1. Name of the medicinal product:

ZACOCEF 500

1.1 Name of the medicinal product:

Cefuroxime Axetil Tablets USP 500 mg

1.2 Strength:

Each film coated tablet contains:

Cefuroxime Axetil (Amorphous) USP

Equivalent to Cefuroxime 500 mg

Excipients q.s.

Colour: Titanium Dioxide BP

1.3 Pharmaceutical form:

Film Coated Tablets for Oral use

2. Qualitative and quantitative composition

Qualitative declaration:

Cefuroxime Axetil (Amorphous) USP

Equivalent to Cefuroxime 500 mg

Quantitative declaration:

Each film coated tablet contains:

Cefuroxime Axetil (Amorphous) USP

Equivalent to Cefuroxime 500 mg

Excipients q.s.

Colour: Titanium Dioxide BP

3. Pharmaceutical form

Film Coated Tablets for Oral use

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4. Clinical particulars:

4.1 Therapeutic indications:

ZACOCEF 500 is indicated for the treatment of the infections listed below in adults and children from the age of 3 months

- 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)

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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 ZACOCEF 500 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).

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.

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Table 5. Recommended doses for ZACOCEF 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
During haemodialysis	2–4	a single additional 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

Oral use

ZACOCEF 500 should be taken after food for optimum absorption.

ZACOCEF 500 should not be crushed and are therefore unsuitable for treatment of patients who cannot swallow tablets. Depending on the dosage, there are other presentations available.

4.3 Contraindications

Hypersensitivity to cefuroxime or to any of the excipients.

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.

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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 Coombs 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.

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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 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. ZACOCEF 500 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:

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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

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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		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).

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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

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.

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 (2.1 mcg/ml for a 125 mg dose, 4.1 mcg/ml for a 250 mg dose, 7.0 mcg/ml for a 500 mg dose and 13.6 mcg/ml for a 1000 mg dose) occur approximately 2 to 3 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.

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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 m2.

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.

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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.

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 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

Microcrystalline Cellulose (PH 102) BP

Crospovidone USP

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Hydrophobic Colloidal Anhydrous Silica BP

Sodium Lauryl Sulfate BP

Hydrogenated Castor Oil BP

Polacrilin Potassium (Kyron T 314) USP

Magnesium Stearate BP

Purified Talc BP

Sodium Lauryl Sulfate BP

Hydrophobic Colloidal Anhydrous Silica BP

Microcrystalline Cellulose (PH 102) BP

Crospovidone USP

Sprycell SC-MB-3185 In house

Titanium Dioxide BP

Purified Talc BP

Diethyl Phthalate BP

Macrogol 400 BP

Isopropyl Alcohol BP

Dichloromethane BP

6.2 Incompatibilities

None

6.3 Shelf life

36 months from date of manufacturing

6.4 Special precautions for storage

Store below 30°C in a dry place. Keep medicines out of reach of children.

6.5 Nature and contents of container

10 Tablets to be packed in Alu-Alu blister. Such 1 blister to be packed in a carton along with pack insert.

6.6 Special precautions for disposal:

None

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7. Registrant: Marketing Authorisation Holder

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9. Date of revision of the text: NA

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