ZINNAT

Cefuroxime axetil

QUALITATIVE AND QUANTITATIVE COMPOSITION

ZINNAT Suspension contains granules of cefuroxime axetil for oral suspension. Reconstitution of multidose bottles as directed yields a suspension containing 125 mg or 250 mg of cefuroxime (as cefuroxime axetil) in each 5 ml.

ZINNAT Sachets contain 125 mg, 250 mg or 500 mg granules of cefuroxime (as cefuroxime axetil) for single dose administration when reconstituted.

PHARMACEUTICAL FORM

Dry, white to off-white, tutti-frutti flavoured granules for oral suspension.

CLINICAL PARTICULARS

Indications

ZINNAT 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 *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 from 3 months old and above**~~.

Dosage and Administration

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

For optimal absorption, *ZINNAT* should be taken with food.

- **Adults**

Most infections	250 mg twice daily
Urinary tract infections	250 mg twice daily
Mild to moderate lower respiratory tract infections e.g. bronchitis	250 mg twice daily
More severe lower respiratory tract infections, or if pneumonia is suspected	500 mg twice daily
Pyelonephritis	250 mg twice daily
Uncomplicated gonorrhoea	single dose of 1 g
Lyme disease in adults and children over the age of 12 years.	500 mg twice daily for 14 days (range of 10- 21 days)

- **Children**

~~**When prescription of a fixed dose is preferred, the recommended dose for most infections is 125 mg twice daily. In children aged two years or older with otitis media or where appropriate, with more severe infections, the dose is 250 mg twice daily, to a maximum of 500 mg daily. In children aged 3 months to 12 years with Lyme disease, the dose is 250 mg twice daily to a maximum of 500 mg daily for 14 days (range of 10 to 21 days).**~~

There are no clinical trial data available on the use of *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 10 mg/kg twice daily for most infections, to a maximum of 250 mg daily. In otitis media or more severe infections the recommended dose is 15 mg/kg twice daily to a maximum of 500 mg daily. In Lyme disease, the recommended dose is 15 mg/ kg twice daily to a maximum of 500 mg daily for 14 days (range of 10 to 21 days).

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

10 mg/kg dosage for most infections

Age	**Approximate weight range (kg)**	**Dose (mg) twice daily**	**No. of measuring spoons (5 ml) or sachets per dose**	
			125 mg	**250 mg**
3 - 6 months	4 - 6	40 - 60	½	-
6 months - 2 years	6 - 12	60 - 120	½ - 1	-
2 - 12 years	12 - more than 20	125	1	½

15 mg/kg dosage for otitis media, more serious infections and Lyme disease

Age	**Approximate weight range (kg)**	**Dose (mg) twice daily**	**No. of measuring spoons (5 ml) or sachets per dose**	
			125 mg	**250 mg**
3 - 6 months	4 - 6	60 - 90	½	-
6 months - 2 years	6 - 12	90 - 180	1 - 1½	½
2 - 12 years	12 – more than 20	180-250	1½ - 2	½ - 1

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:

10 mg/kg/dose (Paediatric dosing syringe)

Child's weight (kg)	Dose twice daily (mg)	125 mg/5 ml dose twice daily (ml)	250 mg/5 ml 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)	125 mg/5 ml dose twice daily (ml)	250 mg/5 ml 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

ZINNAT is also available as the sodium salt (*ZINACEF*) for parenteral administration. This permits parenteral therapy with *ZINNAT* 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 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 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 *ZINNAT* suspension and granules (*see List of Excipients*) should be taken into account when treating diabetic patients, and appropriate advice provided.

The Jarisch-Herxheimer reaction has been seen following *ZINNAT* treatment of Lyme disease. It results directly from the bactericidal activity of *ZINNAT* on the causative organism 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.

ZINNAT suspension contains aspartame, which is a source of phenylalanine and so should be used with caution in patients with phenylketonuria.

Interactions

Drugs which reduce gastric acidity may result in a lower bioavailability of cefuroxime compared with that of the fasting state and tend to cancel the effect of enhanced absorption after food.

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.

ZINNAT 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 <1/1000) 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: Eosinophilia

Uncommon: Positive Coombs' test, thrombocytopenia, leucopenia (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-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: *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, *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 is enhanced in the presence of food.

Following administration of *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 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.

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.

Pre-clinical Safety Data

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

PHARMACEUTICAL PARTICULARS

List of Excipients

Aspartame
Xantham gum
Acesulfame potassium
Povidone K30
Stearic acid
Sucrose
Tutti-frutti flavour

Sucrose Quantities:

Sucrose quantity (g per dose)				
125 mg/5 ml Suspension	250 mg/5 ml Suspension	125 mg Sachet	250 mg Sachet	500 mg sachet
3.062 g	2.289 g	3.062 g	6.124g	12.248 g

Incompatibilities

None.

Shelf-Life

The expiry date of the granules is indicated on the packaging.

The reconstituted suspension when refrigerated between 2 and 8°C can be kept for up to 10 days.

Special Precautions for Storage

The reconstituted suspension must be refrigerated immediately at between 2 and 8°C.

Nature and Contents of Container

Multidose bottles:

ZINNAT Suspension is supplied in PhEur Type III amber glass bottles with an induction heat seal membrane containing either 125 mg/5 ml or 250 mg/5 ml product. Dosing syringes are available with multidose bottles of both strengths.

Sachets:

ZINNAT Suspension in sachets for oral use is supplied in paper/polyethylene/foil/ ethylenemethacrylic acid ionomer laminated sachet. When reconstituted as directed, it provides the equivalent of 125 mg, 250 mg or 500 mg of *ZINNAT* (as cefuroxime axetil) per sachet.

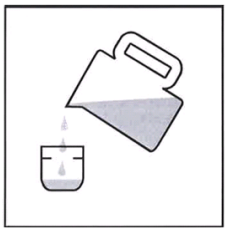
Instructions for Use/Handling

- **Constitution/Administration Instructions**

- Cefuroxime axetil suspension is supplied in a bottle packed in a carton box with either a measuring cup, dosing spoon or syringe and package leaflet.

Directions for reconstituting suspension in multidose bottles:

Shake the bottle to loosen the content. All the granules should be free-flowing in the bottle. Remove the cap and the heat-seal membrane. If the latter is damaged or not present, return the product to the pharmacist.



Add an amount of cold water up to the volume line on the cup provided. If the water was previously boiled it must be allowed to cool to room temperature before adding. Do not mix *ZINNAT* oral suspension with hot or warm liquids. Cold water must be used to prevent the suspension becoming too thick.

Pour the total amount of cold water into the bottle. Replace the cap. Allow the bottle to stand to allow the water to fully soak through the granules; this should take about one-minute

Invert the bottle and shake well (for at least 15 seconds) until all the granules have mixed with the water.

Turn the bottle into an upright position and shake well for at least one-minute until all the granules have blended with the water.

- Store the cefuroxime axetil suspension immediately at between 2 and 8°C (do not freeze) and let it rest for at least one hour before taking the first dose. The reconstituted suspension when refrigerated between 2 and 8°C can be kept for up to 10 days.
- Always shake the bottle well before taking the medication. A dosing syringe or spoon is provided for the administration of each dose.
- If desired, cefuroxime axetil suspension from multidose bottles can be further diluted in cold fruit juices, or cold milk drinks and should be taken immediately after mixing.

- **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 barrels 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 patient's mouth, pointing towards the inside of the cheek.

5. Press the plunger of the syringe in slowly to expel the medicine without causing choking.

6. After giving the dose, replace the bottle cap without removing the plastic collar. Dismantle the syringe and wash it thoroughly in water. Allow the plunger and the barrel to dry naturally.

- **Directions for reconstituting suspension from sachets**

1. Empty granules from sachet into a glass.

2. Add a small volume of cold water.

   If desired, cefuroxime axetil granules from the sachet can be further diluted in cold fruit juices, or cold milk drinks and should be taken immediately after mixing.

3. Stir well and drink immediately.

Not all presentations are available in every country.

Version number: GDS ~~26~~*27*/ IPI ~~06~~*07*

Date of issue: ~~25th~~-*21st* August ~~2016~~*2017*

ZINNAT and *ZINACEF* are trademarks of the GSK group of companies