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

Registration & Regulatory Affairs (R & R) Directorate

SUMMARY OF PRODUCT CHARACTERISTICS

CEFUROXIME 125 SUSPENSION

1. NAME OF THE MEDICINAL PRODUCT

Cefuroxime 125 mg Suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2. Qualitative and quantitative composition

No	Ingredients	Specifi-cation	Label Claim (mg)	Quantity /5 ml (mg)	Qty per Bottle (gm)	Reason for inclusion
1	Cefuroxime Axetil*	USP	125	150.38	2.105	Active
2	Mannitol	BP	-	399.29	5.590	Diluent
3	Methaccrylic acid copolymer	USP	-	25.36	0.355	Dispersing agent
4	Sucrose#	BP	-	2593.64	36.311	Sweetening agent
5	Aspartame	BP	-	50.00	0.700	Sweetening
6	Xanthan gum	BP	-	4.36	0.061	Thickening
7	Sodium benzoate	BP	-	11.64	0.163	Preservative
8	Powdarome orange	IH	-	43.29	0.606	Flavoring agent
9	Powdarome pipperment premium	IH	-	25.00	0.350	Flavoring agent
10	Sunset yellow W.S	IH	-	0.64	0.009	Coloring agent
11	Colloidal anhydrous silica (Colloidal silicon Dioxide)	BP	-	30.00	0.420	Suspending agent
12	Isopropyl alcohol$	BP	-	q.s.	q.s.	Solvent
13	Purified water$	BP	-	q.s.	q.s.	Vehicle

3. PHARMACEUTICAL FORM

Powder for Oral Suspensions

4. Clinical particulars

4.1 Therapeutic indications

1. Pharyngitis/Tonsillitis caused by Streptococcus pyogenes.
2. NOTE: The usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever, is penicillin given by the intramuscular route. CEFUROXIME SUSPENSION 125 for Oral Suspension is generally effective in the eradication of streptococci from the nasopharynx; however, substantial data establishing the efficacy of cefuroxime in the subsequent prevent ion of rheumatic fever are not available. Please also note that in all clinical trials, all isolates had to be sensitive to both penicillin and cefuroxime. There are no data from adequate and well-controlled trials to demonstrate the effectiveness of cefuroxime in the treatment of penicillin-resistant strains of Streptococcus pyogenes.
3. 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.

4.Impetigo caused by Staphylococcus aureus (including beta-lactamase-producing strains) or Streptococcus pyogenes.

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.

There is no experience of using cefuroxime 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, and 125 mg or 250 mg single dose sachets

Table 3. 10 mg/kg dosage for most infections

Age	**Dose (mg) twice daily**	**Volume per dose (mL)**		**No. of sachets per dose**	
		125 mg	250 mg	125 mg	250 mg
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	1	-

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

Age	**Dose (mg)**	**Volume per dose (mL)**		**No. of sachets per dose**	
		125 mg	250 mg	125 mg	250 mg
3 to 6 months	60 to 90	2.5	-	-	-
6 months to 2 years	90 to 180	5 to 7.5	2.5	1 (125 mg)	-
2 to 18 years	180 to 250	7.5 to 10	2.5 to 5	2 (250 mg)	1 (250 mg)

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 Groxime 125 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

Constitution/Administration instructions

The bottle should be shaken vigorously before the medication is taken.

The reconstituted suspension when refrigerated between 2 and 8°C can be kept for up to 10 days.

If desired, FIDSON CEFUROXIME SUSPENSION 125 from multidose Bottles can be further diluted in cold fruit juices, or milk drinks and should be taken immediately.

Directions for reconstituting suspension in multidose Bottles

1. Shake the bottle to loosen the content. All the granules should be free-flowing in the bottle. Remove the cap and the heat-seal membrane. If the latter is damaged or not present, the product should be returned to the pharmacist.
2. Add the total amount of cold water as stated on the label or up to the volume line on the cup provided. If the water was previously boiled it must be allowed to cool to room temperature before adding. Do not mix granules for oral suspension with hot or warm liquids. Cold water must be used to prevent the suspension becoming too thick.
3. Replace the cap. Allow the bottle to stand to allow the water to fully soak through the granules; this should take about one minute.
4. Invert the bottle and shake well (for at least 15 seconds) until all the granules have mixed with the water.
5. Turn the bottle into an upright position and shake well for one minute until all the granules have blended with the water.

Store the FIDSON CEFUROXIME SUSPENSION 125 immediately at between 2 and 8°C (do not freeze) and let it rest for at least one hour before taking the first dose. The reconstituted suspension when refrigerated between 2 and 8°C can be kept for up to 10 days.

Always shake the bottle well before taking the medication.

4.3 Contraindications

FIDSON CEFUROXIME SUSPENSION 125 products are contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

4.4 Special warnings and precautions for use

CEFUROXIME 125 SUSPENSION. Before therapy with CEFUROXIME 125 SUSPENSION products is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to CEFUROXIME 125 SUSPENSION product, other cephalosporins, penicillins, or other drugs. If this product is to be given to penicillin-sensitive patients, caution should be exercised because cross- hypersensitivity among betalactam antibiotics has been clearly documented and may occur in up to 10% of patients with a history of penicillin allergy. If a clinically significant allergic reaction to CEFUROXIME 125 SUSPENSION products occurs, discontinue the drug and institute appropriate therapy. Serious acute hypersensitivity reactions may require treatment with epinephrine and other emergency measures, including oxygen, intravenous fluids, intravenous antihistamines, corticosteroids, pressor amines, and airway management, as clinically indicated. Pseudomembranous colitis has been reported with nearly all antibacterial agents, including cefuroxime, and may range from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents. Treatment with antibacterial agents alters normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by Clostridium difficile is one primary cause of antibiotic-associated colitis. After the diagnosis of pseudomembranous colitis has been established, appropriate therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug effective against Clostridium difficile.

PRECAUTIONS

General As with other broad-spectrum antibiotics, prolonged administration of cefuroxime axetil may result in overgrowth of nonsusceptible microorganisms. If superinfection occurs during therapy, appropriate measures should be taken. Cephalosporins, including cefuroxime axetil, should be given with caution to patients receiving concurrent treatment with potent diuretics because these diuretics are suspected of adversely affecting renal function. Cefuroxime axetil, as with other broadspectrum antibiotics, should be prescribed with caution in individuals with a history of colitis. The safety and effectiveness of cefuroxime axetil have not been established in patients with gastrointestinal malabsorption. Patients with gastrointestinal malabsorption were excluded from participating in clinical trials of cefuroxime axetil. Cephalosporins may be associated with a fall in prothrombin activity. Those at risk include

patients with renal or hepatic impairment or poor nutritional state, as well as patients receiving a protracted course of antimicrobial therapy, and patients previously stabilized on anticoagulant therapy. Prothrombin time should be monitored in patients at risk and exogenous Vitamin K administered as indicated. Prescribing FIDSON CEFUROXIME SUSPENSION 125 in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug- resistant bacteria.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant administration of probenecid with Cefuroxime Axetil for Oral Suspensions 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 FIDSON CEFUROXIME SUSPENSION 125 compared with that of fasting state and tend to cancel the effect of postprandial absorption.

4.6 Pregnancy and Lactation

Teratogenic Effects Pregnancy Category B.Reproduction studies have been performed in mice at doses up to 3,200 mg/kg/day (14 times the recommended maximum human dose based on mg/m2) and in rats at doses up to 1,000 mg/kg/day (9 times the recommended maximum human dose based on mg/m2) and have revealed no evidence of impaired fertility or harm to the fetus due to cefuroxime axetil. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. Nursing Mothers Because cefuroxime is excreted in human milk, consideration should be given to discontinuing nursing temporarily during treatment with cefuroxime axetil. elderly and younger adult patients.

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

In clinical trials using multiple doses of Cefuroxime Axetil for Oral Suspension, pediatric patients (96.7% of whom were younger than 12 years of age) were treated with the recommended dosages of cefuroxime axetil (20 to 30 mg/kg/day divided

twice a day up to a maximum dose of 500 or 1,000 mg/day, respectively). There were no deaths or permanent disabilities in any of the patients in these studies. Eleven US patients (1.2%) discontinued medication due to adverse events thought by the investigators to be possibly, probably, or almost certainly related to drug toxicity. The discontinuations were primarily for gastrointestinal disturbances, usually diarrhea or vomiting. During clinical trials, discontinuation of therapy due to the taste and/or problems with administering this drug occurred in 13 (1.4%) pediatric patients enrolled at centers in the United States. The following adverse events were thought by the investigators to be possibly, probably, or almost certainly related to cefuroxime axetil for oral suspension in multiple-dose clinical trials (n = 931 cefuroxime axetil-treated US patients).

General The following hypersensitivity reactions have been reported: anaphylaxis, angioedema, pruritus, rash, serum sickness-like reaction, urticaria.
Gastrointestinal
Pseudomembranous colitis (see WARNINGS). Hematologic
Hemolytic anemia, leukopenia, pancytopenia, thrombocytopenia, and increased prothrombin time.
Hepatic
Hepatic impairment including hepatitis and cholestasis, jaundice.
Neurologic Seizure. Skin
Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis.
Urologic
Renal dysfunction.

4.9 Overdose

Overdosage of cephalosporins can cause cerebral irritation leading to convulsions. Serum levels of cefuroxime can be reduced by hemodialysis and peritoneal dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics 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

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)*
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

5.2 Pharmacokinetic properties

Absorption and Metabolism
After oral administration. cefuroxime axetil is absorbed from the gastrointestinal tract and rapidly hydrolyzed by nonspecific esterases in the intestinal mucosa and blood to cefuroxime.
Cefuroxime is subsequently distributed throughout the extracellular fluids. The axetil moiety is metabolized to acetaldehyde and acetic acid.

Pharmacokinetics
Approximately 50% of serum cefuroxime is bound to protein. Serum pharmacokinetic parameters for CEFUROXIME 125 SUSPENSION and FIDSON CEFUROXIME 125 SUSPENSION powder for Oral Suspension are shown in Tables 1 and 2.

Table 1. Postprandial Pharmacokinetics of Cefuroxime Administered as FIDSON CEFUROXIME 125 SUSPENSION

Dose (Cefuroxime Equivalent)	Peak Plasma Concentration	Time of Peak Plasma Concentration (hr)	Mean Elimination Half-Life(hr)	AUC (mcg-hr mL)
125 mg	2.1	2.2	1.2	6.7
250 mg	4.1	2.5	1.2	12.9
500 mg	7.0	3.0	1.2	27.4
1000 mg	13.6	2.5	1.3	50.0

*Mean values of 12 healthy adult volunteers. Drug administered immediately after a meal.

Table 2. Postprandial Pharmacokinetics of Cefuroxime Administered as FIDSON CEFUROXIME SUSPENSION 125 for powder Oral Suspension to Pediatric

Dose (Cefuroxime Equivalent)	n	Peak Plasma Concentration	Time of Peak Plasma Concentratio	Mean Elimination Half-Life (hr)	AUC (mcg-hr mL)
10 mg/kg	8	3.3	3.6	1.4	12.4
15 mg/kg	12	5.1	2.7	1.9	22.5
20 mg/kg	8	7.0	3.1	1.9	32.8

*Mean age = 23 months
Drug administered with milk or milk products.

Comparative Pharmacokinetic Properties
A 250 mg/5 mL-dose of CEFUROXIME 125 SUSPENSION Suspension is bioequivalent to 2 times 125 mg/5 mL-dose of CEFUROXIME 125 SUSPENSION
Suspension when administered with food (see Table 3). FIDSON CEFUROXIME SUSPENSION 125 powder for Oral Suspension was not bioequivalent to FIDSON CEFUROXIME 125 SUSPENSION when tested in healthy adults. The Powder for Oral Suspension and powder for oral suspension formulations are NOT substitutable

on a milligram- per-milligram basis. The area under the curve for the suspension averaged 91% of that for the Powder for Oral Suspension, and the peak plasma concentration for the suspension averaged 71% of the peak plasma concentration of the Powder for Oral Suspensions. Therefore, the safety and effectiveness of both the Powder for Oral Suspension and oral suspension formulations had to be established in separate clinical trials.

Table 3. Pharmacokinetics of Cefuroxime Administered as 250 mg/5 mL or 2 x 125 mg/5 mL CEFUROXIME 125 SUSPENSION powder for Oral Suspension to Adults* With Food

Dose (Cefuroxime Equivalent)	Peak Plasma Concentration (mcg/m L)	Time of Peak Plasma Concentration	Mean Elimination Half-Life (hr)	AUC (mcg-hr mL)
250 mg/5mL	2.23	3	1.40	8.92

*Mean values of 18 healthy adult volunteers.

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

Colloidal silicon Dioxide	BP	Sucrose	BP
Sodium Saccharin	BP	Sodium carboxymethylcellulose	BP
Aspartame	BP	Citric Acid	BP
Flavour Strawberry	IH		

6.2 Incompatibilities

Not applicable

6.3 Shelf life: Powder for Oral Suspension: 24 months
Reconstituted suspension: 10 days

6.4 Special precautions for storage

Powder for Oral Suspension: Stored below 30°C.

Reconstituted suspension: When Refrigerated between 2 and 8°C can be kept for up to 10 days.

6.5 Nature and contents of container

130 ml white coloured HDPE bottle duly sealed with white colour plastic natural screw Cap and packed in a printed carton along with pack inert and 10 ml measuring cup.

6.6 Special precautions for disposal and other handling

No special requirements.

7. APPLICANT

FIDSON HEALTHCARE PLC
268 IKORODU ROAD, OBANIKORO, LAGOS STATE, NIGERIA

MANUFACTURER

THE MADRAS PHARMACEUTICALS
137-B, OLD MAHABALIPURAM ROAD, KARAPAKKAM, CHENNAI – 600 096
INDIA