ZINNAT Suspension
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 125mg of cefuroxime (as cefuroxime axetil) in each 5ml.

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

CLINICAL INFORMATION
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 it should be used in accordance with local official antibiotic prescribing guidelines and local susceptibility data *(*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 and acute exacerbations of chronic bronchitis).

Genito-urinary tract infections (for example: pyelonephritis, cystitis and urethritis).

Gonorrhoea, acute uncomplicated gonococcal urethritis and cervicitis.

Skin and soft tissue infections (for example: furunculosis, pyoderma and impetigo).

Dosage and Administration
Pharmaceutical Form:
Dry, white to off-white, tutti-frutti flavoured granules for oral suspension.

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

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

Dosage in adults:

Indication	**Dosage**
Most infections	250mg twice daily
Urinary tract infections	250mg twice daily
Mild to moderate lower respiratory tract infections	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

Dosage in children:
There is no clinical trial data available on the use of *ZINNAT* in children under the age of 3 months.

Indication	**Dosage**
Acute tonsillitis and pharyngitis	10 mg/kg twice daily to a maximum of 500 mg daily
Acute otitis media	15 mg/kg twice daily to a maximum of 1000 mg daily
Acute bacterial sinusitis	
Community acquired pneumonia	
Urinary tract infections	
Skin and soft tissue infections	

The following two tables serve as a guideline for simplified administration from measuring spoons (5ml) for the 125mg/5ml or the 250mg/5ml multidose suspension, and125mg or 250mg single dose sachets.

10mg/kg dosage

Weight range (kg)	**Dose (mg) twice daily**	**No. of measuring spoons (5ml) or sachets per dose**	
		125mg	**250mg**
4 to 6	40 to 60	½	-
6 to 12	60 to 120	½ to 1	-
12 to 25	120 to 250	1 to 2	½ to 1
Greater than 25	250	2	1

15mg/kg dosage

Weight range (kg)	**Dose (mg) twice daily**	**No. of measuring spoons (5ml) or sachets per dose**	
		125mg	**250mg**
4 to 6	60 to 90	½	-
6 to 12	90 to 180	1 to 1½	½
12 to 16	180 to 240	1½ to 2	½ to 1
16 to 32	240 to 480	2 to 4	1 to 2
Greater than 32	500	4	2

To enhance compliance and improve the dosing accuracy in very young children, a dosing syringe can be supplied with a multidose bottle containing 50ml 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 body weight in the following tables.

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

15mg/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

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).

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

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 *ZINNAT* 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
Pregnancy
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.

Lactation
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 ≥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, 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.

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 producingstrains)

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.

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:
Clostridioides 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 (2.1mg/l for a 125mg dose, 4.1mg/l for a 250mg dose, 7.0mg/l for a 500mg dose and 13.6 mg/l for a 1g dose) occur approximately 2 to 3 hours after dosing when taken after 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.

PHARMACEUTICAL INFORMATION

List of Excipients

Aspartame (see *Warnings and Precautions*)
Xantham gum
Acesulfame potassium
Povidone K30
Stearic acid
Sucrose
Tutti-frutti flavour

Sucrose Quantities:

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

Shelf Life

The shelf life of unconstituted *ZINNAT* suspension from date of manufacture is 24 months when not stored above 30ºC.

The reconstituted suspension when refrigerated between 2 and 8ºC can be kept for up to 10 days (see *Use and Handling*).

Storage

The storage conditions are detailed on the packaging.

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

Nature and Contents of Container

Multidose bottles:

ZINNAT Suspension is supplied in Ph. Eur. Type III amber glass bottles with an induction heat seal membrane containing either 125mg/5ml or 250mg/5ml product. Dosing syringes are available with multidose bottles of both strengths. *ZINNAT* Suspension 125mg/5ml is available in 50ml bottle.

Sachets:

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

Use and Handling

Reconstitution/Administration Instructions

Please note that the time taken to prepare *ZINNAT* suspension before administration of the first dose will take more than one hour. This includes time for the suspension to "settle" in the refrigerator.

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 bottlecap 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 measuring 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 bottle 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 in the refrigerator 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 should be refrigerated at all times; when refrigerated between 2 and 8°C, the reconstituted suspension can be kept for up to 10 days.

- Always shake the bottle well before taking the medication. A dosing syringe or spoonis 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 (if supplied):

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 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.

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