ANNEX III

SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET

Note: This SPC, labelling and package leaflet is the version valid at the time of Commission decision.

After the Commission decision the Member State competent authorities, in liaison with the reference Member State, will update the product information as required. Therefore, this SPC, labelling and package leaflet may not necessarily represent the current text.

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Zinnat and associated names (see Annex I) 125 mg film-coated tablets
Zinnat and associated names (see Annex I) 250 mg film-coated tablets
Zinnat and associated names (see Annex I) 500 mg film-coated tablets
Zinnat and associated names (see Annex I) 125 mg/5 mL granules for oral suspension
Zinnat and associated names (see Annex I) 250 mg/5 mL granules for oral suspension
Zinnat and associated names (see Annex I) 125 mg granules for oral suspension
Zinnat and associated names (see Annex I) 250 mg granules for oral suspension
Zinnat and associated names (see Annex I) 500 mg granules for oral suspension

[See Annex I - To be completed nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

[To be completed nationally]

3. PHARMACEUTICAL FORM

125 mg, 250 mg, 500 mg film-coated tablets
Film-coated tablet (tablet)
[To be completed nationally]

125 mg/5 mL, 250 mg/5 mL granules for oral suspension
Granules for oral suspension
[To be completed nationally]

125 mg, 250 mg, 500 mg granules for oral suspension
Granules for oral suspension
[To be completed nationally]

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Zinnat is indicated for the treatment of the infections listed below in adults and children from the age of 3 months (see sections 4.4 and 5.1).

- Acute streptococcal tonsillitis and pharyngitis.
- Acute bacterial sinusitis.
- Acute otitis media.
- Acute exacerbations of chronic bronchitis.
- Cystitis.
- Pyelonephritis.
- Uncomplicated skin and soft tissue infections.
- Treatment of early Lyme disease.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Posology

The usual course of therapy is seven days (may range from five to ten days).

Table 1. Adults and children (≥40 kg)

Indication	Dosage
Acute tonsillitis and pharyngitis, acute bacterial sinusitis	250 mg twice daily
Acute otitis media	500 mg twice daily
Acute exacerbations of chronic bronchitis	500 mg twice daily
Cystitis	250 mg twice daily
Pyelonephritis	250 mg twice daily
Uncomplicated skin and soft tissue infections	250 mg twice daily
Lyme disease	500 mg twice daily for 14 days (range of 10 to 21 days)

Table 2. Children (<40 kg)

Indication	Dosage
Acute tonsillitis and pharyngitis, acute bacterial sinusitis	10 mg/kg twice daily to a maximum of 125 mg twice daily
Children aged two years or older with otitis media or, where appropriate, with more severe infections	15 mg/kg twice daily to a maximum of 250 mg twice daily
Cystitis	15 mg/kg twice daily to a maximum of 250 mg twice daily
Pyelonephritis	15 mg/kg twice daily to a maximum of 250 mg twice daily for 10 to 14 days
Uncomplicated skin and soft tissue infections	15 mg/kg twice daily to a maximum of 250 mg twice daily
Lyme disease	15 mg/kg twice daily to a maximum of 250 mg twice daily for 14 days (10 to 21 days)

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

Cefuroxime axetil tablets and cefuroxime axetil granules for oral suspension are not bioequivalent and are not substitutable on a milligram-per-milligram basis (see section 5.2).

125 mg/5 mL, 250 mg/5 mL granules for oral suspension
In infants (from the age of 3 months) and children with a body mass of less than 40 kg, it may be preferable to adjust dosage according to weight or age. The dose in infants and children 3 months to 18 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.

The following two tables, divided by age group, serve as a guideline for simplified administration, e.g measuring spoon (5 mL), for the 125 mg/5 mL or the 250 mg/5 mL multi-dose suspension if provided, and 125 mg or 250 mg single dose sachets.

Table 3. 10 mg/kg dosage for most infections

Age	Dose (mg) twice daily	Volume per dose (mL)		No. of sachets per dose	
		125 mg	250 mg	125 mg	250 mg
3 to 6 months	40 to 60	2.5	-	-	-
6 months to 2 years	60 to 120	2.5 to 5	-	-	-
2 to 18 years	125	5	2.5	1	-

Table 4. 15 mg/kg dosage for otitis media and more serious infections

Age	Dose (mg) twice daily	Volume per dose (mL)		No. of sachets per dose	
		125 mg	250 mg	125 mg	250 mg
3 to 6 months	60 to 90	2.5	-	-	-
6 months to 2 years	90 to 180	5 to 7.5	2.5	1 (125 mg)	-
2 to 18 years	180 to 250	7.5 to 10	2.5 to 5	2 (250 mg)	1 (250 mg)

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. In patients with markedly impaired renal function it is recommended that the dosage of cefuroxime should be reduced to compensate for its slower excretion. Cefuroxime is effectively removed by dialysis.

Table 5. Recommended doses for Zinnat in renal impairment

Creatinine clearance	$T_{1/2}$ (hrs)	Recommended dosage
≥30 mL/min/1.73 m^2	1.4–2.4	no dose adjustment necessary (standard dose of 125 mg to 500 mg given twice daily)
10-29 mL/min/1.73 m^2	4.6	standard individual dose given every 24 hours
<10 mL/min/1.73 m^2	16.8	standard individual dose given every 48 hours
Patients on haemodialysis	2–4	a further standard individual dose should be given at the end of each 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.

Method of administration

125 mg, 250 mg, 500 mg film-coated tablets
Oral use
Zinnat tablets should be taken after food for optimum absorption.

Zinnat tablets should not be crushed and are therefore unsuitable for treatment of patients who cannot swallow tablets. In children Zinnat oral suspension may be used.

125 mg/5 mL, 250 mg/5 mL granules for oral suspension and 125 mg, 250 mg, 500 mg granules for oral suspension
Oral use
For optimal absorption cefuroxime axetil suspension should be taken with food.

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

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 betalactam antibacterial agent (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 agents, serious and occasionally fatal hypersensitivity reactions have been reported. 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.

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 cefuroxime axetil 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.

Important information about excipients

125 mg, 250 mg, 500 mg film-coated tablets
Zinnat tablets contain parabens which may cause allergic reactions (possibly delayed).

125 mg/5 mL, 250 mg/5 mL granules for oral suspension and 125 mg, 250 mg, 500 mg granules for oral suspension
The sucrose content of cefuroxime axetil suspension and granules should be taken into account when treating diabetic patients and appropriate advice provided.

125 mg/5 mL granules for oral suspension
Contains 3 g of sucrose per 5 mL dose

250 mg/5 mL granules for oral suspension
Contains 2.3 g of sucrose per 5 mL dose

125 mg granules for oral suspension
Contains 3 g of sucrose per unit dose

250 mg granules for oral suspension
Contains 6.1 g of sucrose per unit dose

500 mg granules for oral suspension
Contains 12.2 g of sucrose per unit dose

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

4.5 Interaction with other medicinal products and other forms of interaction

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

Cefuroxime is excreted by glomerular filtration and tubular secretion. Concomitant use of probenicid 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. Zinnat 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 cefuroxime axetil 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 utilised 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 and not known (cannot be estimated from the available data).

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
Immune system			drug fever, serum sickness,

disorders			anaphylaxis, Jarisch-Herxheimer reaction
Nervous system disorders	headache, dizziness		
Gastrointestinal disorders	diarrhoea, nausea, abdominal pain	vomiting	pseudomembranous colitis
Hepatobiliary disorders	transient increases of hepatic enzyme levels		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
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 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.			

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

Mechanism of action

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.

Cefuroxime axetil breakpoints

Minimum inhibitory concentration (MIC) breakpoints established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) are as follows:

Microorganism	**Breakpoints (mg/L)**	
	S	R
Enterobacteriaceae [1, 2]	≤8	>8
Staphylococcus spp.	Note[3]	Note[3]
Streptococcus A, B, C and G	Note[4]	Note[4]
Streptococcus pneumoniae	≤0.25	>0.5
Moraxella catarrhalis	≤0.125	>4
Haemophilus influenzae	≤0.125	>1
Non-species related breakpoints[1]	IE[5]	IE[5]

[1] The cephalosporin breakpoints for *Enterobacteriaceae* will detect all clinically important resistance mechanisms (including ESBL and plasmid mediated AmpC). Some strains that produce beta-lactamases are susceptible or intermediate to 3rd or 4th generation cephalosporins with these breakpoints and should be reported as found, i.e. the presence or absence of an ESBL does not in itself influence the categorization of susceptibility. In many areas, ESBL detection and characterization is recommended or mandatory for infection control purposes.
[2] Uncomplicated UTI (cystitis) only (see section 4.1).
[3] Susceptibility of staphylococci to cephalosporins is inferred from the methicillin susceptibility except for ceftazidme and cefixime and ceftibuten, which do not have breakpoints and should not be used for staphylococcal infections.
[4] The beta-lactam susceptability of beta-haemolytic streptococci groups A, B, C and G is inferred from the penicillin susceptibility.
[5] insufficient evidence that the species in question is a good target for therapy with the drug. An MIC with a comment but without an accompanying S or R-categorization may be reported.

S=susceptible, R=resistant

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.

Cefuroxime is usually active against the following microorganisms *in vitro.*

Commonly susceptible species
Gram-positive aerobes: *Staphylococcus aureus* (methicillin susceptible)* *Streptococcus pyogenes* *Streptococcus agalactiae*
Gram-negative aerobes: *Haemophilus influenzae* *Haemophilus parainfluenzae* *Moraxella catarrhalis*
Spirochaetes: *Borrelia burgdorferi*
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 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 cefuroxime axetil tablets peak serum levels (2.9 µg/mL for a 125 mg dose, 4.4 µg/mL for a 250 mg dose, 7.7 µg/mL for a 500 mg dose and 13.6 µg/mL for a 1000 mg dose) occur approximately 2.4 hours after dosing when taken with 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 (see section 4.2).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 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. 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 (see section 4.2).

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. C1cr <30 mL/minute) it is recommended that the dosage of cefuroxime should be reduced to compensate for its slower excretion (see section 4.2). 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.

PK/PD 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 inhibition is less with cefuroxime. This may have significance in the interference in clinical laboratory tests in humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

[To be completed nationally]

6.2 Incompatibilities

[To be completed nationally]

6.3 Shelf life

[To be completed nationally]

6.4 Special precautions for storage

[To be completed nationally]

6.5 Nature and contents of container

[To be completed nationally]

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

125 mg/5mL, 250 mg/5mL granules for oral suspension

Constitution/Administration instructions
The bottle should be shaken vigorously before the medication is taken.

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

If desired, Zinnat suspension from multidose bottles can be further diluted in cold fruit juices, or milk drinks and should be taken immediately.

Directions for reconstituting suspension in multidose bottles

1. Shake the bottle to loosen the granules. Remove the cap and the heat-seal membrane. If the latter is damaged or not present, the product should be returned to the pharmacist.
2. Add the total amount of water to the bottle as stated on its label or as stated on the cup (if supplied). Replace the cap.
3. Invert the bottle and rock vigorously (for at least 15 seconds).
4. Turn the bottle into an upright position and shake vigorously.
5. Refrigerate immediately at between 2 and 8°C.
6. If using a dosing syringe, allow the reconstituted suspension to stand for at least one hour before taking the first dose.

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. Do NOT squirt the medicine out in a jet.
6. After giving the dose replace the bottle cap without removing the plastic collar. Dismantle the syringe and wash it thoroughly in fresh drinking water. Allow the plunger and the barrel to dry naturally.

125 mg, 250 mg, 500 mg granules for oral suspension
Directions for reconstituting suspension from sachets

1. Empty granules from sachet into a glass.
2. Add a small volume of water.
3. Stir well and drink immediately.

The reconstituted suspension or granules should not be mixed with hot liquids.

7. MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

{DD month YYYY}

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

[To be completed nationally]

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Zinnat and associated names (see Annex I) 125 mg film-coated tablets
Zinnat and associated names (see Annex I) 250 mg film-coated tablets
Zinnat and associated names (see Annex I) 500 mg film-coated tablets
Zinnat and associated names (see Annex I) 125 mg granules for oral suspension
Zinnat and associated names (see Annex I) 250 mg granules for oral suspension
Zinnat and associated names (see Annex I) 500 mg granules for oral suspension

[See Annex I - To be completed nationally]

Cefuroxime

2. STATEMENT OF ACTIVE SUBSTANCE(S)

[To be completed nationally]

3. LIST OF EXCIPIENTS

[To be completed nationally]

4. PHARMACEUTICAL FORM AND CONTENTS

[To be completed nationally]

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM YYYY}

9. SPECIAL STORAGE CONDITIONS

[To be completed nationally]

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and Address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

[To be completed nationally]

16. INFORMATION IN BRAILLE

[To be completed nationally]

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Zinnat and associated names (see Annex I) 125 mg/5 mL granules for oral suspension
Zinnat and associated names (see Annex I) 250 mg/5 mL granules for oral suspension

[See Annex I - To be completed nationally]
Cefuroxime

2. STATEMENT OF ACTIVE SUBSTANCE(S)

[To be completed nationally]

3. LIST OF EXCIPIENTS

[To be completed nationally]

4. PHARMACEUTICAL FORM AND CONTENTS

[To be completed nationally]

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM YYYY}

9. SPECIAL STORAGE CONDITIONS

[To be completed nationally]

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and Address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

[To be completed nationally]

16. INFORMATION IN BRAILLE

[To be completed nationally]

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS/STRIPS

1. NAME OF THE MEDICINAL PRODUCT

Zinnat and associated names (see Annex I) 125 mg film-coated tablets
Zinnat and associated names (see Annex I) 250 mg film-coated tablets
Zinnat and associated names (see Annex I) 500 mg film-coated tablets

[See Annex I - To be completed nationally]
Cefuroxime

2. NAME OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

3. EXPIRY DATE

EXP {MM YYYY}

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE

1. NAME OF THE MEDICINAL PRODUCT

Zinnat and associated names (see Annex I) 125 mg film-coated tablets
Zinnat and associated names (see Annex I) 250 mg film-coated tablets
Zinnat and associated names (see Annex I) 500 mg film-coated tablets
[See Annex I - To be completed nationally]

Cefuroxime

2. STATEMENT OF ACTIVE SUBSTANCE(S)

[To be completed nationally]

3. LIST OF EXCIPIENTS

[To be completed nationally]

4. PHARMACEUTICAL FORM AND CONTENTS

[To be completed nationally]

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM YYYY}

9. SPECIAL STORAGE CONDITIONS

[To be completed nationally]

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and Address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

[To be completed nationally]

16. INFORMATION IN BRAILLE

[To be completed nationally]

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE

1. NAME OF THE MEDICINAL PRODUCT

Zinnat and associated names (see Annex I) 125 mg/5 mL granules for oral suspension
Zinnat and associated names (see Annex I) 250 mg/5 mL granules for oral suspension
[See Annex I - To be completed nationally]

Cefuroxime

2. STATEMENT OF ACTIVE SUBSTANCE(S)

[To be completed nationally]

3. LIST OF EXCIPIENTS

[To be completed nationally]

4. PHARMACEUTICAL FORM AND CONTENTS

[To be completed nationally]

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM YYYY}

9. SPECIAL STORAGE CONDITIONS

[To be completed nationally]

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and Address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

[To be completed nationally]

16. INFORMATION IN BRAILLE

[To be completed nationally]

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SACHETS

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Zinnat and associated names (see Annex I) 125 mg granules for oral suspension
Zinnat and associated names (see Annex I) 250 mg granules for oral suspension
Zinnat and associated names (see Annex I) 500 mg granules for oral suspension
[See Annex I - To be completed nationally]

Cefuroxime
Oral use

2. METHOD OF ADMINISTRATION

Oral use
Read the package leaflet before use.

3. EXPIRY DATE

EXP {MM YYYY}

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

[To be completed nationally]

5. OTHER

PACKAGE LEAFLET

Package leaflet: Information for the user

Zinnat and associated names (see Annex I) 125 mg film-coated tablets
Zinnat and associated names (see Annex I) 250 mg film-coated tablets
Zinnat and associated names (see Annex I) 500 mg film-coated tablets
Zinnat and associated names (see Annex I) 125 mg/5 mL granules for oral suspension
Zinnat and associated names (see Annex I) 250 mg/5 mL granules for oral suspension
Zinnat and associated names (see Annex I) 125 mg granules for oral suspension
Zinnat and associated names (see Annex I) 250 mg granules for oral suspension
Zinnat and associated names (see Annex I) 500 mg granules for oral suspension
[SeeAnnex I - To be completed nationally]

Cefuroxime

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

What is in this leaflet:

1. What Zinnat is and what it is used for

Zinnat is an antibiotic used in adults and children. It works by killing bacteria that cause infections. It belongs to a group of medicines called *cephalosporins.*

Zinnat is used to treat infections of:
- the throat
- sinus
- middle ear
- the lungs or chest
- the urinary tract
- the skin and soft tissues.

Zinnat can also be used:
- to treat Lyme disease (an infection spread by parasites called ticks).

2. What you need to know before you take Zinnat

Don’t take Zinnat:

- **if you are allergic** (*hypersensitive*) to **any cephalosporin antibiotics** or any of the other ingredients of Zinnat.
- if you have ever had a severe allergic (hypersensitive) reaction to any other type of betalactam antibiotic (penicillins, monobactams and carbapenems).

➔ If you think this applies to you, **don't take Zinnat** until you have checked with your doctor.

Take special care with Zinnat

Zinnat is not recommended for children aged under 3 months, as the safety and effectiveness are not known in this age group.

You must look out for certain symptoms, such as allergic reactions, fungal infections (such as *candida*) and severe diahorrea (*pseudomembranous colitis*) while you are taking Zinnat. This will reduce the risk of any problems. See 'Conditions you need to look out for' in Section 4.

If you need a blood test

Zinnat can affect the results of a test for blood sugar levels, or a blood screen called the *Coombs test*. If you need a blood test:

➔ **Tell the person taking the sample** that you are taking Zinnat.

Other medicines and Zinnat

Tell your doctor or pharmacist if you are taking any other medicines, if you've started taking any recently or you start taking new ones. This includes medicines you can obtain without a prescription.

Medicines used to **reduce the amount of acid in your stomach** (e.g. *antacids* used to treat **heartburn**) can affect how Zinnat works.
Probenecid
Oral anticoagulants

➔ **Tell your doctor or pharmacist** if you are taking any medicine like this.

Contraceptive pills

Zinnat may reduce the effectiveness of the contraceptive pill. If you are taking the contraceptive pill while you are being treated with Zinnat you also need to use a **barrier method of contraception** (such as condoms). Ask your doctor for advice.

Pregnancy and breast-feeding and fertility

Tell your doctor before you take Zinnat:
- if you are pregnant, think you might be pregnant or are planning to become pregnant
- if you are breastfeeding.

Your doctor will consider the benefit of treating you with Zinnat against the risk to your baby.

Driving and using machines

Zinnat **can make you dizzy** and have other side effects that make you less alert.

➔ **Don't drive or use machines** if you do not feel well.

125 mg/5 mL, 250 mg/5 mL granules for oral suspension and 125 mg, 250 mg, 500 mg granules for oral suspension

Important information about some of the ingredients of Zinnat

Zinnat suspension contains sugar (sucrose). If you are diabetic you need to take this into account for your diet.

Zinnat suspension also contains **aspartame**, which is a source of phenylalanine. If you have an intolerance to aspartame or have a condition called **phenylketonuria (PKU)**:

➔ **Check with your doctor** that Zinnat is suitable for you.

3. How to take Zinnat

Always take this medicine exactly as your doctor or pharmacist has told you to. Check with your doctor or pharmacist if you are not sure.

Take Zinnat after food. This will help to make the treatment more effective.

125 mg, 250 mg, 500 mg film-coated tablets
Swallow Zinnat tablets whole with some water.

Don't chew, crush or split the tablets — this may make the treatment less effective.

125 mg/5 mL, 250 mg/5 mL granules for oral suspension
Shake the bottle before use.

Zinnat suspension can be diluted in cold fruit juices, or milk drinks but should be taken immediately.

Don’t mix Zinnat with hot liquids.

For step-by-step instructions on how to make up Zinnat suspension see **Instructions for reconstitution** at the end of this leaflet.

125 mg, 250 mg, 500 mg granules for oral suspension
For step-by-step instructions on how to make up Zinnat sachets see **Instructions for reconstitution** at the end of this leaflet.

The usual dose

Adults
The usual dose of Zinnat is 250 mg to 500 mg twice daily depending on the severity and type of infection.

Children
The usual dose of Zinnat is 10 mg/kg (to a maximum of 125 mg) to 15 mg/kg (to a maximum of 250 mg) twice daily depending on:

- the severity and type of infection

125 mg/5 mL, 250 mg/5 mL granules for oral suspension and 125 mg, 250 mg, 500 mg granules for oral suspension

- the weight and age of the child, up to a maximum of 500 mg per day.

Zinnat is not recommended for children aged under 3 months, as the safety and effectiveness are not known in this age group.

Depending on the illness or how you or your child responds to treatment, the initial dose may be changed or more than one course of treatment may be needed.

Patients with kidney problems

If you have a kidney problem, your doctor may change your dose.
➔ **Talk to your doctor** if this applies to you.

If you take too much Zinnat

If you take too much Zinnat you may have neurological disorders, in particular you may be **more likely to have fits** *(seizures).*
➔ **Don't delay. Contact your doctor or your nearest hospital emergency department immediately**. If possible, show them the Zinnat pack.

If you forget to take Zinnat

Don't take an extra dose to make up for a missed dose. Just take your next dose at the usual time.

Don’t stop Zinnat without advice

It is important that you take the full course of Zinnat. Don’t stop unless your doctor advises you to – even if you are feeling better. If you don't complete the full course of treatment, the infection may come back.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Conditions you need to look out for
A small number of people taking Zinnat get an allergic reaction or potentially serious skin reaction. Symptoms of these reactions include:

- **severe allergic reaction**. Signs include **raised and itchy rash**, **swelling**, sometimes of the face or mouth causing **difficulty in breathing**.
- **skin rash,** which may **blister**, and looks like **small targets** (central dark spot surrounded by a paler area, with a dark ring around the edge).
- **a widespread rash** with **blisters** and **peeling skin.** (These may be signs of *Stevens-Johnson syndrome* or *toxic epidermal necrolysis*).
- **fungal infections.** Medicines like Zinnat can cause an overgrowth of yeast (*Candida*) in the body which can lead to fungal infections (such as thrush). This side effect is more likely if you take Zinnat for a long time.
- **severe diarrhoea (*Pseudomembranous colitis*).** Medicines like Zinnat can cause inflammation of the colon (large intestine), causing severe diarrhoea, usually with blood and mucus, stomach pain, fever
- **Jarisch-Herxheimer reaction.** Some patients may get a high temperature (fever), chills, headache, muscle pain and skin rash while being treated with Zinnat for Lyme disease. This is known as the *Jarisch-Herxheimer reaction.* Symptoms usually last a few hours or up to one day.

➔ **Contact a doctor or nurse immediately if you get any of these symptoms.**

Common side effects

These may affect **up to 1 in 10** people:

- fungal infections (such as *Candida*)
- headache
- dizziness
- diarrhoea
- feeling sick
- stomach pain.

Common side effects that may show up in blood tests:

- an increase in a type of white blood cell (*eosinophilia*)
- an increase in liver enzymes.

Uncommon side effects

These may affect **up to 1 in 100** people:

- being sick
- skin rashes.

Uncommon side effects that may show up in blood tests:

- a decrease in the number of blood platelets (cells that help blood to clot)
- a decrease in the number of white blood cells
- positive Coomb's test.

Other side effects
Other side effects have occurred in a very small number of people, but their exact frequency is unknown:

- severe diarrhoea (*pseudomembranous colitis*)
- allergic reactions
- skin reactions (including severe)
- high temperature (*fever*)
- yellowing of the whites of the eyes or skin
- inflammation of the liver (*hepatitis*).

Side effects that may show up in blood tests:

- red blood cells destroyed too quickly (*haemolytic anaemia*).

If you get any side effects
➔ **Tell your doctor or pharmacist.** This includes any possible side effects not listed in this leaflet.

5 How to store Zinnat

[To be completed nationally]

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the pack after EXP. The expiry date refers to the last day of that month.

Don’t throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Zinnat contains

[To be completed nationally]

What Zinnat looks like and contents of the pack

[To be completed nationally]

Marketing Authorisation Holder and Manufacturer

[To be completed nationally]

This medicinal product is authorised in the Member States of the EEA under the following names:

125 mg film-coated tablets
Czech Republic, Denmark, Finland, France, Germany, Hungary, Ireland, Lithuania, Netherlands, Poland, Romania, Slovakia, Spain, United Kingdom – Zinnat
Germany – Elobact

250 mg film-coated tablets
Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Poland, Romania, Slovakia, Slovenia, Spain, Sweden, United Kingdom – Zinnat
Germany – Elobact
Greece – Zinadol
Italy – Zoref
Italy – Oraxim
Portugal – Zipos
Portugal – Zoref
Spain – Cefuroxima Allen
Spain – Cefuroxima Solasma

500 mg film– coated tablets
Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, France, Germany, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Poland, Romania, Slovakia, Slovenia, Spain, United Kingdom – Zinnat
Germany – Elobact
Greece – Zinadol
Italy– Zoref
Italy – Oraxim
Portugal– Zipos
Portugal – Zoref
Spain – Cefuroxima Allen
Spain – Cefuroxima Solasma

125 mg/5mL granules for oral suspension
Austria, Bulgaria, Czech Republic, Denmark, Estonia, France, Germany, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Malta, Netherlands, Poland, Romania, Slovakia, Slovenia, Spain, Sweden, United Kingdom – Zinnat
Germany – Elobact
Italy – Zoref
Italy – Oraxim
Portugal – Zipos
Portugal – Zoref

250 mg/5mL granules for oral suspension
Austria, Belgium, Bulgaria, Czech Republic, Cyprus, Finland, Ireland, Italy, Luxembourg, Malta, Poland, Slovakia, Slovenia, Spain, United Kingdom – Zinnat
Greece – Zinadol
Italy – Zoref
Italy – Oraxim
Portugal – Zipos
Portugal – Zoref

125 mg granules for oral suspension
France, Spain, United Kingdom – Zinnat
Germany – Elobact

250 mg granules for oral suspension
Austria, Italy, Spain, United Kingdom – Zinnat
Italy – Oraxim
Germany – Elobact
Spain – Nivador

500 mg granules for oral suspension
Spain – Zinnat

This leaflet was last approved in {MM/YYYY}.

Instructions for reconstitution

125 mg/5 mL and 250 mg/5 mL granules for oral suspension
Directions for making up the suspension

1. **Shake the bottle** to loosen the granules and **remove the cap**
2. Add the **amount of water stated on the bottle** label, or as stated on the cup (if supplied), and **replace the cap**.
3. **Turn the bottle upside** down and **rock vigorously** for at least 15 seconds.
4. **Turn the bottle the right way up** and **shake vigorously**.
5. Zinnat suspension, **must be stored in the fridge** between 2°C and 8°C.
6. If using a dosing syringe, allow the reconstituted suspension to stand for at least one hour before taking the first dose.

For children who can't take Zinnat using a spoon, a dosing syringe with a 5 mL graduation is supplied. Use the oral dosing syringe supplied with the pack to measure your dose accurately:

1. **Remove the bottle cap**. Keep it safely.
2. Hold the bottle firmly. **Push the plastic adapter into the neck of the bottle**.
3. **Insert the syringe** firmly into the adapter.
4. Turn the bottle upside down.
5. **Pull out syringe plunger** until the syringe contains the first part of your full dose.
6. Turn the bottle the correct way up. **Remove the syringe** from the adapter.
7. **Put the syringe into your mouth,** placing the tip of the syringe against the inside of your cheek. **Slowly push the plunger in,** allowing time to swallow. **Don't** push too hard and squirt the liquid into the back of your throat or you may choke.
8. **Repeat steps 3 to 7** in the same way until you have taken your whole dose.
9. **Take the syringe out of the bottle** and **wash** it thoroughly in clean water. Let it dry completely before you use it again.
10. **Close the bottle tightly** with the cap, leaving the adaptor in place.

125 mg, 250 mg, 500 mg granules for oral suspension

Directions for making up suspension from sachets

1. **Empty granules** from sachet into a **glass**.
2. Add a **small amount of water**.
3. **Stir well** and **drink straight away.**

➔ **Don't mix the suspension or granules with hot liquids.**