1. NAME OF THE MEDICINAL PRODUCT

Zinnat Suspension 125mg/5ml
Zinnat Suspension 250mg/5ml

2. 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.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

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

4. CLINICAL PARTICULARS

4.1 Therapeutic 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 section 5.1).

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 exacerbations of chronic obstructive pulmonary disease)
- 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

4.2 Posology and method of administration

The usual course of therapy is seven days (range 5 to 10 days). The dose of cefuroxime that is selected to treat an individual infection should take into account:

- The expected pathogens and their likely susceptibility to cefuroxime axetil
- The severity and the site of the infection
- The age, weight and renal function of the patient; as shown below.

The duration of therapy should be determined by the type of infection and the response of the patient, and should generally not be longer than recommended.

- **Adults and Children weighing more than 40 kg**

Indication	**Dosage**
Acute tonsillitis and pharyngitis	250 mg twice daily
Acute otitis media	500 mg twice daily
Acute bacterial sinusitis	500 mg twice daily
Community acquired pneumonia	
Acute exacerbations of chronic obstructive pulmonary disease	
Urinary tract infections	250 mg - 500 mg twice daily
Uncomplicated gonorrhoea	Single dose of 1 g
Skin and soft tissue infections	250 mg - 500 mg twice daily

- **Children**

There are 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 (5 ml) for the 125 mg/5 ml or the 250 mg/5 ml multi-dose suspension.

10 mg/kg dosage

Weight range (kg)	Dose (mg) twice daily	No. of measuring spoons (5 ml) per dose	
		125 mg	250 mg
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

15 mg/kg dosage

Weight range (kg)	Dose (mg) twice daily	No. of measuring spoons (5 ml) per dose	
		125 mg	250 mg
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 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

Method of administration
Oral use.
For optimal absorption *ZINNAT* should be taken after food.

4.3 Contraindications

Hypersensitivity to cefuroxime or to any of the excipients listed in section 6.1.
Patients with known hypersensitivity to cephalosporin antibiotics.
History of severe hypersensitivity (e.g. anaphylactic reaction) to any other type of beta-lactam antibacterial agent (penicillins, monobactams and carbapenems).

4.4 Special warnings and precautions for use

Hypersensitivity reactions
Serious and occasionally fatal hypersensitivity reactions (including anaphylactoid and severe cutaneous adverse reactions) have been reported in patients receiving therapy with beta-lactams. Before initiating therapy with *ZINNAT*, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, carbapenems or other beta-lactam agents. If an allergic reaction occurs, *ZINNAT* must be discontinued immediately and appropriate alternative therapy instituted.

Special care is indicated in patients who have experienced an allergic reaction to penicillins or other beta-lactam antibiotics because there is a risk of cross-sensitivity. As with all beta-lactam antibacterial agents, serious and occasionally fatal hypersensitivity reactions have been reported. There have been reports of hypersensitivity reactions which progressed to Kounis syndrome (acute allergic coronary arteriospasm that can result in myocardial infarction, see section 4.8). In case of severe hypersensitivity reactions, treatment with cefuroxime must be discontinued immediately and adequate emergency measures must be initiated.

Before beginning treatment, it should be established whether the patient has a history of severe hypersensitivity reactions to cefuroxime, to other cephalosporins or to any other type of beta-lactam agent. Caution should be used if cefuroxime is given to patients with a history of non-severe hypersensitivity to other beta-lactam agents.

Severe cutaneous adverse reactions (SCAR), such as Stevens Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), erythema multiforme (EM) and acute generalised exanthematous pustulosis (AGEP) have been reported in patients

receiving cefuroxime (see section 4.8). If signs and symptoms suggestive of these reactions appear, cefuroxime should be withdrawn immediately and an alternative treatment should be considered.

Jarisch-Herxheimer reaction
The Jarisch-Herxheimer reaction has been seen following cefuroxime axetil treatment of Lyme disease. It results directly from the bactericidal activity of cefuroxime axetil on the causative bacteria 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 (see section 4.8).

Overgrowth of non-susceptible microorganisms
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 microorganisms (e.g. enterococci and *Clostridium difficile*), which may require interruption of treatment (see section 4.8).

Antibacterial agent-associated pseudomembranous colitis have been reported with nearly all antibacterial agents, including cefuroxime and may range in severity from mild to life threatening. This diagnosis should be considered in patients with diarrhoea during or subsequent to the administration of cefuroxime (see section 4.8). Discontinuation of therapy with cefuroxime and the administration of specific treatment for *Clostridium difficile* should be considered. Medicinal products that inhibit peristalsis should not be given (see section 4.8).

Interference with diagnostic tests
The development of a positive Coomb's Test associated with the use of cefuroxime may interfere with cross matching of blood (see section 4.8).

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.

The sucrose content of *ZINNAT* suspension and granules (see section 6.1) 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.

4.5 Interactions with other medicinal products and other forms of interaction
Medicinal products which reduce gastric acidity may result in a lower bioavailability of cefuroxime axetil compared with that of the fasting state and tend to cancel the effect of enhanced absorption after food.
ZINNAT may affect the gut flora.

Cefuroxime is excreted by glomerular filtration and tubular secretion. Concomitant use of probenecid is not recommended. Concurrent administration of probenecid significantly increases the peak concentration, area under the serum concentration time curve and elimination half-life of cefuroxime.

Concomitant use with oral anticoagulants may give rise to increased INR.

4.6 Fertility, pregnancy and lactation
Pregnancy
There are limited data from the use of cefuroxime in pregnant women. Studies in animals have shown no harmful effects on pregnancy, embryonal or foetal development, parturition or postnatal development. Cefuroxime axetil should be prescribed to pregnant women only if the benefit outweighs the risk.

Breastfeeding
Cefuroxime is excreted in human milk in small quantities. Adverse effects at therapeutic doses are not expected, although a risk of diarrhoea and fungus infection of the mucous membranes cannot be excluded.

Breastfeeding might have to be discontinued due to these effects. The possibility of sensitisation should be taken into account. Cefuroxime should only be used during breastfeeding after benefit/risk assessment by the physician in charge.

Fertility
There are no data on the effects of cefuroxime axetil on fertility in humans. Reproductive studies in animals have shown no effects on fertility.

4.7 Effects on ability to drive and use machines
No studies on the effects on the ability to drive and use machines have been performed. However, as this medicine may cause dizziness, patients should be warned to be cautious when driving or operating machinery.

4.8 Undesirable effects
The most common adverse reactions are *Candida* overgrowth, eosinophilia, headache, dizziness, gastrointestinal disturbances and transient rise in liver enzymes.

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. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Treatment related adverse reactions, all grades, are listed below by MedDRA body system organ class, frequency and grade of severity. 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
Not known (cannot be estimated from the available data)

Infections and infestations
Common: *Candida* overgrowth
Not known: *Clostridium difficile* overgrowth

Blood and lymphatic system disorders
Common: Eosinophilia
Uncommon: Positive Coomb's test, thrombocytopenia, leucopenia (sometimes profound)
Not known: Haemolytic anaemia

Immune system disorders
Not known: Drug fever, serum sickness, anaphylaxis, Jarisch-Herxheimer reaction

Cardiac disorders
Very rare: Kounis syndrome

Nervous system disorders
Common: Headache, dizziness

Gastrointestinal disorders

Common: Diarrhoea, nausea, abdominal pain
Uncommon: Vomiting
Not known: Pseudomembranous colitis (see section 4.4)

Hepatobiliary disorders
Common: Transient increases of hepatic enzyme levels
Not known: Jaundice (predominantly cholestatic), hepatitis

Skin and subcutaneous tissue disorders
Uncommon: Skin rashes
Not known: Urticaria, pruritus, Severe cutaneous adverse reactions (SCARs), including erythema multiforme (EM), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (exanthematic necrolysis) (TEN) (see Immune system disorders), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalised exanthematous pustulosis (AGEP), angioneurotic oedema

Description of selected adverse reactions
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 Coomb's test (which can interfere with cross-matching of blood) and very rarely haemolytic anaemia.

Transient rises in serum liver enzymes have been observed which are usually reversible.

Paediatric population
The safety profile for cefuroxime axetil in children is consistent with the profile in adults.

4.9 Overdose
Overdose can lead to neurological sequelae including encephalopathy, convulsions and coma. Symptoms of overdose can occur if the dose is not reduced appropriately in patients with renal impairment (see sections 4.2 and 4.4).

Serum levels of cefuroxime can be reduced by haemodialysis and peritoneal dialysis.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: antibacterials for systemic use, second-generation cephalosporins.
ATC Code: J01DC02

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.
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 *P. aeruginosa* *Serratia* spp. *Stenotrophomonas maltophilia*
Gram-Positive Anaerobes: *Clostridioides difficile*
Gram-Negative Anaerobes: *Bacteroides fragilis*
Others: *Chlamydia* species *Mycoplasma* species *Legionella* species

5.2 Pharmacokinetic properties

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 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 section 4.2). 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.

5.3 Preclinical safety data
Animal toxicity studies indicated that cefuroxime is of low toxicity with no significant findings.

6. PHARMACEUTICAL PARTICULARS
6.1 List of Excipients
Aspartame (see section 4.4)
Xanthan gum
Acesulfame potassium
Povidone K30
Stearic acid
Sucrose
Tutti frutti flavour
Purified water

Sucrose Quantities:

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

6.2 Incompatibilities
In the absence of compatibility studies, *ZINNAT* must not be mixed with other medicinal products.

6.3 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 (see section 6.6).

6.4 Special precautions for storage
The storage conditions are detailed on the packaging.
Before reconstitution, store below 30°C.
The reconstituted suspension must be refrigerated immediately between 2 and 8°C.

6.5 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 125 mg/5 ml or 250 mg/5 ml product. Dosing syringes are available with multidose bottles of both strengths.

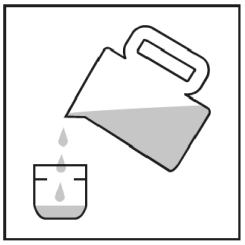
Pack Sizes:
ZINNAT Suspension 125mg/5ml is available in amber glass bottles of 50ml or 100ml.
ZINNAT Suspension 250mg/5ml is available in amber glass bottles of 50ml or 100ml.

Not all presentations may be available locally.

6.6 Instructions for 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.

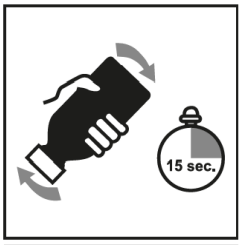
Directions for reconstituting suspension in multidose bottles:

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

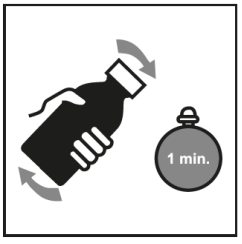


Add an amount of cold water up to the volume line on the measuring cup provided. If the water was previously boiled it must be allowed to cool to room temperature before adding. Do not mix *ZINNAT* oral suspension with hot or warm liquids. Cold water must be used to prevent the suspension becoming too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

Not all presentations are available in every country.

7. PRODUCT REGISTRATION HOLDER

Sandoz Products Malaysia Sdn. Bhd.
3A-2 & 3A-3, Level 3A, Menara KEN TTDI,
No. 37, Jalan Burhanuddin Helmi, Taman Tun Dr Ismail,
60000 Kuala Lumpur, Malaysia

8. DATE OF REVISION OF THE TEXT

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