1. NAME OF THE MEDICINAL PRODUCT

Generic Name: Cefuroxime Axetil Tablets USP 500 mg

Brand Name: ---

Strength: 500mg

2. QUALITATIVE AND QUANTITATIVES COMPOSITION:

Each film Coated tablets contains :
Cefuroxime Axetil USP
Equivalent to anhydrous Cefuroxime... 500 mg
Excipients ..... q.s.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM:

Pharmaceutical Form: Film Coated Tablets

Visual description of finished product:

White to off white coloured, capsule shaped, standard biconvex and film coated tablets with break line on one side.
The finished product is packed in a Alu- Alu blister of 10 tablets. One such blister packed in Preprinted carton along with pack insert.

4. CLINICAL PARTICULARS

4.1 Indications and Usage

Cefuroxime Axetil Tablets are indicated for the treatment of patients with mild to moderate infections caused by susceptible strains of the designated microorganisms in the conditions listed below:
Pharyngitis/Tonsillitis caused by Streptococcus pyogenes. 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 Axetil Tablets are generally effective in the eradication of streptococci from the nasopharynx; however, substantial data establishing the efficacy of cefuroxime in the subsequent prevention 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.

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.

Acute Bacterial Maxillary Sinusitis caused by Streptococcus pneumoniae or Haemophilus influenzae (non-beta-lactamase-producing strains only).

Acute Bacterial Exacerbations of Chronic Bronchitis and Secondary Bacterial Infections of Acute Bronchitis caused by Streptococcus pneumoniae, Haemophilus influenzae (beta-lactamase negative strains), or Haemophilus parainfluenzae (beta-lactamase negative strains).

Uncomplicated Skin and Skin-Structure Infections caused by Staphylococcus aureus (including beta-lactamase-producing strains) or Streptococcus pyogenes.

Uncomplicated Urinary Tract Infections caused by Escherichia coli or Klebsiella pneumoniae.
Uncomplicated Gonorrhea, urethral and endocervical, caused by penicillinase-producing and non-penicillinase-producing strains of Neisseria gonorrhoeae and uncomplicated gonorrhea, rectal, in females, caused by non-penicillinase-producing strains of Neisseria gonorrhoeae.
Early Lyme Disease (erythema migrans) caused by Borrelia burgdorferi.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Cefuroxime Axetil Tablets and other antibacterial drugs, Cefuroxime Axetil Tablets should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

4.2 Posology and method of administration

Table 4: Cefuroxime Axetil Tablets

Population/Infection	Dosage	Duration (days)
Adolescents and Adults (13 years and older)		
Pharyngitis/tonsillitis	250 mg b.i.d.	10
Acute bacterial maxillary sinusitis	250 mg b.i.d.	10
Acute bacterial exacerbations of chronic bronchitis	250 or 500 mg b.i.d.	10*
Secondary bacterial infections of acute bronchitis	250 or 500 mg b.i.d.	5 to 10

Uncomplicated skin and skin-structure infections	250 or 500 mg b.i.d.	10
Uncomplicated urinary tract infections	250 mg b.i.d.	7 to 10
Uncomplicated gonorrhea	1,000 mg once	single dose
Early Lyme disease	500 mg b.i.d.	20
Pediatric Patients (who can swallow tablets whole)		
Acute otitis media	250 mg b.i.d.	10
Acute bacterial maxillary sinusitis	250 mg b.i.d.	10

*The safety and effectiveness of cefuroxime axetil administered for less than 10 days in patients with acute exacerbations of chronic bronchitis have not been established.

Patients with Renal Failure: The safety and efficacy of Cefuroxime axetil in patients with renal failure have not been established. Since Cefuroxime is renaly eliminated, its half-life will be prolonged in patients with renal failure.

Route/ Way of administration: oral

4.3 Contraindications

Cefuroxime axetil products are contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

4.4 Special Warning and Precautions for use

Before therapy with Cefuroxime Axetil product is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reaction to Cefuroxime Axetil products, other Cephalosporins, penicillins, or other drugs. If this product to be given to penicillin-sensitive patients, caution should be exercised because cross hypersensitivity among beta lactam antibiotics has been clearly documented and may occur in up to 10% of patient with a history of penicillin allergy. If a clinically significant allergic reaction to Cefuroxime Axetil product occurs, discontinue the drug and institute appropriate therapy. Serious epinephrine and other emergency measures, including oxygen, intravenous fluid, intravenous antihistamines, corticosteroids, pressor amines and airway management, as clinically indicated.

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including cefuroxime axetil tablets, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of C. difficile.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of C. difficile cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against C. difficile may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of C. difficile, and surgical evaluation should be instituted as clinically indicated.

PRECAUTIONS

General

As with other broad-spectrum antibiotics, prolonged administration of cefuroxime axetil may result in overgrowth of non-susceptible microorganisms. If super infection 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 broad-spectrum 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 cefuroxime axetil tablets 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.

Diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as 2 or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.

Information for Patients

Patients should be counseled that antibacterial drugs, including cefuroxime axetil tablets, should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When cefuroxime axetil tablets are prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may: (1) decrease the effectiveness of the immediate treatment, and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by cefuroxime axetil tablets or other antibacterial drugs in the future.

4.5 Interaction with other medicinal products and other forms of interaction

Drug/Drug Interactions
Concomitant administration of probenecid with cefuroxime axetil tablets 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 cefuroxime axetil 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
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/m 2) 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.

Labor and Delivery
Cefuroxime axetil has not been studied for use during labor and delivery.

Nursing Mothers
Because cefuroxime is excreted in human milk, consideration should be given to discontinuing nursing temporarily during treatment with cefuroxime axetil.

4.7 Effects on ability to drive and use machines

Not reported

4.8 Undesirable Effects

Multiple-Dose Dosing Regimens: *7 to 10 Days Dosing:* Using multiple doses of cefuroxime axetil tablets, 912 patients were treated with cefuroxime axetil (125 to 500 mg twice daily). There were no deaths or permanent disabilities thought related to drug toxicity. Twenty (2.2%) patients discontinued medication due to adverse events thought by the investigators to be possibly, probably, or almost certainly related to drug toxicity. Seventeen (85%) of the 20 patients who discontinued therapy did so because of gastrointestinal disturbances, including diarrhea, nausea, vomiting, and abdominal pain. The percentage of cefuroxime axetil tablet-treated patients who discontinued study drug because of adverse events was very similar at daily doses of 1,000, 500, and 250 mg (2.3%, 2.1%, and 2.2%, respectively). However, the incidence of gastrointestinal adverse events increased with the higher recommended doses.

The following adverse events were thought by the investigators to be possibly, probably, or almost certainly related to cefuroxime axetil tablets in multiple-dose clinical trials (n = 912 cefuroxime axetil-treated patients).

Table 2: Adverse Reactions Cefuroxime Axetil Tablets Multiple-Dose Dosing Regimens—Clinical Trials

Incidence ≥ 1%	Diarrhea/loose stools	3.7%
	Nausea/vomiting	3%
	Transient elevation in AST	2%
	Transient elevation in ALT	1.6%
	Eosinophilia	1.1%
	Transient elevation in LDH	1%
Incidence	Abdominal pain	
< 1% but > 0.1%	Abdominal cramps	
	Flatulence	
	Indigestion	
	Headache	
	Vaginitis	
	Vulvar itch	

	Rash	
	Hives	
	Itch	
	Dysuria	
	Chills	
	Chest pain	
	Shortness of breath	
	Mouth ulcers	
	Swollen tongue	
	Sleepiness	
	Thirst	
	Anorexia	
	Positive Coombs' test	

5-Day Experience: In clinical trials using cefuroxime axetil in a dose of 250 mg twice daily in the treatment of secondary bacterial infections of acute bronchitis, 399 patients were treated for 5 days and 402 patients were treated for 10 days. No difference in the occurrence of adverse events was found between the 2 regimens.

In Clinical Trials for Early Lyme Disease With 20 Days Dosing: Two multicenter trials assessed cefuroxime axetil tablets 500 mg twice a day for 20 days. The most common drug-related adverse experiences were diarrhea (10.6% of patients), Jarisch-Herxheimer reaction (5.6%), and vaginitis (5.4%). Other adverse experiences occurred with frequencies comparable to those reported with 7 to 10 days dosing.

Single-Dose Regimen for Uncomplicated Gonorrhea: In clinical trials using a single dose of cefuroxime axetil tablets, 1,061 patients were treated with the recommended dosage of cefuroxime axetil (1,000 mg) for the treatment of uncomplicated gonorrhea. There were no deaths or permanent disabilities thought related to drug toxicity in these studies.
The following adverse events were thought by the investigators to be possibly, probably, or almost certainly related to cefuroxime axetil in 1,000 mg single-dose clinical trials of cefuroxime axetil tablets in the treatment of uncomplicated gonorrhea conducted in the United States.

Table 3: Adverse Reactions Cefuroxime Axetil Tablets1 g Single-Dose Regimen for Uncomplicated Gonorrhea—Clinical Trials		
Incidence ≥ 1%	Nausea/vomiting	6.8%
	Diarrhea	4.2%
Incidence	Abdominal pain	
< 1% but > 0.1%	Dyspepsia	
	Erythema	
	Rash	
	Pruritus	
	Vaginal candidiasis	
	Vaginal itch	
	Vaginal discharge	
	Headache	
	Dizziness	
	Somnolence	
	Muscle cramps	
	Muscle stiffness	
	Muscle spasm of neck	
	Tightness/pain in chest	
	Bleeding/pain in urethra	
	Kidney pain	
	Tachycardia	
	Lockjaw-type reaction	

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:

Clinical Pharmacology

Cefuroxime is used to treat a wide variety of bacterial infections. It works by stopping the growth of bacteria.

Inhibits bacterial cell wall synthesis by binding to one or more of the penicillin-binding proteins (PBPs) which in turn inhibits the final transpeptidation step of peptidoglycan synthesis in bacterial cell walls, thus inhibiting cell wall biosynthesis. Bacteria eventually lyse due to ongoing activity of cell wall autolytic enzymes (autolysins and murein hydrolases) while cell wall assembly is arrested.

5.2 Pharmacokinetics 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 axetil tablets are shown in Table 1.

Table 1: Postprandial Pharmacokinetics of Cefuroxime Administered as Cefuroxime Axetil Tablets to Adults*

Dose† (Cefuroxime Equivalent)	Peak Plasma Concentration (mcg/mL)	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	3	1.2	27.4
1,000 mg	13.6	2.5	1.3	50

*Mean values of 12 healthy adult volunteers.

†Drug administered immediately after a meal.

Comparative Pharmacokinetic Properties

Cefuroxime axetil for oral suspension was not bioequivalent to cefuroxime axetil tablets when tested in healthy adults. The tablet 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 tablet, and the peak plasma concentration for the suspension averaged 71% of the peak plasma concentration of the tablets. Therefore, the safety and effectiveness of both the tablet and oral suspension formulations had to be established in separate clinical trials.

Food Effect on Pharmacokinetics
Absorption of the tablet is greater when taken after food (absolute bioavailability of cefuroxime axetil tablets increases from 37% to 52%). Despite this difference in absorption, the clinical and bacteriologic responses of patients were independent of food intake at the time of tablet administration in 2 studies where this was assessed.
Renal Excretion
Cefuroxime is excreted unchanged in the urine; in adults, approximately 50% of the administered dose is recovered in the urine within 12 hours. The pharmacokinetics of cefuroxime in the urine of pediatric patients have not been studied at this time. Until further data are available, the renal pharmacokinetic properties of cefuroxime axetil established in adults should not be extrapolated to pediatric patients.

Because cefuroxime is renally excreted, the serum half-life is prolonged in patients with reduced renal function. In a study of 20 elderly patients (mean age = 83.9 years) having a mean creatinine clearance of 34.9 mL/min, the mean serum elimination half-life was 3.5 hours. Despite the lower elimination of cefuroxime in geriatric patients, dosage adjustment based on age is not necessary.
Microbiology
The *in vivo* bactericidal activity of cefuroxime axetil is due to cefuroxime's binding to essential target proteins and the resultant inhibition of cell-wall synthesis.
Cefuroxime has bactericidal activity against a wide range of common pathogens, including many beta-lactamase–producing strains. Cefuroxime is stable to many bacterial beta-lactamases, especially plasmid-mediated enzymes that are commonly found in enterobacteriaceae.
Cefuroxime has been demonstrated to be active against most strains of the following microorganisms both *in vitro* and in clinical infections

Aerobic Gram-Positive Microorganisms:
Staphylococcus aureus (including beta-lactamase-producing strains)
Streptococcus pneumoniae
Streptococcus pyogenes
Aerobic Gram-Negative Microorganisms:
Escherichia coli
Haemophilus influenzae (including beta-lactamase–producing strains)
Haemophilus parainfluenzae
Klebsiella pneumoniae
Moraxella catarrhalis (including beta-lactamase–producing strains)
Neisseria gonorrhoeae (including beta-lactamase-producing strains)
Spirochetes:
Borrelia burgdorferi

Cefuroxime has been shown to be active *in vitro* against most strains of the following microorganisms; however, the clinical significance of these findings is unknown.

Cefuroxime exhibits *in vitro* minimum inhibitory concentrations (MICs) of 4 mcg/mL or less (systemic susceptible breakpoint) against most (≥90%) strains of the following microorganisms; however, the safety and effectiveness of cefuroxime in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled trials.

Aerobic Gram-Positive Microorganisms:
Staphylococcus epidermidis
Staphylococcus saprophyticus
Streptococcus agalactiae
NOTE: *Listeria monocytogenes* and certain strains of enterococci, e.g., *Enterococcus faecalis* (formerly *Streptococcus faecalis*), are resistant to cefuroxime. Methicillin-resistant staphylococci are resistant to cefuroxime.
Aerobic Gram-Negative Microorganisms:
Morganella morganii
Proteus inconstans
Proteus mirabilis

Providencia rettgeri
NOTE: *Pseudomonas* spp., *Campylobacter* spp., *Acinetobacter calcoaceticus*, *Legionella* spp., and most strains of *Serratia* spp. and *Proteus vulgaris* are resistant to most first- and second-generation cephalosporins. Some strains of *Morganella morganii*, *Enterobacter cloacae*, and *Citrobacter* spp. have been shown by *in vitro* tests to be resistant to cefuroxime and other cephalosporins.

Anaerobic Microorganisms:
Peptococcus niger
NOTE: Most strains of *Clostridium difficile* and *Bacteroides fragilis* are resistant to cefuroxime.
Susceptibility Tests

Dilution Techniques
Quantitative methods that are used to determine MICs provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure uses a standardized dilution method 1 (broth, agar, or microdilution) or equivalent with cefuroxime powder. The MIC values obtained should be interpreted according to the following criteria:

MIC (mcg/mL)	Interpretation
≤ 4	(S) Susceptible
8 to 16	(I) Intermediate
≥ 32	(R) Resistant

A report of "Susceptible" indicates that the pathogen, if in the blood, is likely to be inhibited by usually achievable concentrations of the antimicrobial compound in blood. A report of "Intermediate" indicates that inhibitory concentrations of the antibiotic may be achieved if high dosage is used or if the infection is confined to tissues or fluids in which high antibiotic concentrations are attained. This category also provides a buffer zone that prevents small, uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that usually achievable concentrations of the antimicrobial compound in the blood are unlikely to be inhibitory and that other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control microorganisms. Standard cefuroxime powder should give the following MIC values:

Microorganism	MIC (mcg/mL)
Escherichia coli ATCC 25922	2 to 8
Staphylococcus aureus ATCC 29213	0.5 to 2

Diffusion Techniques
Quantitative methods that require measurement of zone diameters provide estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure 2 that has been recommended (for use with disks) to test the susceptibility of microorganisms to cefuroxime uses the 30 mcg cefuroxime disk. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for cefuroxime.
Reports from the laboratory providing results of the standard single-disk susceptibility test with a 30 mcg cefuroxime disk should be interpreted according to the following criteria:

Zone Diameter (mm)	Interpretation
≥ 23	(S) Susceptible
15 to22	(I) Intermediate
≤ 14	(R) Resistant

Interpretation should be as stated above for results using dilution techniques.

As with standard dilution techniques, diffusion methods require the use of laboratory control microorganisms. The 30 mcg cefuroxime disk provides the following zone diameters in these laboratory test quality control strains:

Microorganism	Zone Diameter (mm)
Escherichia coli ATCC 25922	20 to 26
Staphylococcus aureus ATCC 25923	27 to 35

5.3 Preclinical safety Data:

Carcinogenesis, Mutagenesis, Impairment of Fertility

Although lifetime studies in animals have not been performed to evaluate carcinogenic potential, no mutagenic activity was found for cefuroxime axetil in a battery of bacterial mutation tests. Positive results were obtained in an *in vitro* chromosome aberration assay; however, negative results were found in an *in vivo* micronucleus test at doses up to 1.5 g/kg. Reproduction studies in rats at doses up to 1,000 mg/kg/day (9 times the recommended maximum human dose based on mg/m2) have revealed no impairment of fertility.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients:

S. No.	Name of ingredient	Pharmacopoeia
1.	Microcrystalline Cellulose PH 102	BP
2.	Croscarmellose Sodium	BP
3.	Cross Povidone	BP
4.	Colloidal Anhydrous Silica	BP
5.	Sodium Citrate	BP
6.	Sodium Bicarbonate	BP
7.	Purified Talcum	BP
8.	Kyron T 314	BP
9.	Magnesium Stearate	BP
10.	Hydroxy Propyl Methyl Cellulose (E-5)	BP
11.	Hydroxy Propyl Methyl Cellulose (E-15)	BP
12.	Diethyl Pthalate	BP
13.	Titanium Dioxide	BP
14.	Talcum	BP
15.	MDC	BP
16.	IPA	BP

6.2 Incompatibilities:

All the excipients are compatible to each other and also compatible with primary packaging material and container closure system, hence do not interfere in the formulation.

6.3 Shelf life:

3 years (36 Months)

6.4 Special precautions for storage:

Store below 30°C in a dry place. Protect from light.

Keep out of reach of children

6.5 Nature and contents of container:

The finished product is packed in a Alu- Alu blister of 10 tablets. One such blister packed in preprinted carton along with pack insert

Pack Presentation: of 1 x10's

6.6. Special precautions for disposal

None

7. MARKETING AUTHORIZATION HOLDER

Name :
Address :

Tel. :
Fax :
Email :

8. MARKETING AUTHORIZATION NUMBER

New Applicable

9. DATE OF FIRST AUTHORIZATION/ RENEWAL OF THE AUTHORIZATION

New Applicable

10. DATE OF REVISION OF THE TEXT

New Applicable