
Molecular weight of Cefuroxime= 424.386 g/mol
Dose for Cefuroxime = 2500 mg

$$= \frac{510.475 \times 2500}{424.386}$$

= 3007.139 mg of cefuroxime axetil required

USP- United States of pharmacopoeia, Current version
USP-**NF**-United states of pharmacopoeia National Formulary, Current version
IHS - In-house specification

3. PHARMACEUTICAL FORM

Light pink color free flowing powder when reconstituted it gives light pink coloured suspension (100 ml).

4. Clinical particulars

4.1 Therapeutic indications

Cefuroxime axetil for Oral Suspension is indicated for the treatment of pediatric 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 with Cefuroxime suspension is 7 days (with a range of 5 to 10 days). Cefuroxime axetil should be taken with a light meal for optimum absorption. The recommended dose for most infections is 125 mg twice daily. In children aged two years or older with otitis media or

where appropriate in children, with more severe infections, the dose is 250 mg twice daily. There is no clinical experience with the use of Cefuroxime in infants under the age of 3 months. In infants and children, it may be preferable to adjust dosage according to weight or age. The dose of Cefuroxime oral suspension recommended for treatment of tonsillitis and pharyngitis is 10 mg/kg twice daily, to a maximum of 250 mg daily. The dose of Cefuroxime oral suspension recommended for the treatment of acute bacterial otitis media is 15 mg/kg twice daily, to a maximum of 500 mg daily. The following tables, divided by age group and weight, serve as a guideline for simplified administration from measuring spoons (5 mL) for the 125 mg/5 mL or the 250 mg/5 mL multidose suspension, and 125 mg or 250 mg single dose sachets.

Table 1. Adults

Indication	**Dosage**
Most infections	250 mg twice daily
Urinary tract infections	250 mg twice daily
Mild to moderate lower respiratory tract infections	250 mg twice daily
More severe lower respiratory tract infections, or if pneumonia is suspected	500 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

Indication	**Dosage**
Acute tonsillitis and pharyngitis, acute bacterial sinusitis	10 mg/kg twice daily to a maximum of 125 mg twice daily
Acute otitis media	15 mg/kg twice daily to a maximum of 1000 mg daily
Acute bacterial sinusitis	
Community acquired pneumonia	
Urinary tract infections	
Skin and soft tissue infections	
Lyme Disease in children under the age of 12 years	15 mg/kg twice daily to a maximum of 1000 mg daily for 14 days (range of 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	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
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

Cefuroxime axetil for oral suspension 125mg/5ml is contraindicated in patients with known allergy to the cephalosporin group of antibiotics

4.4 Special warnings and precautio ns for use

Hypersensitivity reactions

Special care is indicated in patients who have experienced an allergic reaction to penicillin 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 spirochete 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 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.

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. 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 considered. 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.

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
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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Yellow Card Scheme: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in Google play or Apple App store.

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

Pharmacodynamics properties

Pharmacotherapeutic group: antibacterial 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 depressed 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 penicillin may demonstrate reduced susceptibility or resistance to cefuroxime.

5.1 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	1.1.-
(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 chromatobgtraphy 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

5.2 Preclinical safety 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

Beta-cyclodextrin
IPA
Purified Water
Sucrose (Pharma grade 40#)
Xanthan gum
Aspartame
Acesulfame-k
Talc
Sodium Benzoate
Citric acid anhydrous
Tutti fruity flavor

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

24 months from the date of manufacture.

6.4 Special precautions for storage

Store Protected from moisture, at temperature not exceeding 30˚C.

This medicinal product does not require any special temperature storage conditions.

6.5 Nature and contents of container

100 ml of 28mm HDPE round bottle fitted with 28mm screw cap and 28mm Measuring cup.

Pack 1 HDPE bottle with sticker label on it in 1 carton along with 1 leaflet.

Must have 2D barcode overprinting on the carton.

Pack such cartons in export worthy shipper.

6.6 Special precautions for disposal <and other handling>

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

7. APPLICANT/MANUFACTURER

MANUFACTURER:

NAME	:	GLOBELA LABORATORIES PVT. LTD
ADDRESS	:	PLOT NO. 5536, ROAD NUMBER 55, SACHIN G.I.D.C, SURAT- 394230 GUJARAT, INDIA.
COUNTRY	:	INDIA
TELEPHONE	:	+91–0261–6158000
E-MAIL	:	glpra@globelapharma.com

APPLICANT:

NAME	:	SJS LIFE SCEINCE LTD
ADDRESS	:	H.NO.11, OLU-AKERELE STREET, IKEJA, LAGOS STATE, NIGERIA.
COUNTRY	:	NIGERIA
TELEPHONE	:	+234–8114441430
E-MAIL	:	jkpandey3s@gmail.com

Marketing authorization numbers

Not applicable

Date of first authorization/renewal of the authorization

Not applicable

Date of revision of the text

To be given after approval of the product