PROFESSIONAL INFORMATION

SCHEDULING STATUS **S4**

1. NAME OF THE MEDICINE

Zinnat® Tablet 125 mg

Zinnat® Tablet 250 mg

Zinnat® Tablet 500 mg

Zinnat® Suspension 125 mg (Granules for oral suspension)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ZINNAT TABLET 125 mg: Each tablet contains cefuroxime 125 mg (as cefuroxime axetil).

ZINNAT TABLET 250 mg: Each tablet contains cefuroxime 250 mg (as cefuroxime axetil).

ZINNAT TABLET 500 mg: Each tablet contains cefuroxime 500 mg (as cefuroxime axetil).

Sugar free.

ZINNAT SUSPENSION 125 mg: Reconstitution of the contents of the multidose bottle as directed yields a suspension containing 125 mg of cefuroxime (as cefuroxime axetil) in each 5 ml.

Excipient(s) with known effect:

ZINNAT TABLET 125 mg contains propylene glycol 0,142 % *m/m*, methyl parahydroxybenzoate 0,026 % *m/m* and propyl parahydroxybenzoate, 0,017 % *m/m* as preservatives.

ZINNAT TABLET 250 mg contains propylene glycol 0,096 % *m/m*, methyl parahydroxybenzoate 0,015 % *m/m* and propyl parahydroxybenzoate 0,013 % *m/m* as preservatives.

ZINNAT TABLET 500 mg contains propylene glycol 0,120 % *m/m*, methyl parahydroxybenzoate 0,019 % *m/m* and propyl parahydroxybenzoate 0,016 % *m/m* as preservatives.

ZINNAT SUSPENSION 125 mg contains sugar (sucrose 3,062 g/5 ml).

ZINNAT SUSPENSION 125 mg contains sweetener (aspartame 0,021 g/5 ml).

3. PHARMACEUTICAL FORM

ZINNAT TABLET 125 mg:	White to off-white film-coated, capsule-shaped tablets, engraved ‘GXES5’ on one side and plain on the other.
ZINNAT TABLET 250 mg:	White to off-white film-coated, capsule-shaped tablets, engraved ‘GXES7’ on one side and plain on the other.
ZINNAT TABLET 500 mg:	White to off-white film-coated, capsule-shaped tablets, engraved ‘GXEG2’ on one side and plain on the other.
ZINNAT SUSPENSION 125 mg:	White to off-white free-flowing granules for preparing a suspension, producing a white to pale yellow suspension on reconstitution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ZINNAT is indicated for the treatment of patients with infections caused by susceptible organisms in the following diseases:

- **Pharyngitis and Tonsillitis** caused by *Streptococcus pyogenes*. (Penicillin is the usual medicine of choice in the treatment and prevention of Streptococcal infections, including the prophylaxis of rheumatic fever. ZINNAT is generally effective in the eradication of streptococci from the oral pharynx. ZINNAT is not indicated for the prophylaxis of subsequent rheumatic fever because data to support such use is not available.)
- **Otitis Media** caused by *Streptococcus pneumoniae*, *Haemophilus influenzae* (ampicillin-susceptible and ampicillin-resistant strains), *Moraxella (Branhamella) catarrhalis*, and *Streptococcus pyogenes*.
- **Sinusitis** caused by *Streptococcus pneumoniae* and *Haemophilus influenzae*.
- **Acute and chronic bronchitis** caused by *Streptococcus pneumoniae*, *Haemophilus influenzae* (ampicillin-susceptible strains), and *Haemophilus parainfluenzae* (ampicillin-susceptible strains).

- **Acute uncomplicated cystitis** caused by *Escherichia coli* and *Klebsiella pneumoniae*.
- **Lyme Disease** caused by the spirochaete *Borrelia burgdorferi*. ZINNAT is indicated for the treatment of early Lyme disease and subsequent prevention of late Lyme disease in adults and children over 12 years old.

4.2 Posology and method of administration

Adults:

Sinusitis: 250 mg twice daily.

Acute and chronic bronchitis: 250 mg twice daily.

Acute uncomplicated cystitis: 125 mg twice daily.

Lyme disease: 500 mg twice daily for 20 days.

Children:

Usual dose - 125 mg twice daily.

For **otitis media** in children less than 2 years of age the usual dose is 125 mg twice daily and in children over 2 years of age 250 mg twice daily.

For **Lyme disease** in children over the age of 12 years the usual dose is 500 mg twice daily for 20 days.

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

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

Method of administration

Because of the bitter taste of cefuroxime axetil, ZINNAT tablets should not be crushed.

Note: Cefuroxime axetil should be taken half an hour after food for optimum absorption.

Patient Instructions:

Shake the bottle vigorously until the suspension can be heard moving in the bottle before each dose is withdrawn.

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 medicine (penicillins, monobactams and carbapenems).

4.4 Special warnings and precautions for use

Hypersensitivity reactions

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 medicines, 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 medicine. Caution should be used if cefuroxime is given to patients with a history of non-severe hypersensitivity to other beta-lactam medicines.

Severe cutaneous adverse reactions (SCARS)

Severe cutaneous adverse reactions including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS), which can be life-threatening or fatal, have been reported in association with cefuroxime treatment (see section 4.8).
At the time of prescription patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of these reactions appear, cefuroxime should be

withdrawn immediately, and an alternative treatment considered. If the patient has developed a serious reaction such as SJS, TEN or DRESS with the use of cefuroxime, treatment with cefuroxime must not be restarted in this patient at any time.

Overgrowth of non-susceptible microorganisms

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 discontinuation of treatment.

Antibacterial agent–associated pseudomembranous colitis have been reported with nearly all antibacterial medicines, including cefuroxime (ZINNAT) 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. Discontinuation of therapy with cefuroxime and the administration of specific treatment for *Clostridium difficile* should be considered. Medicines that inhibit peristalsis should not be given.

Jarisch-Herxheimer reaction

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.

Interference with diagnostic tests

ZINNAT does not interfere in the alkaline picrate assay for creatinine.

Serum levels of cefuroxime are reduced by dialysis.

The development of a positive Coomb's Test associated with the use of cefuroxime may interfere with cross matching of blood. As a false negative result may occur in the ferricyanide test, it is recommended that either glucose oxidase or hexokinase methods are used to determine blood/plasma glucose levels in patients receiving ZINNAT.

Important information about excipients

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

ZINNAT SUSPENSION contains sucrose. Patients with rare hereditary conditions such as fructose intolerance, glucose-galactose mal-absorption or sucrose-isomaltase insufficiency should not take ZINNAT SUSPENSION. Sucrose may have an effect on the glycaemic control of patients with diabetes mellitus.

4.5 Interaction with other medicines and other forms of interaction

Cefuroxime axetil may affect the gut flora, leading to lower oestrogen reabsorption and reduced efficacy of combined oral contraceptives.

Concomitant use of ZINNAT and furosemide should be avoided when possible, and the combined use of cephalosporins and aminoglycosides should be undertaken with caution.

ZINNAT must not be administered simultaneously with other medicines.

Cefuroxime does not interfere in enzyme-based tests for glucosuria. Slight interference with copper reduction methods (Benedict's, Fehling's, Clinitest) may be observed. However, this should not lead to false-positive results. Cefuroxime may cause false-negative reactions in the ferricyanide test. ZINNAT can cause a falsely high reading in the alkaline picrate assay for creatinine, although the degree of elevation is unlikely to be of clinical importance. It is possible that cefuroxime may also interfere with this determination.

Medicines 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.

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

Safety in pregnancy and lactation has not been established.

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.

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.

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 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.

System organ class	Common	Uncommon	Not known

Infections and infestations	*Candida* overgrowth		*Clostridium difficile* overgrowth
Blood and lymphatic system disorders	eosinophilia	positive Coomb's test, thrombocytopenia, leukopenia (sometimes profound)	haemolytic anaemia
Cardiac disorders			Kounis syndrome
Immune system disorders			drug fever, serum sickness, anaphylaxis, Jarisch-Herxheimer reaction
Nervous system disorders	headache, dizziness		
Gastrointestinal disorders	diarrhoea, nausea, abdominal pain	vomiting	pseudomembranous colitis (see section 4.4)
Hepatobiliary disorders	transient increases of hepatic enzyme levels [alanine aminotransferase, (serum glutamic pyruvic acid transaminase), aspartate aminotransferase (serum glutamic oxaloacetic transaminase), and LDH]		jaundice (predominantly cholestatic), hepatitis
Skin and subcutaneous tissue disorders		skin rashes	urticaria, pruritus, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (exanthematic necrolysis) (*see Immune system disorders*), angioneurotic oedema, Drug Reactions with Eosinophilia and Systemic Symptoms (DRESS)

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 medicine to produce a positive Coombs' 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.

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

Suspected adverse reactions can also be reported directly to the HCR via the link: pvi1j.solutions.iqvia.com or the e-mail address, adverse.event.sac@sandoz.com.

4.9 Overdose

Symptoms of 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.

Treatment of overdose:

Treatment is symptomatic and supportive.

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

5. PHARMACOLOGICAL PROPERTIES

Pharmacological classification: A 20.1.1 Broad and medium spectrum antibiotics

Pharmacotherapeutic group: antibacterials for systemic use, second-generation cephalosporins, ATC code: J01DC02

5.1 Pharmacodynamic properties

Mechanism of action

Cefuroxime axetil is an oral prodrug of the bactericidal cephalosporin antibiotic cefuroxime. Cefuroxime axetil owes its *in vivo* bactericidal activity to the parent compound, cefuroxime.

Cefuroxime has bactericidal activity against a wide range of common organisms, including beta-lactamase producing strains.

Cefuroxime has stability to bacterial beta-lactamase.

Cefuroxime axetil undergoes hydrolysis by esterase enzymes to the active antibiotic, cefuroxime.

Cefuroxime inhibits bacterial cell wall synthesis following attachment to penicillin binding proteins (PBPs). This results in the interruption of cell wall (peptidoglycan) biosynthesis, which leads to bacterial cell lysis and death.

Mechanism of resistance

Bacterial resistance to cefuroxime may be due to one or more of the following mechanisms:

- hydrolysis by beta-lactamases; including (but not limited to) by extended-spectrum beta-lactamases (ESBLs), and AmpC enzymes that may be induced or stably derepressed in certain aerobic Gram-negative bacteria species.
- reduced affinity of penicillin-binding proteins for cefuroxime.
- outer membrane impermeability, which restricts access of cefuroxime to penicillin binding proteins in Gram-negative bacteria.
- bacterial efflux pumps.

Organisms that have acquired resistance to other injectable cephalosporins are expected to be resistant to cefuroxime.

Depending on the mechanism of resistance, organisms with acquired resistance to penicillins may demonstrate reduced susceptibility or resistance to cefuroxime.

Microbiological susceptibility

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of cefuroxime axetil in at least some types of infections is questionable.

Microorganisms for which acquired resistance may be a problem.

Gram-positive aerobes:

Streptococcus pneumoniae

Gram-negative aerobes:

Citrobacter freundii

Enterobacter aerogenes

Enterobacter cloacae

Escherichia coli

Klebsiella pneumoniae

Proteus mirabilis

Proteus spp. (other than *P. vulgaris*)

Providencia spp.

Gram-positive anaerobes:

Peptostreptococcus spp.

Propionibacterium spp.

Gram-negative anaerobes:

Fusobacterium spp.

Bacteroides spp.

Inherently resistant microorganisms

Gram-positive aerobes:

Enterococcus faecalis

Enterococcus faecium

Gram-negative aerobes:

Acinetobacter spp.

Campylobacter spp.

Morganella morganii

Proteus vulgaris

Pseudomonas aeruginosa

Serratia marcescens

Gram-negative anaerobes:

Bacteroides fragilis

Others:

Chlamydia spp.

Mycoplasma spp.

Legionella spp.

*All methicillin-resistant *S. aureus* are resistant to cefuroxime.

5.2 Pharmacokinetic properties

Absorption

After oral administration cefuroxime axetil is absorbed from the gastrointestinal tract and hydrolysed in the intestinal mucosa and blood to release cefuroxime into the circulation. Optimum absorption occurs when it is administered after a meal. Peak serum levels (2-3 mg/ml for a 125 mg dose, 4-5 mg/ml for a 250 mg dose, 5-7 mg/ml for a 500 mg dose) occur approximately two to three hours after dosing when taken after food. The rate of absorption of cefuroxime from the suspension is reduced compared with the tablets, leading to later, lower peak serum levels and reduced systemic bioavailability (4 to 17 % less). Cefuroxime axetil oral suspension was not bioequivalent to cefuroxime axetil tablets when tested in healthy adults and therefore is not substitutable on a milligram-per-milligram basis. The pharmacokinetics of cefuroxime is linear over the oral dosage range of 125 to 1000 mg. No accumulation of cefuroxime occurred following repeat oral doses of 250 to 500 mg.

Distribution

Protein binding has been variously stated as 33 to 50% depending on the methodology used. Following a single dose of cefuroxime axetil 500 mg tablet to 12 healthy volunteers, the apparent volume of distribution was 50 L (CV %=28 %). Concentrations of cefuroxime in excess of the minimum inhibitory levels for common pathogens can be achieved in the tonsilla, sinus tissues, bronchial mucosa, bone, pleural fluid, joint fluid, synovial fluid, interstitial fluid, bile, sputum and aqueous humor. Cefuroxime passes the blood-brain barrier when the meninges are inflamed.

Biotransformation

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 concentration time-curve by 50 %. Serum levels of cefuroxime are reduced by dialysis. The renal clearance is in the region of 125 to 148 ml/min/1.73 m^2.

Special patient populations

Gender

No differences in the pharmacokinetics of cefuroxime were observed between males and females.

Elderly

No special precaution is necessary in the elderly patients with normal renal function at dosages up to the normal maximum of 1 g per day. Elderly patients are more likely to have decreased renal function; therefore, the dose should be adjusted in accordance with the renal function in the elderly.

Paediatrics

In older infants (aged >3 months) and in children, the pharmacokinetics of cefuroxime are similar to that observed in adults.

There is no clinical trial data available on the use of cefuroxime axetil in children under the age of 3 months.

Renal impairment

The safety and efficacy of cefuroxime axetil in patients with renal failure have not been established. Cefuroxime is primarily excreted by the kidneys. Therefore, as with all such antibiotics, in patients with markedly impaired renal function (i.e., CLcr <30 ml/minute) it is recommended that the dosage of cefuroxime should be reduced to compensate for its slower excretion. Cefuroxime is effectively removed by dialysis.

Hepatic impairment

There are no data available for patients with hepatic impairment. Since cefuroxime is primarily eliminated by the kidney, the presence of hepatic dysfunction is expected to have no effect on the pharmacokinetics of cefuroxime.

Pharmacokinetic/pharmacodynamic relationship

For cephalosporins, the most important pharmacokinetic-pharmacodynamic index correlating with *in vivo* efficacy has been shown to be the percentage of the dosing interval (%T) that the unbound concentration remains above the minimum inhibitory concentration (MIC) of cefuroxime for individual target species (i.e., %T>MIC).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on studies of safety pharmacology, repeated dose toxicity, genotoxicity and toxicity to reproduction and development. No carcinogenicity studies have been performed; however, there is no evidence to suggest carcinogenic potential.

Gamma glutamyl transpeptidase activity in rat urine is inhibited by various cephalosporins, however the

level of inhibitions less with cefuroxime. This may have significance in the interference in clinical laboratory tests in humans.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

ZINNAT Tablets

Excipient Core: microcrystalline cellulose, croscarmellose sodium, silica colloidal anhydrous, sodium lauryl sulphate, hydrogenated vegetable oil.

Excipient Coating: propylene glycol, methyl para-hydroxybenzoate, propyl para-hydroxybenzoate, Hypromellose, opaspray white M-1-7120J

ZINNAT SUSPENSION 125 mg

Excipients: aspartame, xanthan gum, acesulfame potassium, povidone K30, stearic acid, sucrose and tutti-frutti flavour.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

ZINNAT TABLETS: 36 months

ZINNAT SUSPENSION 125 mg: 24 months

6.4 Special precautions for storage

ZINNAT tablets should be stored below 30 °C.

ZINNAT SUSPENSION 125 mg:

The granules (un-constituted suspension) must be stored below 30 °C.

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

6.5 Nature and contents of container

All strengths of ZINNAT tablets are supplied in double foil blister pack of 10 tablets comprising of an aluminium laminate base material and a hard tempered aluminium foil/heat seal lacquer lid.

ZINNAT SUSPENSION 125 mg: Granules for reconstitution are supplied in amber glass bottles of 50 ml and 100 ml with plastic, child-resistant screw closures. A 5 ml dosing spoon and measuring cup are provided in the carton.

Not all packs may be marketed.

6.6 Special precautions for disposal and other handling

Directions for use of suspension:

1. Shake the bottle to loosen the granules and remove the cap.
2. Fill the measuring cup with water to the line (20 ml of water for 50 ml pack and 37 ml of water for the 100 ml pack).
3. Add the water to the bottle all at once and replace the cap.
4. Invert the bottle and rock the bottle vigorously until the sound of the granules in the container disappears.
5. Turn the bottle into an upright position and shake vigorously.
6. Once mixed with the correct amount of water, ZINNAT SUSPENSION must be immediately stored in the fridge between 2 °C and 8 °C. Throw away the bottle 10 days after first opening it.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Sandoz SA (Pty) Ltd[1]

Magwa Crescent West

Waterfall City

Jukskei View

Midrand

2090

Sandoz SA Customer Call Centre 0861 726 225 (SANCAL)

8. REGISTRATION NUMBERS

ZINNAT TABLET 125 mg: V/20.1.1/362

ZINNAT TABLET 250 mg: V/20.1.1/363

ZINNAT TABLET 500 mg: V/20.1.1/364

ZINNAT SUSPENSION 125 mg: Z/20.1.1/148

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

ZINNAT TABLET 125 mg: 25 September 1989

ZINNAT TABLET 250 mg: 25 September 1989

ZINNAT TABLET 500 mg: 25 September 1989

ZINNAT SUSPENSION 125 mg: 10 August 1993

10. DATE OF REVISION OF THE TEXT

23 January 2025

Additional country registration details:

Country	***Product name***	***Scheduling status (or Category of distribution)***	***Registration number***
Botswana	Zinnat 500 mg Tablets	S2	B9304180
	Zinnat 125mg/5ml suspension	S2	BOT0200518
Malawi	Zinnat 250 mg Tablets	POM	PMPB/PL270/68
	Zinnat 125mg/5ml suspension	POM	PMPB/PL270/67
Namibia	Zinnat 125 Tablets	NS2	90/20.1.1/00598
	Zinnat 250 Tablets	NS2	90/20.1.1/00599
	Zinnat 500 Tablets	NS2	90/20.1.1/00600

	Zinnat 125mg/5ml suspension	NS2	04/20.1.1/0915
Zambia	Zinnat 250 Tablets	POM	179/017
	Zinnat 500 Tablets	POM	179/015
	Zinnat 125mg/5ml suspension	POM	179/013
Zimbabwe	Zinnat 250 Tablets	P.P.	88/7.2.2/2191
	Zinnat 500 Tablets	P.P.	88/7.2.2/2192
	Zinnat 125mg/5ml suspension	P.P.	92/7.2.2/2576

[1]Company Reg. No.: 1990/001979/07