1. NAME OF THE MEDICINAL PRODUCT
Zinnat Tablet 250mg
Zinnat Tablets 500mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
ZINNAT tablets containing 250 mg or 500 mg of cefuroxime (as cefuroxime axetil).

3. PHARMACEUTICAL FORM
Zinnat Tablet 250mg: White to off-white, oblong, biconvex tablets engraved "GXES7" on one side and plain on the other.

Zinnat Tablets 500mg: White to off-white, oblong, biconvex tablets engraved "GXEG2" on one side and plain on the other.

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 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.

4.2 Posology and method of administration
The usual course of therapy is seven days (range 5 to 10 days).

- **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 1g

Sequential therapy
Pneumonia
1.5 g *ZINACEF* twice daily (given i.v. or i.m.) for 48 to 72 hours, followed by 500 mg twice daily *ZINNAT* (cefuroxime axetil) oral therapy for 7 to 10 days.

Acute exacerbations of chronic bronchitis
750 mg *ZINACEF* twice daily (given i.v. or i.m.) for 48 to 72 hours, followed by 500 mg twice daily *ZINNAT* (cefuroxime axetil) oral therapy for 5 to 10 days.

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

- **Children**

Most infections	125 mg (1 x 125 mg tablet) twice daily
Children with otitis media or, where appropriate, with more severe infections	250 mg (1 x 250 mg tablet or 2 x 125 mg tablets) twice daily

ZINNAT tablets should not be crushed or split and are therefore unsuitable for treatment of patients, such as younger children, who cannot swallow whole tablets.

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

- **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 ½ (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.
ZINNAT should be taken after food for optimum absorption.

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.

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.

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 *ZINNAT* 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 <1/10,000) 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. 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 ≥1/1,000 to <1/100
Rare ≥1/10,000 to <1/1,000
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, leukopenia (sometimes profound)
Very rare: 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 Pharmacodynamics 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 *Pseudomonas aeruginosa*
Serratia spp.
Stenotrophomonas maltophilia
Gram-Positive Anaerobes:
Clostridioides difficile
Gram-Negative Anaerobes:
Bacteroides fragilis
Others:
Chlamydia species
Mycoplasma species
Legionella species

5.2 Pharmacokinetics properties

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 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.

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 axetil is of low toxicity with no significant findings.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients
Core:
Microcrystalline cellulose
Croscarmellose sodium

Sodium lauryl sulphate
Hydrogenated vegetable oil
Silicon dioxide

Coating:
Hypromellose
Propylene glycol
Opaspray White

6.2 Incompatibilities
In the absence of compatibility studies cefuroxime axetil must not be mixed with other medicinal products.

6.3 Shelf-Life
The expiry date is indicated on the packaging.

6.4 Special precautions for storage
The storage conditions are detailed on the packaging.
ZINNAT tablets should be stored at temperatures not exceeding 30°C.

6.5 Nature and contents of container
Double foil blister pack.
Zinnat Tablet 250mg is available in pack sizes of 10 or 50 tablets.
Zinnat Tablets 500mg is available in pack sizes of 10 tablets.

Not all presentations are available in every country.

6.6 Instructions for use and handling
None.

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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