PRODUCT INFORMATION

ZINNAT® TABLETS

NAME OF THE MEDICINE

Cefuroxime axetil

Cefuroxime axetil is the 1-(acetyl oxy)ethyl ester of cefuroxime. Its chemical name is (RS)-1-hydroxyethyl(6R,7R)-7-[2-(2-furyl)gly oxylamido]-3-(hydroxymethyl)-8-oxo-5-thia-1-azabicyclo [4.2.0]-oct-2-ene-2-carboxylate, 7 2)–(Z)–(O-methoxyime), 1-acetate 3-carbamate. Its molecular formula is C_{20}H_{22}N_{4}O_{10}S, and it has a molecular weight of 510.48.

Cefuroxime axetil is in the amorphous form, and it has the following structural formula:

![Structural formula of Cefuroxime axetil]

Chiral centre at C*  
CAS Registry Number : 64544-07-6

PHARMACOLOGY

Mode Of Action:

Cefuroxime axetil is a semisynthetic cephalosporin. It is a prodrug which owes its \textit{in vivo} bactericidal activity to the release of the active compound cefuroxime.

Cefuroxime has bactericidal activity against a wide range of common pathogens, including beta-lactamase producing strains. The bactericidal action of cefuroxime results from inhibition of cell wall synthesis by binding to essential target proteins. Cefuroxime has good stability to bacterial beta-lactamases.

Microbiology:

Cefuroxime has been shown to be usually active against the following organisms \textit{in vitro} and in clinical studies:

- \textit{Aerobes Gram-negative:}
  - \textit{Escherichia coli}
  - \textit{Haemophilus influenzae} (including ampicillin-resistant strains)
  - \textit{Haemophilus parainfluenzae}
  - \textit{Neisseria gonorrhoeae} (non-penicillinase producing strains)
- \textit{Aerobes Gram-positive}
  - \textit{Staphylococcus aureus} and \textit{Staphylococcus epidermidis} (including penicillinase producing strains but
The following organisms are not susceptible to Cefuroxime:

- **Clostridium difficile**
- Pseudomonas spp
- Campylobacter spp
- *Acinetobacter calcoaceticus*
- Methicillin resistant strains of *Staphylococcus aureus* and *Staphylococcus epidermidis*
- *Proteus vulgaris*
- Morganella morganii
- Serratia spp
- *Bacteroides fragilis*
- Most strains of *Streptococcus faecalis*
- Citrobacter spp
- Enterobacter spp

**Susceptibility Tests:**

**Diffusion Techniques**

Quantitative methods that require measurement of zone diameters give the most precise estimate of antibiotic susceptibility. One such standard procedure that has been recommended for use with disks to test susceptibility of organisms to cefuroxime uses the 30 mcg cefuroxime disk. Interpretation involves the correlation of the diameters obtained in the disk test with the minimum inhibitory concentration (MIC) for cefuroxime.

Reports from the laboratory giving results of the standard single-disk susceptibility test with a 30 mcg cefuroxime disk should be interpreted according to the following criteria:

<table>
<thead>
<tr>
<th>Zone diameter (mm)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥23</td>
<td>(S) Susceptible</td>
</tr>
<tr>
<td>15-22</td>
<td>(MS) Moderately Susceptible</td>
</tr>
<tr>
<td>≤14</td>
<td>(R) Resistant</td>
</tr>
</tbody>
</table>

A report of "Susceptible" indicates that the pathogen is likely to be inhibited by generally achievable blood levels. A report of "Moderately Susceptible" suggests that the organism would be susceptible if high dosage is used or if the infection is confined to tissues and fluids in which high antibiotic levels are attained. A report of "Resistant" indicates that achievable concentrations of the antibiotic are unlikely to be inhibitory and other therapy should be selected.

Standardized procedures require the use of laboratory control organisms. The 30 mcg cefuroxime disk should give the following zone diameters:

<table>
<thead>
<tr>
<th>Organism</th>
<th>Zone Diameter (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Staphylococcus aureus</em> ATCC 25923</td>
<td>27-36</td>
</tr>
<tr>
<td><em>Escherichia coli</em> ATCC 25922</td>
<td>20-26</td>
</tr>
</tbody>
</table>

**Dilution Techniques**

Use a standardized dilution method (broth, agar, microdilution) or equivalent with cefuroxime powder. The MIC values obtained should be interpreted according to the following criteria:
MIC (mcg/mL) Interpretation

\[ \leq 4 \quad \text{Susceptible} \\
8-16 \quad \text{Moderately Susceptible} \\
\geq 32 \quad \text{Resistant} \\

As with standard diffusion techniques, dilution methods require the use of laboratory control organisms. Standard cefuroxime powder should provide the following MIC values:

<table>
<thead>
<tr>
<th>Organism</th>
<th>MIC (mcg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Staphylococcus aureus</em> ATCC 29213</td>
<td>0.5-2</td>
</tr>
<tr>
<td><em>Escherichia coli</em> ATCC 25922</td>
<td>2-8</td>
</tr>
</tbody>
</table>

**PHARMACOKINETICS**

After oral administration cefuroxime axetil is absorbed from the gastrointestinal tract and rapidly hydrolysed in the body to release cefuroxime into the circulation. Approximately 60\% of an administered dose is absorbed. Optimum absorption occurs when it is administered after a light meal. Absorption is not decreased by drugs which affect gastrointestinal motility eg loperamide, diphenoxylate or castor oil. However, absorption is decreased by concurrent administration of drugs such as ranitidine.

The mean peak serum level of cefuroxime following a 250 mg dose in normal healthy adults, after food, was 4.1 mg/L and occurred two to three hours after dosing. Serum levels were significantly higher in the elderly, apparently due to slower excretion. Unhydrolysed drug has not been detected in the serum but 1-2\% of the administered dose is excreted in the urine in a form which indicates that small amounts of the intact ester are absorbed into circulation. The mean serum half life of cefuroxime is approximately 1.2 hours. Protein binding has been variously stated as 33-50\% depending on the methodology used. Cefuroxime is not metabolised to any significant extent.

Excretion occurs mainly through the kidney both by glomerular filtration and tubular secretion. Approximately 49\% of an administered dose, after food, is recovered in the urine in 24 hours; urinary recovery is significantly reduced if the drug is taken on an empty stomach. After a 250 mg dose urinary concentrations at 0-6 and 6-12 hours were 227 mcg/mL (range 92-515) and 35.3 mcg/mL (range 7.6-102) respectively.

Concurrent administration of probenecid prolongs the terminal half life of cefuroxime. Serum levels of cefuroxime are reduced by haemodialysis.

**INDICATIONS**

Cefuroxime is indicated for the treatment of the following mild to moderately severe infections in adults caused by sensitive bacteria.

Acute upper respiratory infections: otitis media, sinusitis, tonsillitis and pharyngitis.

Acute exacerbations of chronic bronchitis, or acute bronchitis.

Skin and skin structure infections for example, furunculosis, pyoderma and impetigo.

Acute uncomplicated gonococcal urethritis, and cervicitis due to non-penicillinase producing gonococci.
CONTRAINDICATIONS

Patients with known hypersensitivity to cephalosporin antibiotics or who have experienced a major allergy to penicillin (anaphylaxis, angioneurotic oedema, urticaria).

PRECAUTIONS

Serious and occasionally fatal hypersensitivity (anaphylactic/ anaphylactoid) reactions have been reported in patients on penicillin/cephalosporin therapy. Although anaphylaxis is more frequent following parenteral therapy, it has occurred in patients on oral penicillins/cephalosporins. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity and/or a history of sensitivity to multiple allergens. There have been reports of individuals with a history of penicillin/cephalosporin hypersensitivity who have experienced severe reactions when treated with a penicillin/cephalosporin. Past history of a severe allergic reaction to penicillin/cephalosporin is a contraindication to the use of cefuroxime axetil. Before initiating therapy with any penicillin/cephalosporin careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, or other allergens. If an allergic reaction occurs, cefuroxime axetil should be discontinued and the appropriate therapy instituted. Serious anaphylactoid reactions require immediate emergency treatment with adrenaline. Oxygen, intravenous steroids, and airway management, including intubation, should also be administered as indicated.

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 organisms (eg Enterococci and Clostridium), which may require interruption of treatment.

Antibiotic associated pseudomembranous colitis has been reported with many antibiotics including cefuroxime axetil. A toxin produced by Clostridium difficile appears to be the primary cause. The severity of the colitis may range from mild to life threatening. It is important to consider this diagnosis in patients who develop diarrhoea or colitis in association with antibiotic use (this may occur up to several weeks after cessation of antibiotic therapy). Mild cases usually respond to drug discontinuation alone although cholestyramine may help by binding the toxin in the colonic lumen. However, in moderate to severe cases appropriate therapy with a suitable oral antibacterial agent effective against Clostridium difficile should be considered. Fluids, electrolytes and protein replacement should be provided when indicated.

Drugs which delay peristalsis eg opiates and diphenoxylate with atropine (Lomotil) may prolong and/or worsen the condition and should not be used.

Patients with Severe Renal Impairment: Dosage of cefuroxime should not exceed 500 mg per day and should be repeated after dialysis.

Use in the Elderly: The serum half life of cefuroxime is increased and plasma levels raised in elderly patients with declining renal function. No dosage reduction is necessary in such patients at recommended dosages.

Use in Pregnancy: Pregnancy Category: B1
There is no experimental evidence of embryopathic or teratogenic effects attributable to cefuroxime axetil. However, there is no clinical data on the use of cefuroxime axetil during pregnancy. Therefore it should be administered during pregnancy only if such use is considered essential.

Use in Lactation: Cefuroxime is excreted in human milk, and consequently caution should be exercised when cefuroxime axetil is administered to a nursing mother.
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.

Interactions with other medicines:

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.

Drugs such as ranitidine may result in a lower bioavailability of cefuroxime axetil compared with that of the fasting state.

In common with other antibiotics, cefuroxime axetil may affect the gut flora, leading to lower oestrogen reabsorption and reduced efficacy of combined oral contraceptives.

DOSAGE AND ADMINISTRATION

The usual course of therapy with Zinnat tablets is 5 to 7 days for treatment of bronchitis, and 7 to 10 days for other infections.

Cefuroxime axetil should be taken after a light meal for optimum absorption.

Adults
Acute exacerbations of

<table>
<thead>
<tr>
<th>Condition</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute bronchitis</td>
<td>250 mg to 500 mg twice daily</td>
</tr>
<tr>
<td>Uncomplicated gonococcal urethritis or cervicitis</td>
<td>single dose of 1 g</td>
</tr>
<tr>
<td>Other infections</td>
<td>250 mg twice daily</td>
</tr>
</tbody>
</table>

ADVERSE EFFECTS

Adverse reactions to cefuroxime axetil have been generally mild and transient in nature. The drug was discontinued in 2.1% of cases, mainly due to diarrhoea/nausea.

The following adverse reactions to cefuroxime axetil have been reported in clinical trials. However, the possibility of the occurrence of other adverse reactions, seen with the cephalosporin class of antibiotics, should be borne in mind.

Gastrointestinal
Diarrhoea, nausea, vomiting, abdominal discomfort, abdominal pain, flatulence, indigestion, dry mouth, mouth ulcers, pseudomembranous colitis.

Hepatic
Jaundice (predominantly cholestatic), hepatitis, transient elevations of AST, ALT and LDH.

CNS
Headache, dizziness

Haemopoietic
Eosinophilia, positive Coomb's test, increased coagulation time, leukopenia, haemolytic anaemia.

Hypersensitivity
Rash, pruritus, urticaria
Patients with a history of delayed hypersensitivity to penicillin (but not a cephalosporin) experienced delayed hypersensitivity reaction to cefuroxime axetil in 2.9% cases.

As with other cephalosporins, rare cases of severe hypersensitivity reactions, including Stevens Johnsons Syndrome, erythema multiforme, toxic epidermal necrosis, drug fever, serum sickness-like reaction and anaphylaxis have been reported with cefuroxime axetil.

**Infections and infestations**  
Candida overgrowth

**Others**  
Vaginitis

**OVERDOSAGE**

Overdosage of cephalosporins can cause cerebral irritation leading to convulsions.

Serum levels of cefuroxime can be reduced by haemodialysis.

Contact the Poisons Information Centre (telephone 13 11 26) for advice on overdose management.

**PRESENTATION AND STORAGE CONDITIONS**

When stored below 30°C Zinnat tablets have a 3 year shelf life.

Zinnat Tablets 125 mg*: White, film coated, capsule shaped, biconvex tablets engraved "GXES5" on one face and blank on the other. Each tablet contains cefuroxime (as axetil) 125 mg in foil blisters of 2, 10, 14 and 50.

Zinnat Tablets 250 mg: White, film coated, capsule shaped, biconvex tablets engraved "GXES7" on one face and blank on the other. Each tablet contains cefuroxime (as axetil) 250 mg in foil blisters of 2*, 10*, 14 and 50*.

Zinnat tablets also contain cellulose-microcrystalline, croscarmellose sodium, hypromellose, methyl hydroxybenzoate, Opaspray White M-1-7120, propylene glycol, propyl hydroxybenzoate, silica-colloidal anhydrous, sodium lauryl sulphate and hydrogenated vegetable oil.

*currently not marketed

**NAME AND ADDRESS OF THE SPONSOR**

GlaxoSmithKline Australia Pty Ltd  
Level 4,  
436 Johnston Street,  
Abbotsford, Victoria, 3067

**POISON SCHEDULE OF THE MEDICINE**

Schedule 4 – Prescription Only Medicine

Zinnat® is a registered trade mark of the GlaxoSmithKline group of companies
Date of TGA Approval: 21 December 1993
Date of most recent amendment: 28 April 2011
Version 3.0