ZINNAT Tablets
Cefuroxime axetil

QUALITATIVE AND QUANTITATIVE COMPOSITION

250 mg tablet – engraved GXES7 on one side and plain on the other. Each tablet contains cefuroxime 250 mg (as cefuroxime axetil).

500 mg tablet – engraved GXEG2 on one side and plain on the other. Each tablet contains cefuroxime 500 mg (as cefuroxime axetil).

PHARMACEUTICAL FORM

Coated tablet.

CLINICAL PARTICULARS

Indications

ZINNAT is an oral prodrug of the bactericidal cephalosporin antibiotic cefuroxime, which is resistant to most β(lactamase) 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 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.

Cefuroxime is also available as the sodium salt (ZINACEF) for parenteral administration. This permits the use of sequential therapy with the same antibiotic, when a change from parenteral to oral therapy is clinically indicated.

Where appropriate ZINNAT is effective when used following initial parenteral ZINACEF (cefuroxime sodium) in the treatment of pneumonia and acute exacerbations of chronic
bronchitis.

**Dosage and Administration**

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

*ZINNAT* should be taken after food for optimum absorption.

**Dosage in adults:**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most infections</td>
<td>250mg twice daily</td>
</tr>
<tr>
<td>Urinary tract infections</td>
<td>250mg twice daily</td>
</tr>
<tr>
<td>Mild to moderate lower respiratory tract infections e.g. bronchitis</td>
<td>250mg twice daily</td>
</tr>
<tr>
<td>More severe lower respiratory tract infections, or if pneumonia is suspected</td>
<td>500mg twice daily</td>
</tr>
<tr>
<td>Pyelonephritis</td>
<td>250mg twice daily</td>
</tr>
<tr>
<td>Uncomplicated gonorrhoea</td>
<td>single dose of 1g</td>
</tr>
</tbody>
</table>

Sequential therapy:

**Pneumonia:**

1.5g *ZINACEF* tds or bd (intravenous (i.v.) or intramuscular (i.m.) for 48-72 hours, followed by 500mg bd *ZINNAT* (cefuroxime axetil) oral therapy for 7-10 days.

**Acute exacerbations of chronic bronchitis:**

750 mg *ZINACEF* tds or bd (i.v. or i.m.) for 48-72 hours, followed by 500mg bd *ZINNAT* (cefuroxime axetil) oral therapy for 5-10 days.

Duration of both parenteral and oral therapy is determined by the severity of the infection and the clinical status of the patient.

**Dosage in children:**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most infections</td>
<td>125mg (1 x 125mg tablet) twice daily, to a maximum of 250mg daily.</td>
</tr>
<tr>
<td>Children aged two years or older with otitis media or, where appropriate, with more severe infections</td>
<td>250mg (1 x 250mg tablet or 2 x 125mg tablets) twice daily, to a maximum of 500mg daily.</td>
</tr>
</tbody>
</table>
ZINNAT tablets should not be crushed and are therefore unsuitable for treatment of patients, such as younger children, who cannot swallow tablets. In children ZINNAT oral suspension may be used.

There is no experience of using ZINNAT in children under the age of 3 months.

**Dosage in 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).

<table>
<thead>
<tr>
<th>Creatinine Clearance</th>
<th>T(_{1/2}) (hours)</th>
<th>Recommended Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥30 mL/min</td>
<td>1.4 - 2.4</td>
<td>No dose adjustment necessary (standard dose of 125 mg to 500 mg given twice daily)</td>
</tr>
<tr>
<td>10-29 mL/min</td>
<td>4.6</td>
<td>Standard individual dose given every 24 hours</td>
</tr>
<tr>
<td>&lt;10 mL/min</td>
<td>16.8</td>
<td>Standard individual dose given every 48 hours</td>
</tr>
<tr>
<td>During haemodialysis</td>
<td>2 – 4</td>
<td>A single additional standard individual dose should be given at the end of each dialysis</td>
</tr>
</tbody>
</table>

**Contra-indications**

Patients with known hypersensitivity to cephalosporin antibiotics.

**Warnings and 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 ZINNAT may result in the overgrowth of *Candida*. Prolonged use may 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.
With a sequential therapy regime the timing of change to oral therapy is determined by severity of the infection, clinical status of the patient and susceptibility of the pathogens involved. If there is no clinical improvement within 72 hours, then the parenteral course of treatment must be continued.

Please refer to the relevant prescribing information for cefuroxime sodium before initiating sequential therapy.

**Interactions**

Drugs which reduce gastric acidity may result in a lower bioavailability of ZINNAT compared with that of the fasting state and tend to cancel the effect of enhanced post-prandial absorption.

In common with other antibiotics, 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 ZINNAT. 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 ZINNAT 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 ZINNAT is administered to a nursing mother.

**EFFECTS ON ABILITY TO DRIVE AND USE MACHINES**

As this medicine may cause dizziness, patients should be warned to be cautious when driving or operating machinery.

**Adverse Reactions**

Adverse drug reactions to 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 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 $\geq 1/10$
- common $\geq 1/100$ to $< 1/10$
- uncommon $\geq 1/1000$ to $< 1/100$
- rare $\geq 1/10,000$ to $< 1/1000$
- very rare $< 1/10,000$

**Infections and infestations**

Common: Overgrowth of Candida

**Blood and lymphatic system disorders**

Common: Eosinophilia
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*.

**Overdose**

**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.

**PHARMACOLOGICAL 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.

*In vitro* susceptibility of micro-organisms to Cefuroxime
Where clinical efficacy of cefuroxime axetil has been demonstrated in clinical trials this is indicated with an asterisk (*).

**Commonly Susceptible Species**

**Gram-Negative Aerobes:**

- *Haemophilus influenzae* including ampicillin-resistant strains
- *Haemophilus parainfluenzae*
- *Moraxella catarrhalis*
- *Neisseria gonorrhoeae* including penicillinase and non-penicillinase producing strains

**Gram-Positive Aerobes:**

- *Staphylococcus aureus* (methicillin susceptible)
- *Coagulase negative staphylococcus* (methicillin susceptible)
- *Streptococcus pyogenes*
- *Beta-hemolytic streptococci*

**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:

*Enterococcus* spp. including *E. faecalis* and *E. faecium*
*Listeria monocytogenes*
*Methicillin resistant strains of Staphylococcus aureus* and *Staphylococcus* spp.

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 ZINNAT is slowly 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 ZINNAT tablets peak serum levels (2.1 mg/l for a 125mg dose, 4.1 mg/l for a 250mg dose, 7.0 mg/l for a 500mg dose and 13.6 mg/l for a 1g dose) occur approximately 2 to 3 hours after dosing when taken with food.

Distribution

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

Metabolism

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. 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.

PHARMACEUTICAL PARTICULARS

Special precautions for storage

*ZINNAT* tablets should be stored below 25°C

Not all presentations are available in every country.

GlaxoSmithKline

Glaxo Wellcome Operations, UK

*ZINNAT* and *ZINACEF* are trademarks of the GSK Group of Companies.

Version number: GDS26/IPI06(SI)
Date of issue: 25th August 2016

[GSK logo]