

Front

210 mm



## CEFUXIME AXETIL

### KEFEZY

500 mg Film-Coated Tablet

ANTIBACTERIAL

**PRODUCT NAME:**  
Kefezy 500

**DOSAGE FORM AND STRENGTH:**  
Cefuroxime (as axetil) 500mg film-coated tablets

**PHARMACOLOGIC CATEGORY:** Antibacterial

**PRODUCT DESCRIPTION:**  
White oblong shaped film-coated tablet having breakline on one side and plain on another side.

**FORMULATION/COMPOSITION:**  
Each film-coated tablet contains:

Cefuroxime Axetil USP  
equivalent to Cefuroxime ..... 500 mg

#### PHARMACODYNAMICS/PHARMACOKINETICS:

##### Pharmacodynamics:

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.

##### Pharmacokinetics:

###### 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 (2.1 mcg/ml for a 125 mg dose, 4.1 mcg/ml for a 250 mg dose, 7.0 mcg/ml for a 500 mg dose and 13.6 mcg/ml for a 1000 mg dose) occur approximately 2 to 3 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 humour. 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 m<sup>2</sup>.

#### 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.

#### DOSAGE AND MODEL ROUTE OF ADMINISTRATION:

##### Posology

The usual course of therapy is seven days (may range from five to ten days).

Table 1. Adults and children ( $\geq 40$  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 5. Recommended doses for Cefuroxime Axetil in renal impairment

Creatinine clearance	T <sub>1/2</sub> (hrs)	Recommended dosage
$\geq 30$ ml/min/1.73 m <sup>2</sup>	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 <sup>2</sup>	4.6	standard individual dose given every 24 hours
<10 ml/min/1.73 m <sup>2</sup>	16.8	standard individual dose given every 48 hours
During haemodialysis	2–4	a single additional 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 film-coated tablets should be taken after food for optimum absorption.

Cefuroxime Axetil film-coated 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.

Depending on the dosage, there are other presentations available.

#### CONTRAINdications & PRECAUTION(S), WARNING(S)

##### 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.

#### PRECAUTIONS & WARNINGS:

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Size: 210 x 240 mm  
Folding size: 105 x 30±5 mm

240 mm

**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.

**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.

**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 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.

**INTERACTIONS:**

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.

**ADVERSE EFFECTS:**

The most common adverse reactions are *Candida* overgrowth, eosinophilia, headache, dizziness, gastrointestinal disturbances and transient rise in liver enzymes.

The frequency categories assigned to the adverse reactions below are estimates, as for most reactions suitable data (for example from placebo-controlled studies) for calculating incidence were not available. In addition the incidence of adverse reactions associated with cefuroxime Axetil may vary according to the indication.

Data from large clinical studies were used to determine the frequency of very common to rare undesirable effects. The frequencies assigned to all other undesirable effects (i.e. those occurring at <1/10,000) were mainly determined using post-marketing data and refer to a reporting rate rather than true frequency. Placebo-controlled trial data were not available. Where incidences have been calculated from clinical trial data, these were based on drug-related (investigator assessed) data. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Treatment related adverse reactions, all grades, are listed below by MedDRA body system organ class, frequency and grade of severity. The following convention has been utilised for the classification of frequency: very common ≥ 1/10; common ≥ 1/100 to < 1/10, uncommon ≥ 1/1,000 to < 1/100; rare ≥ 1/10,000 to < 1/1,000; very rare < 1/10,000 and not known (cannot be estimated from the available data).

System organ class	Common	Uncommon	Not known
Infections and infestations	<i>Candida</i> overgrowth		<i>Clostridium difficile</i> overgrowth
Blood and lymphatic system disorders	eosinophilia	positive Coomb's test, thrombocytopenia, leukopenia (sometimes profound)	haemolytic anaemia

Immune system disorders			drug fever, serum sickness, anaphylaxis, Jarisch-Herxheimer reaction
Nervous system disorders	headache, dizziness		
Gastrointestinal disorders	diarrhoea, nausea, abdominal pain	vomiting	pseudomembranous colitis
Hepatobiliary disorders	transient increases of hepatic enzyme levels		jaundice (predominantly cholestatic), hepatitis
Skin and subcutaneous tissue disorders		skin rashes	urticaria, pruritus, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (exanthematic necrolysis), angioneurotic oedema

**Description of selected adverse reactions**

Cephalosporins as a class tend to be absorbed onto the surface of red cells membranes and react with antibodies directed against the drug to produce a positive Coombs' test (which can interfere with cross-matching of blood) and very rarely haemolytic anaemia. Transient rises in serum liver enzymes have been observed which are usually reversible.

**Paediatric population**

The safety profile for cefuroxime Axetil in children is consistent with the profile in adults.

**OVERDOSAGE AND TREATMENT:**

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.

**STORAGE CONDITION:**

Store at temperatures not exceeding 30°C.

**DOSAGE FORMS AND PACKAGING AVAILABLE:**

Alu/Alu Blister Pack of 4's (Box of 12's and Box of 30's)

**INSTRUCTIONS AND SPECIAL PRECAUTIONS FOR HANDLING AND DISPOSAL (IF APPLICABLE):**

Not Applicable

**NAME AND ADDRESS OF MARKETING AUTHORIZATION HOLDER:**

Marketing Authorization Holder

Brown & Burk Philippines Inc

U-501, 5/F., SEDCCO 1 Bldg., 120 Rada cor., Legaspi Sts., Legaspi Village, Makati City, Philippines

**NAME AND ADDRESS OF MANUFACTURER:**

MICRO LABS LIMITED

No. 121-124, 4th Phase, K.I.A.D.B.

Bommasandra Industrial Area, Anekal Taluk, Bangalore-560 099, India

**CAUTION STATEMENT:**

FOODS, DRUGS, DEVICES, AND COSMETICS ACT PROHIBITS DISPENSING WITHOUT PRESCRIPTION.

**ADR REPORTING STATEMENT:**

"FOR SUSPECTED ADVERSE DRUG REACTION, REPORT TO THE FDA: www.fda.gov.ph Seek medical attention immediately at the first sign of Adverse Drug Reaction.

**REGISTRATION NUMBER:**

DRP-560

**DATE OF FIRST AUTHORIZATION:**

28 MAY 2008

**DATE OF REVISION OF PACKAGE INSERT:**

April 2018

EXG-ML07I-0011/C

MICRO LABS LIMITED, BANGALORE, INDIA						
1	Product Name	Kefezy			Colours Used ■ BLACK	
2	Strength	500 mg				
3	Component	Leaflet				
4	Category	Export - Philippines				
5	Dimension	210 x 240 mm				
6	Artwork Code	EXG-ML07I-0011/C				
7	Pharma Code	NA				
8	Reason for Change	Size and New text				
		Prepared by (DTP)	Checked by (PD)	Approved by		
Sign		Kantharaju L.		Head CQA	Head Production/ Packing (Site)	
Date		05-06-2020		Head QC (Site)	Head QA (Site)	