CEFUROXIME TABLETS 500mg

PULMOCEF

13. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT
Cefuroxime tablets

13.1 Strength:
500mg

13.2 Pharmaceutical form
Tablets for oral administration

14. Quality and Quantitative Composition
Each film coated tablet contains:
Cefuroxime Axetil USP (Amorphous)
Equivalet to Cefuroxime 500 mg
Colour : Titanium Dioxide

15. Pharmaceutical Form
Tablets

16. Clinical Particulars
16.1 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.

16.2 Posology 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 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.
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 hemodialysis	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.

16.3 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.

16.4 Contraindications

It is contraindicated in patients with a known hypersensitivity (e.g., anaphylaxis) to Cefuroxime or to other β-lactam antibacterial drugs (e.g., penicillins and cephalosporins).

16.5 Special warning and precautions

Anaphylactic Reactions

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients on β-lactam Antibacterials. These reactions are more likely to occur in individuals with a history of β-lactam hypersensitivity and/or a history of sensitivity to multiple allergens. There have been reports of individuals with a history of penicillin hypersensitivity who have experienced severe reactions when treated with cephalosporins. Cefuroxime is contraindicated in patients with a known hypersensitivity to Cefuroxime or other β-lactam antibacterial drugs. Before initiating therapy with Cefuroxime, inquire about previous hypersensitivity reactions to penicillins, cephalosporins, or other allergens. If an allergic reaction occurs, discontinue Cefuroxime and institute appropriate therapy.

Clostridium difficile-associated Diarrhea

Clostridium difficile-associated diarrhoea (CDAD) has been reported with use of nearly all antibacterial agents, including Cefuroxime, and may range in severity from mild diarrhoea 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 2 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.

Potential for Microbial Overgrowth

The possibility of super infections with fungal or bacterial pathogens should be considered during therapy.

Development of Drug-resistant Bacteria

Prescribing Cefuroxime either 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.

Phenylketonuria

Cefuroxime for oral suspension 125 mg/5 mL contains phenylalanine 11.8 mg per 5 mL (1 teaspoonful) of reconstituted suspension. Cefuroxime for oral suspension 250 mg/5 mL contains phenylalanine 25.2 mg per 5 mL (1 teaspoonful) of reconstituted suspension.

Interference with Glucose Tests

A false-positive result for glucose in the urine may occur with copper reduction tests, and a false-negative result for blood/plasma glucose may occur with ferricyanide tests in subjects receiving Cefuroxime.

16.6 Paediatric population

None

16.7 Interaction with other medicinal products and other forms of interactions

Oral Contraceptives

Cefuroxime axetil may affect the gut flora, leading to lower estrogen reabsorption and reduced efficacy of combined oral estrogen/progesterone contraceptives. Counsel patients to consider alternate supplementary (non-hormonal) contraceptive measures during treatment

Drugs that Reduce Gastric Acidity

Drugs that reduce gastric acidity may result in a lower bioavailability of Cefuroxime axetil compared with administration in the fasting state. Administration of drugs that reduce gastric acidity may negate the food effect of increased absorption of Cefuroxime axetil when administered in the postprandial state. Administer Cefuroxime axetil at least 1 hour before or 2 hours after administration of short-acting antacids. Histamine-2 (H2) antagonists and proton pump inhibitors should be avoided.

Probenecid

Concomitant administration of Probenecid with cefuroxime axetil tablets increases serum concentrations of cefuroxime. Co-administration of Probenecid with cefuroxime axetil is not recommended.

Drug/Laboratory Test Interactions

A false-positive reaction for glucose in the urine may occur with copper reduction tests (e.g., Benedict's or Fehling's solution), but not with enzyme-based tests for glycosuria. As a false-negative result may occur in the ferricyanide test, it is recommended that either the glucose oxidase or hexokinase method be used to determine blood/plasma glucose levels in patients receiving cefuroxime axetil. The presence of cefuroxime does not interfere with the assay of serum and urine creatinine by the alkaline picrate method.

16.8 Additional information on special populations

None

16.9 Paediatric population

None

16.10 Fertility, pregnancy and lactation

16.10.1 General principles

16.10.2 Women of childbearing potential / Contraception in males and females

Not known

16.10.3 ***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.

16.10.4 ***Lactation***

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 sensitization should be taken into account. Cefuroxime should only be used during breastfeeding after benefit/risk assessment by the physician in charge.

16.4.5 ***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.

16.11 Effects on ability to drive and use machine

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.

16.12 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 utilized 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 Coomb's test, thrombocytopenia, leukopenia (sometimes profound)	haemolytic anemia
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 multiform, Stevens-Johnson syndrome, toxic epidermal necrolysis (exanthematic necrolysis), 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 anemia.
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.

16.13 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 hemodialysis and peritoneal dialysis.

17. Pharmacological Properties
17.1 Pharmacodynamic Properties
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 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*
Spirochaete: *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: *Peptostreptococci* 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.

17.2 Pharmacokinetic Properties:

Absorption

After oral administration cefuroxime axetil is absorbed from the gastrointestinal tract and rapidly hydrolyzed 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.

Pediatrics

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).

17.3 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 trans peptidase 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.

17.4 Environmental Risk Assessment (ERA)

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

18. Pharmaceutical Particulars

18.1 List of excipients

Sodium Lauryl Sulphate, Cross Carmellose Sodium, Hydrogenated Castor Oil, Microcrystalline Cellulose, Anhydrous Colloidal Silicon Dioxide, Methylene Chloride, Isopropyl Alcohol, Tab Coat TC-1004.

18.2 Incompatibilities

None

18.3 Shelf life

36 months from the date of manufacturing.

18.4 Special precautions for storage

Store below 30°C. Keep this medicine out of reach of children

18.5 Nature and contents of container

Alu/Alu Blister pack of 10 Tablets, such 1 blisters are packed in printed outer carton along with pack insert.

18.6 Special precautions for disposal and other handling

None

19. Marketing Authorization Holder and Manufacturing Site Addresses

Micro Labs Limited
M/s. MICRO LABS LTD
Plot No. 121 - 124, K.I.A.D.B,
Bommasandra Industrial Area,
4th Phase, Anekal Taluk,
Bangalore – 560 099

20. Marketing Authorisation Number

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21. Date of First Registration/Renewal of the registration

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22. Date of revision of the text

April 2019

23. DOSIMETRY

Not applicable

24. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Not applicable