# Cefuroxime axetil

## Zinnat® Suspension

### PRODUCT DESCRIPTION

**Cefuroxime (as axetil) *(Zinnat®) 125mg/5mL granules for suspension:*** when reconstituted gives a white tutti frutti flavored suspension containing 125mg Cefuroxime (as axetil) per teaspoon (5mL) of suspension.
**Cefuroxime (as axetil) *(Zinnat®) 250mg/5mL granules for suspension:*** when reconstituted gives a white tutti frutti flavored suspension containing 250mg Cefuroxime (as axetil) per teaspoon (5mL) of suspension.
**Sachet:**
**Cefuroxime (as axetil) *(Zinnat®)* 125mg Granules for Suspension*:*** Each 4.22g of single-use sachet contains 125mg Cefuroxime (as axetil) which gives a white tutti frutti flavored suspension when reconstituted.

### PHARMACOLOGIC PROPERTIES

**Pharmacodynamics**
The prevalence of acquired resistance is geographically and time dependent and for select species may be very high. Local information on resistance is desirable, particularly when treating severe infections.

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|---|
| In vitro susceptibility of micro-organisms to Cefuroxime<br><br>Where clinical efficacy of cefuroxime axetil has been demonstrated in clinical trials this is indicated with an asterisk (*). |
| Commonly Susceptible Species |
| Gram-Positive Aerobes: |
| *Staphylococcus aureus (methicillin susceptible)** |
| *Coagulase negative staphylococcus (methicillin susceptible)* |
| *Streptococcus pyogenes** |
| *Beta-hemolytic streptococci* |
| Gram-Negative Aerobes: |
| *Haemophilus influenzae* including ampicillin resistant strains* |
| *Haemophilus parainfluenzae** |
| *Moraxella catarrhalis** |
| *Neisseria gonorrhoea* including penicillinase and non-penicillinase producing strains* |
| Gram-Positive Anaerobes: |
| *Peptostreptococcus spp.* |
| *Propionibacterium spp.* |
| Spirochetes: |
| *Borrelia burgdorferi** |
| Organisms for which acquired resistance may be a problem |
| Gram-Positive Aerobes: |
| *Streptococcus pneumoniae** |
| Gram-Negative Aerobes: |
| *Citrobacter spp. not including C. freundii* |
| *Enterobacter spp. not including E. aerogenes and E. cloacae* |
| *Escherichia coli** |
| *Klebsiella spp. including Klebsiella pneumoniae** |
| *Proteus mirabilis* |
| *Proteus spp. not including P. penneri and P. vulgaris* |
| *Providencia spp.* |
| Gram-Positive Anaerobes: |
| *Clostridium spp. not including C. difficile* |
| Gram-Negative Anaerobes: |
| *Bacteroides spp. not including B. fragilis* |
| *Fusobacterium spp.* |
| Inherently resistant organisms |
| Gram-Positive Aerobes: |

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| *Enterococcus spp. including E. faecalis and E. faecium* |
| *Listeria monocytogenes* |
| Gram-Negative Aerobes: |
| *Acinetobacter spp.* |
| *Burkholderia cepacia* |
| *Campylobacter spp.* |
| *Citrobacter freundii* |
| *Enterobacter aerogenes* |
| *Enterobacter cloacae* |
| *Morganella morganii* |
| *Proteus penneri* |
| *Proteus vulgaris* |
| *Pseudomonas spp. including Pseudomonas aeruginosa* |
| *Serratia spp.* |
| *Stenotrophomonas maltophilia* |
| Gram-Positive Anaerobes: |
| *Clostridium difficile* |
| Gram-Negative Anaerobes: |
| *Bacteroides fragilis* |
| Others: |
| *Chlamydia species* |
| *Mycoplasma species* |
| *Legionella species* |

**Pharmacokinetics**

**Absorption**

After oral administration, Cefuroxime axetil *(Zinnat®)* is absorbed from the gastrointestinal tract and rapidly hydrolysed in the intestinal mucosa and blood to release cefuroxime into the circulation.

Absorption of cefuroxime axetil suspension is enhanced in the presence of food.

Following administration of Cefuroxime axetil *(Zinnat®)* tablets peak serum levels (2.1 mg/l for a 125 mg dose, 4.1 mg/l for a 250 mg dose, 7.0 mg/l for a 500 mg dose and 13.6 mg/l for a 1 g dose) occur approximately 2 to 3 hours after dosing when taken with food.

The rate of absorption of cefuroxime from the suspension compared with the tablets is reduced, leading to later, lower peak serum levels and slightly reduced systemic bioavailability (4-17% less).

**Distribution**

Protein binding has been variously stated as 33-50% depending on the methodology used.

**Metabolism**

Cefuroxime is not metabolised.

Cefuroxime is excreted by glomerular filtration and tubular secretion.

Concurrent administration of probenecid increases the area under the mean serum concentrations time curve by 50%.

**Renal impairment:**

Cefuroxime pharmacokinetics have been investigated in patients with various degrees of renal impairment. Cefuroxime elimination half-life increases with decrease in renal function which serves as the basis for dosage adjustment recommendations in this group of patients (See Dosage and Administration). In patients undergoing haemodialysis, at least 60% of the total amount of cefuroxime present in the body at the start of dialysis will be removed during a 4-hour dialysis period. Therefore, an additional single dose of cefuroxime should be administered following the completion of haemodialysis.

**Preclinical Safety Data**

Animal toxicity studies indicated that cefuroxime axetil is of low toxicity with no significant findings.

## INDICATIONS

Cefuroxime is an oral prodrug of the bactericidal cephalosporin antibiotic cefuroxime, which is resistant to most β (beta)-lactamases and is active against a wide range of Gram-positive and Gram-negative organisms. It is indicated for the treatment of infections caused by susceptible bacteria. Susceptibility to Cefuroxime axetil *(Zinnat®)* will vary with geography and time and local susceptibility data should be consulted where available (*See Pharmacological properties, Pharmacodynamics*).

Indications include:

- upper respiratory tract infections for example, ear, nose and throat infections, such as otitis media, sinusitis, tonsillitis and pharyngitis
- lower respiratory tract infections for example, pneumonia, acute bronchitis, and acute exacerbations of chronic bronchitis
- genito-urinary tract infections for example, pyelonephritis, cystitis and urethritis
- skin and soft tissue infections for example, furunculosis, pyoderma and impetigo
- gonorrhoea, acute uncomplicated gonococcal urethritis, and cervicitis.
- treatment of early Lyme disease and subsequent prevention of late Lyme disease in adults and children over 12 years old.
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## DOSAGE AND ADMINISTRATION

The usual course of therapy is seven days. (Range 5 - 10 days).

For optimal absorption cefuroxime axetil should be taken with food.

**Adults:**

| | |
|---|---|
| Most infections | - 250mg twice daily |
| Urinary tract infections | - 125mg twice daily |
| Mild to moderate lower respiratory tract infections e.g. bronchitis | - 250mg twice daily |
| More severe lower respiratory tract infections, or if pneumonia is suspected | - 500mg twice daily |
| Pyelonephritis | - 250mg twice daily |
| Uncomplicated gonorrhoea | - single dose of 1g |

**Children:**

When prescription of a fixed dose is preferred, the recommended dose for most infections is 125mg twice daily. In children aged two years or older with otitis media or where appropriate, with more severe infections, the dose is 250mg twice daily, to a maximum of 500mg daily.

There is no clinical trial data available on the use of Cefuroxime axetil *(Zinnat®)* in children under the age of 3 months.

In infants and children, it may be preferable to adjust dosage according to weight or age. The dose in infants and children 3 months to 12 years is 10mg/kg twice daily for most infections, to a maximum of 250mg daily. In otitis media or more severe infections the recommended dose is 15mg/kg twice daily to a maximum of 500mg daily.

The following two tables, divided by age group and weight, serve as a guideline for simplified administration from measuring spoons (5ml) for the 125mg/5ml or the 250mg/5ml multi-dose suspension.

**10mg/kg dosage for most infections**

| Age | Approximate weight range (kg) | Dose mg twice daily |
|---|---|---|
| 3 - 6 months | 4 - 6 | 40 - 60 |
| 6 months - 2 years | 6 - 12 | 60 - 120 |
| 2 - 12 years | 12 more than 20 | 125 |

**15mg/kg dosage for otitis media and more serious infections**

| Age | Approximate weight range (kg) | Dose mg twice daily |
|---|---|---|
| 3 - 6 months | 4 - 6 | 60 - 90 |
| 6 months - 2 years | 6 - 12 | 90 - 180 |
| 2 - 12 years | 12 more than 20 | 180-250 |

To enhance compliance and improve the dosing accuracy in very young children, a dosing syringe can be supplied with a multidose bottle containing 50 ml of suspension. However, dosing in spoonfuls should be considered a more favourable option if the child is able to take the medication from the spoon.

If required, the dosing syringe may also be used in older children (please refer to the dosing tables below).

The recommended doses for the paediatric dosing syringe are expressed in ml or mg and according to bodyweight in the following tables. (Countries must select the relevant columns as required).

**10mg/kg/dose (Paediatric dosing syringe)**

| Child's weight (kg) | Dose twice daily (mg) | 125mg/5ml dose twice daily (ml) | 250mg/5ml dose twice daily (ml) |
|---|---|---|---|
| 4 | 40 | 1.6 | 0.8 |
| 6 | 60 | 2.4 | 1.2 |
| 8 | 80 | 3.2 | 1.6 |
| 10 | 100 | 4.0 | 2.0 |
| 12 | 120 | 4.8 | 2.4 |
| 14 | 140 | 5.6 | 2.8 |

**15 mg/kg/dose (Paediatric dosing syringe)**

| Child's weight (kg) | Dose twice daily (mg) | 125mg/5ml dose twice daily (ml) | 250mg/5ml dose twice daily (ml) |
|---|---|---|---|
| 4 | 60 | 2.4 | 1.2 |
| 6 | 90 | 3.6 | 1.8 |
| 8 | 120 | 4.8 | 2.4 |
| 10 | 150 | 6.0 | 3.0 |
| 12 | 180 | 7.2 | 3.6 |
| 14 | 210 | 8.4 | 4.2 |

Cefuroxime is also available as the sodium salt for parenteral administration. This permits parenteral therapy with cefuroxime to be followed by oral therapy in situations where a change from parenteral to oral treatment is clinically indicated.

- **Renal impairment**

Cefuroxime is primarily excreted by the kidneys. In patients with markedly impaired renal function it is recommended that the dosage of cefuroxime be reduced to compensate for its slower excretion (see the table below).

| Creatinine Clearance | $T_{1/2}$ (hours) | Recommended Dosage |
|---|---|---|
| ≥30 ml/min | 1.4 - 2.4 | No dose adjustment necessary standard dose of 125 mg to 500 mg given twice daily |
| 10-29 ml/min | 4.6 | Standard individual dose given every 24 hours |
| <10 ml/min | 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 |

## CONTRAINDICATIONS

Patients with known hypersensitivity to cephalosporin antibiotics.

## WARNINGS & PRECAUTIONS

Special care is indicated in patients who have experienced an allergic reaction to penicillins or other beta-lactams.
As with other antibiotics, use of Cefuroxime axetil *(Zinnat®)* may result in the overgrowth of Candida. Prolonged use may also result in the overgrowth of other non-susceptible organisms (e.g. enterococci and *Clostridium difficile*), which may require interruption of treatment.
Pseudomembranous colitis has been reported with the use of antibiotics, and may range in severity from mild to life-threatening. Therefore, it is important to consider its diagnosis in patients who develop diarrhoea during or after antibiotic use. If prolonged or significant diarrhoea occurs or the patient experiences abdominal cramps, treatment should be discontinued immediately and the patient investigated further.
The sucrose content of Cefuroxime axetil *(Zinnat®)* suspension and granules should be taken into account when treating diabetic patients, and appropriate advice provided.
Cefuroxime axetil *(Zinnat®)* suspension contains aspartame, which is a source of phenylalanine and so should be used with caution in patients with phenylketonuria.
**Ability to perform tasks that require judgement, motor or cognitive skills**
As this medicine may cause dizziness, patients should be warned to be cautious when driving or operating machinery.

## DRUG INTERACTIONS

Drugs which reduce gastric acidity may result in a lower bioavailability of Cefuroxime axetil *(Zinnat®)* compared with that of the fasting state and tend to cancel the effect of enhanced absorption after food.
In common with other antibiotics, Cefuroxime axetil *(Zinnat®)* may affect the gut flora, leading to lower oestrogen reabsorption and reduced efficacy of combined oral contraceptives.
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. This antibiotic does not interfere in the alkaline picrate assay for creatinine.

## PREGNANCY AND LACTATION

There is no experimental evidence of embryopathic or teratogenic effects attributable to cefuroxime axetil but, as with all drugs, it should be administered with caution during the early months of pregnancy. Cefuroxime is excreted in human milk, and consequently caution should be exercised when cefuroxime axetil is administered to a nursing mother.

## ADVERSE EFFECTS

Adverse drug reactions to Cefuroxime axetil *(Zinnat®)* are generally mild and transient in nature.
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 *(Zinnat®)* 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.
**The following convention has been used for the classification of frequency:**

very common ≥1/10
common ≥1/100 to <1/10
uncommon ≥1/1000 to <1/100
rare ≥1/10,000 to <1/1000
very rare <1/10,000

**Infections and infestations**
Common: Overgrowth of Candida
**Blood and lymphatic system disorders**
Common: osinophilia
Uncommon: Positive Coombs' test, thrombocytopenia, leukopenia (sometimes profound)
Very rare: Haemolytic anaemia
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.
**Immune system disorders**
Hypersensitivity reactions including
Uncommon: Skin rashes
Rare: Urticaria, pruritus
Very rare: Drug fever, serum sickness, anaphylaxis
**Nervous system disorders**
Common: Headache, Dizziness
**Gastrointestinal disorders**
Common: Gastrointestinal disturbances including diarrhoea, nausea, abdominal pain
Uncommon: Vomiting
Rare: Pseudomembranous colitis *(See Warnings and Precautions)*

**Hepatobiliary disorders**
Common: Transient increases of hepatic enzyme levels, [ALT (SGPT), AST (SGOT), LDH]
Very rare: Jaundice (predominantly cholestatic), hepatitis
**Skin and subcutaneous tissue disorders**
Very rare: Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (exanthematic necrolysis)
See also Immune system disorders.

## OVERDOSAGE

**Signs and symptoms**
Overdosage of cephalosporins can cause cerebral irritation leading to convulsions.
**Treatment**
Serum levels of cefuroxime can be reduced by haemodialysis and peritoneal dialysis.

## STORAGE CONDITION

Cefuroxime axetil *(Zinnat®)* Granules for suspension should be stored at temperatures not exceeding 30°C.

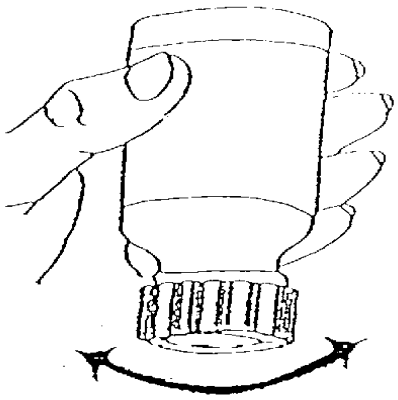
Multi dose bottles: The reconstituted suspension must be refrigerated immediately between 2 and 8°C, and can be kept for up to 10 days.
Sachet: The reconstituted suspension should be taken immediately.

Further diluted suspension added in children's cold fruit juices or milk should be taken immediately.

## INSTRUCTIONS FOR USE / HANDLING

**Constitution / Administration instructions**
Always shake the bottle vigorously before taking the medication.
The reconstituted suspension when refrigerated between 2 and 8°C can be kept for up to 10 days.
If desired Cefuroxime axetil *(Zinnat®)* suspension can be further diluted from multidose bottles 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 granules. Remove the cap and the heat-seal membrane. If the latter is damage or not present, the product should be returned to the pharmacist.
2. Add the total amount of water to the bottle as stated on its label. Replace the cap.
3. Invert the bottle and rock vigorously (for at least 15 seconds) as shown below.



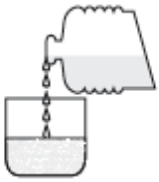
4. Turn the bottle into an upright position and shake vigorously.
5. Refrigerate immediately at between 2 and 8°C.
6. If using a dosing syringe, allow the reconstituted suspension to stand for at least one hour before taking the first dose.

**Directions for using the dosing syringe:-**

1. Remove the bottle cap and insert the syringe-collar assembly into the neck of the bottle. Press it down completely until the collar fits in the neck firmly. Invert the bottle and syringe.
2. Pull the plunger up the barrel until the barrel's rim is aligned with the mark on the plunger corresponding to the required dose.
3. Turn the bottle and syringe into an upright position. While holding onto the syringe and the plunger to ensure that the plunger does not move, remove the syringe from the bottle, leaving the plastic collar in the bottle neck.
4. With the patient seated in an upright position, place the tip of the syringe just inside the patients mouth, pointing towards the inside of the cheek.
5. Press the plunger of the syringe in slowly to expel the medicine without causing choking. Do NOT squirt the medicine out in a jet.
6. After giving the dose replace the bottle cap without removing the plastic collar. Dismantle the syringe and wash it thoroughly in fresh drinking water. Allow the plunger and the barrel to dry naturally.

The reconstituted suspension or granules should not be mixed with hot liquids.

**Directions for reconstituting suspension from <u>sachets</u>:**

| | | |
|---|---|---|
| 1  | 2  | 3  |
| 1. Empty the granules from the sachet into a glass. | 2. Add a small volume of water, atleast 10mL. | 3. Stir well and drink immediately. |

EACH SACHET IS FOR SINGLE USE ONLY.

## AVAILABILITY

Cefuroxime axetil *(Zinnat®) 125mg/5mL granules for suspension:* Multidose bottles of 50mL and 70mL.
Cefuroxime axetil *(Zinnat®) 250mg/5mL granules for suspension:* Multidose bottles of 50mL.

Cefuroxime axetil *(Zinnat®) 125mg Granules for Suspension:* Heat-sealed Laminate of Paper/Polyethylene/Aluminum Foil and Ethylene Methacrylic acid Ionomer in 4.22g (net content) sachet. (Box of 10's).

## CAUTION

Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.
Keep all medicines out of reach of children.



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