1.3 Product Information

1.3.1 Summary of Product Characteristics (SmPC)

1. NAME OF THE DRUG PRODUCT

1.1 Name of the drug product
Cefuroxime Axetil Tablets USP 500 mg

1.2 Strength
Each film coated tablet contains
Cefuroxime Axetil USP
Eq. to Cefuroxime 500 mg
Excipients Q.S.
Colour: Titanium Dioxide

1.3 Pharmaceutical/Dosage form
Oral Film Coated Tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Batch Size: 1,00,000 Tablets

Sr. No.	Name of Ingredient	Label Claim (mg)	Overages	Qty./ Tablet (mg)	Qty./ Batch (Kg)	%	Function
MIXING							
1.	Cefuroxime axetil USP eq. to Cefuroxime	620.000 ≈ 500.000	-	620.000	62.000	66.10	Active
2.	Microcrystalline Cellulose BP	-	-	70.000	7.000	7.46	Diluent
3.	Sodium Starch Glycolate BP	-	-	20.000	2.000	2.13	Diluent
4.	Polacrilin Potassium (Kyron T-314) USP	-	-	35.000	3.500	3.73	Super-Disintegrant
5.	Croscarmellose Sodium BP	-	-	80.000	8.00	8.53	Disintegrant
6.	Sodium Lauryl Sulfate BP	-	-	35.000	3.500	3.73	Emulsifying agent
LUBRICATION							
7.	Colloidal Anhydrous Silica BP	-	-	10.000	1.000	1.07	Glidant
8.	Magnesium Stearate BP	-	-	10.000	1.000	1.07	Lubricant
9.	Crospovidone BP	-	-	35.000	3.500	3.73	Diluent
Total Weight of uncoated Tablets				**915.000**	**91.500**	-	-
COATING							
10.	Titanium Dioxide BP	-	-	23.000	2.300	2.45	Colouring agent
11.	Isopropyl alcohol BP*	-	-	Q.S.	8 Lit.	-	Solvent
12.	Dichloromethane BP*	-	-	Q.S.	12 Lit.	-	solvent
Total Weight of coated Tablets				**938.000**	**93.800**	**100.00**	**-**

*This will not remain in the finished product.

Calculation:

Molecular weight of Cefuroxime axetil: 510.47 & Molecular weight of Cefuroxime: 424.39

Theoretical qty. of Cefuroxime axetil = $\frac{500 \times \text{Molecular wt. of Cefuroxime axetil}}{\text{Molecular wt. of Cefuroxime}}$

Theoretical qty. of Cefuroxime axetil = $\frac{500 \times 510.47}{424.39}$ = 601.41 mg/tablets

3 % overages added= 601.41 * 103.0/100 = 619.45 eq. to 620 mg/tablets

3. PHARMACEUTICAL FORM

White coloured capsule shape biconvex film coated tablets with plain on both side.

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/Dosage and method of administration:

Posology

Course of therapy is seven days (may range from five to ten days). Dosage schedule for tablets:

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	15 mg/kg twice daily to a maximum of 250 mg twice daily

appropriate, with more severe infections	
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. 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 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 cefuroxime or to any of the excipients listed. 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.

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.

Important information about excipients Special care should be taken with phenyl ketonuric patients because of the aspartame containing coating. Cefuroxime axetil 125 mg coated tablets contain 0.2 mg aspartame per tablet. Cefuroxime axetil 250 mg coated tablets contain 0.3 mg aspartame per tablet.

4.5 Interaction with other drug 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 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 Fertility, 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. Because Cefuroxime may cause somnolence and dizziness, patients should be cautioned about operating machinery, including motor vehicles.

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).

Table 1:

System Organ Class	Adverse Reactions	Frequency Category
Infections and infestations	alveolar osteitis	Common
	gastroenteritis, upper respiratory infection, urinary tract infection	Uncommon
Blood and lymphatic system disorders	anaemia (primarily associated with gastrointestinal bleeding), leukopenia, thrombocytopenia	Uncommon
Immune system disorders	hypersensitivity‡ ß	Uncommon
Nervous system disorders	dizziness, headache	Common
Gastrointestinal disorders	abdominal pain	Very common
Hepatobiliary disorders	ALT increased, AST increased	Common
Skin and subcutaneous	ecchymosis	Common

tissue disorders		
	facial oedema, pruritus, rash, erythema‡, urticaria‡	Uncommon
	Stevens-Johnson syndrome‡, toxic epidermal necrolysis‡, fixed drug eruption‡	Rare†
Musculoskeletal and connective tissue disorders	muscular cramp/spasm, musculoskeletal pain/stiffness	Uncommon
Renal and urinary disorders	proteinuria, serum creatinine increased, renal failure/renal insufficiency‡	Uncommon
General disorders and administration site conditions	asthenia/fatigue, flu-like disease	common
	chest pain	Uncommon
Investigations	blood urea nitrogen increased, creatine phosphokinase increased, hyperkalaemia, uric acid increased	Uncommon
	blood sodium decreased	Rare

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. 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 topenicillin 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]

1The 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.

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
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 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. 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

Paediatric

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.

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

Excipients	Specification
Microcrystalline Cellulose	BP
Sodium starch glycolate	BP
Polacrillin potassium	USP
Croscarmellose sodium	BP
Sodium lauryl sulphate	BP
Colloidal Anhydrous Silica	BP
Magnesium Stearate	BP
Crospovidone	BP
Titanium Dioxide	BP
Isopropyl alcohol	BP
Dichloromethane	BP

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

36 months from the date of manufacturing.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

1 X 10 Tablets Alu-Alu Blister Packare packed in printed carton along with package insert.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7. APPLICANT/HOLDER OF CERTIFICATE OF PRODUCT REGISTRATION

Remedial health solutions limited
304b Abisogun Leigh Street, Ogba,
Lagos, Nigeria

8. DRUG PRODUCT MANUFACTURER

SWISS PHARMA PVT. LTD.
Manufacturing At: Plot No. - 3709, GIDC,
Phase-IV, Vatva, Dist-Ahmedabad-382 445,
Gujarat, Country: India.

9. NAFDAC REGISTRATION NUMBER(S)
