Summary of Product Characteristics

1. Name of the medicinal product

Zamur 250 mg, film-coated tablets

Zamur 500 mg, film-coated tablets

2. Qualitative and quantitative composition

Active ingredient

Cefuroxime as cefuroxime axetil.

Excipients

Excipients for film-coated tablets.

3. Pharmaceutical form and amount of active substance per unit

Film-coated tablets (with a score line) of 250 mg and 500 mg cefuroxime (as 300.72 mg and 601.44 mg cefuroxime axetil).

4. Clinical Particulars

4.1 Therapeutic indications

Zamur is indicated in the following infections caused by cefuroxime-sensitive microorganisms:
Upper respiratory tract: tonsillitis, pharyngitis, otitis media, sinusitis.
Lower respiratory tract: acute bronchitis and acute exacerbations of chronic bronchitis, pneumonia.

Urinary tract: pyelonephritis, cystitis, urethritis.

Skin and soft tissue: furunculosis, pyoderma, impetigo.

Gonorrhoea: acute uncomplicated urethritis and cervicitis.

Lyme's disease: stage I, erythema chronicum migrans with possible transient joint symptoms or transitory and limited neurological reactions.
Official recommendations on the appropriate use of antibiotics should be followed, particularly recommendations for use regarding the prevention of increased resistance to antibiotics.

4.2 Posology and Method of administration

The usual duration of treatment is 7 (5-10) days, depending on the severity and course of the infection.

To ensure optimal absorption, Zamur should be taken with meals. Due to their bitter taste, the film-coated tablets should not be chewed or crushed and are therefore unsuitable for children below 5 years of age.

Usual dosage

Adults and children over 12 years

Standard dosage: 250 mg twice daily (every 12 hours).

Mild to moderate lower respiratory tract infections: 250 mg twice daily (every 12 hours).

Severe lower respiratory tract infections: 500 mg twice daily (every 12 hours).

Uncomplicated gonorrhoea: one single dose of 1 g.

Lyme's disease: 500 mg twice daily (every 12 hours) for 20 days.

Alternative dosage

- Mild to moderate community-acquired pneumonia: 1.5 g cefuroxime sodium IV or IM twice daily for 48 – 72 hours, followed by 500 mg Zamur orally twice daily for 7 – 10 days.
- Acute exacerbations of chronic bronchitis: 750 mg cefuroxime sodium IV or IM twice daily for 48 – 72 hours, followed by 500 mg Zamur orally twice daily for 5 – 10 days.

The time for switching from parenteral to oral treatment is dependent on the severity of infection, the patient's clinical condition and microbial sensitivity. If no clinical improvement has occurred within 72 hours, parenteral treatment must be continued.

Children aged 5 to 12 years:

Standard dosage:

For most infections, the dosage for children aged 5-12 years weighing at least 15 kg is 125 mg (2 x ½ film-coated tablet) twice daily (every 12 hours), up to a maximum daily dose of 250 mg.

Otitis media or serious infection in children from 5 years of age weighing at least 20 kg:
250 mg twice daily (every 12 hours). Maximum daily dose: 500 mg.

Children under 5 years:

It is not possible to treat children under 5 years with the pharmaceutical formulations available for Zamur.

Dosage in impaired renal function

Cefuroxime is mainly excreted via the kidneys.

In patients with significant renal impairment (creatinine clearance below 30 mL/min), it is recommended that the cefuroxime dosage be reduced on account of the slower elimination (see table below).

Creatinine clearance	$T_{½}$ (hours)	Recommended dosage
≥30 mL/min/1.73 m^2	1.4-2.4	No dose adjustment required (usual dose of 125 mg to 500 mg twice daily)
10– 29 mL/min/1.73 m^2	4.6	Standard single dose, every 24 hours
<10 mL/min/1.73 m^2	16.8	Standard single dose, every 48 hours
On haemodialysis	2-4	After every dialysis session, an additional standard single dose should be administered.

4.3 Contraindications

Zamur is contraindicated in cases of confirmed hypersensitivity to cephalosporins. The possibility of cross-allergy should be considered in cases of penicillin hypersensitivity.

4.4 Special warnings and precautions for use

In general, caution is advised when administering beta-lactam antibiotics to patients who are susceptible to allergic reactions.
As with other antibiotics, administration may result in increased growth of *Candida*. With prolonged administration, increased growth of non-sensitive microbes (e.g. enterococci, *Clostridium difficile*) may also occur, which may necessitate discontinuation of treatment. Close patient observation is therefore essential. If a superinfection occurs during treatment, appropriate measures must be taken.

The onset of diarrhoea during or after treatment with Zamur, especially if it is severe, persistent and/or bloody, may be a symptom of infection with *Clostridium difficile*. Its most severe form is pseudomembranous colitis. If any such complication is suspected, treatment with Zamur must be discontinued immediately and the patient should be thoroughly examined to initiate, if necessary,

specific antibiotic therapy (e.g. metronidazole, vancomycin). The use of antiperistaltic agents is contraindicated in this clinical situation.

In cases of impaired renal function, the Zamur dosage must be adjusted to the degree of renal insufficiency (see “Dosage in impaired renal function”).
Caution is advised when combining high-dose cephalosporins with potent diuretics and/or aminoglycosides, as this might adversely affect renal function (see “Interactions”).
During treatment, renal function should be constantly monitored in patients on combination therapy, in patients with pre-existing renal damage and generally in elderly patients. In case of (epilepsy-like) seizures (see “Overdose”), the usual appropriate emergency measures are indicated (e.g. maintaining airway patency and administration of anticonvulsants).
In association with cefuroxime treatment for Lyme’s disease, occurrence of a Jarisch-Herxheimer reaction was observed in approximately 17% of patients. This reaction is a direct consequence of the bactericidal action of cefuroxime on *Borrelia burgdorferi*, the spirochete which causes Lyme’s disease. The patient should be assured that this is a usual and normally transient consequence of antibiotic treatment for Lyme’s disease.
Patients must be informed that taking this medicinal product can cause dizziness and may thereby impair the ability to drive and use machines (see sections “Effects on ability to drive and use machines” and “Undesirable effects”).

4.5 Interactions with other medicinal products and other forms of interaction

Cephalosporin antibiotics should only be given with extreme caution in combination with aminoglycosides and potent diuretics such as furosemide, as these combinations can have an adverse effect on renal function.

Taking medicines that reduce gastric acid levels may decrease the bioavailability of Zamur and offset the normally increased rate of absorption after a meal.
Probenecid leads to a reduction in the renal clearance of Zamur, thereby increasing concentrations of Zamur and prolonging its residence time within the body.
As with other antibiotics, cefuroxime can adversely affect the intestinal flora, which can lead to reductions in oestrogen absorption and efficacy of combined oral contraceptives.

Bacteriostatic agents can interfere with the bactericidal action of cephalosporins.

Antagonism with cefoxitin, imipenem and chloramphenicol has been demonstrated in rare cases. The clinical relevance of these *in vitro* results is not known.

For blood/plasma glucose determination, enzymatic methods (glucose oxidase or hexokinase method) should be used, as interference has been observed in reduction tests. To determine creatinine, the alkaline picrate assay (Jaffé reaction) should be used.

4.6 Fertility, Pregnancy and Lactation

Pregnancy

Experimental studies revealed no indications of embryopathic or teratogenic effects. No controlled studies are available on pregnant women. Zamur should not be used during pregnancy unless clearly necessary.

Lactation

Small quantities of cefuroxime are excreted in human milk. Use during lactation is therefore not recommended.

4.7 Effects on ability to drive and use machines

This medicinal product can cause dizziness. Patients should therefore be warned that dizziness occurring while driving or using machines can affect their own safety and that of others.

4.8 Undesirable effects

The frequency categories stated below are estimates, as no appropriate data (e.g. from placebo-controlled studies) were available for calculating the incidence of most reactions. 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. Frequencies for all other undesirable effects (i.e. with an incidence of < 1/10,000) mainly come from post-marketing reports and therefore refer to the reporting rate rather than actual frequency of occurrence. No data were available from placebo-controlled studies. In cases where incidence values were calculated from clinical study data, drug-related data (according to investigator assessment) were used.

The following convention has been used for the classification of frequency:

Very common ≥ 1/10; common ≥ 1/100 and < 1/10; uncommon ≥ 1/1,000 and < 1/100; rare ≥ 1/10,000 and < 1/1,000; very rare < 1/10,000.

Infections and infestations

Common: increased growth of *Candida* with long-term use.

Blood and lymphatic system disorders

Common: eosinophilia.

Uncommon: positive Coombs' test, thrombocytopenia, leukopenia (occasionally very pronounced), neutropenia.
Very rare: haemolytic anaemia.

Cephalosporins as a substance class tend to attach to the surface of red cell membranes and react with antibodies directed against the medicinal product, thus producing a positive Coombs' test and, very rarely, haemolytic anaemia.
Serological cross-matching may be affected.
Immune system disorders

Hypersensitivity reactions including:
Uncommon: rash including maculopapular or morbilliform exanthema.
Rare: urticaria, pruritus (itching).
Very rare: drug fever, serum sickness, anaphylaxis.

Nervous system disorders
Common: headache, dizziness.
Gastrointestinal disorders

Common: gastrointestinal disorders including diarrhoea, nausea, abdominal pain.
Uncommon: vomiting.

Rare: pseudomembranous colitis (see "Special warnings and precautions for use").
Very rare: heartburn.

When treating Lyme's disease, there may be increased incidence of diarrhoea (around 10% in controlled studies), due to the prolonged duration of treatment (20 days).
Hepatobiliary disorders

Common: transient elevations of liver enzyme values: (ALT [SGPT], AST [SGOT], LDH).
Uncommon: transient increase in alkaline phosphatase. The bilirubin concentration may also rise temporarily.
Very rare: jaundice (predominantly cholestatic jaundice), hepatitis.
Skin and subcutaneous tissue disorders

Very rare: erythema exsudativum multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (exanthema necrolysis).

See also Immune system disorders.

To report any side effect(s):

Saudi Arabia:

The National Pharmacovigilance and Drug Safety Centre (NPC)

- Fax: +966-11-205-7662
- Call NPC at +966-11-2038222, Exts: 2317-2356-2353-2354-2334-2340.
- Toll free phone: 8002490000
- E-mail: npc.drug@sfda.gov.sa
- Website: www.sfda.gov.sa/npc

4.9 Overdose

Cases of overdose with cephalosporins can cause cerebral disorders, which may manifest as seizures. Anticonvulsant treatment may be indicated. Excessively high cefuroxime levels can be reduced by haemodialysis or peritoneal dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: J01DC02

Mechanism of action

Cefuroxime axetil (1-acetoxyethylester of cefuroxime) is a semi-synthetic second-generation cephalosporin, which is effective when given orally. Cefuroxime may only be administered parenterally. Cefuroxime axetil, a prodrug, is converted in the body to the active metabolite cefuroxime, which exerts a bactericidal action by inhibiting cell wall synthesis. Zamur is stable against most β-lactamases and is active *in vitro* against the following microorganisms.

The prevalence of acquired resistance varies depending on the geographic region, as well as over time, and may be very high in certain species. Information on resistance in each specific region is useful, especially for the treatment of severe infections.

In vitro sensitivity of pathogens to cefuroxime

* Clinical efficacy of cefuroxime has been proven in clinical studies.

+ All methicillin-resistant *Staphylococcus spp*. are resistant to cefuroxime.

Sensitive microorganisms

Normally sensitive microorganisms:
Gram-positive aerobes:
Streptococcus pyogenes* (and other β-haemolytic streptococci)

Staphylococcus aureus *(methicillin-sensitive isolates) + coagulase-negative staphylococci (methicillin-sensitive isolates)
Gram-negative aerobes:
Haemophilus influenzae (incl. ampicillin-resistant strains)*
Haemophilus parainfluenzae*
Moraxella catarrhalis*
Spirochetes: Borrelia burgdorferi*
Species in which acquired resistance may pose a problem
Gram-positive aerobes:
Streptococcus pneumoniae*
Gram-negative aerobes:
Citrobacter spp. excl. C. freundii
Enterobacter spp. excl. E. aerogenes and E. cloacae
Escherichia coli*
Klebsiella spp. incl. K. pneumoniae*
Neisseria gonorrhoea* (penicillinase-and non-penicillinase-producing strains)
Proteus mirabilis
Proteus spp. excl. P. penneri and P. vulgaris
Providencia spp.
Gram-positive anaerobes:
Clostridium spp. with C. difficile
Peptostreptococcus spp.
Propionibacterium spp.
Gram-negative anaerobes:
Bacteroides spp. excl. B. fragilis
Fusobacterium spp.
Naturally resistant species:
Gram-positive aerobes:
Enterococcus spp. incl. E. faecalis and E. faecium
Listeria monocytogenes
Gram-negative aerobes:
Acinetobacter spp.
Burkholderia cepacia

Campylobacter spp.
Citrobacter freundii
Enterobacter aerogenes
Enterobacter cloacae
Morganella morganii
Proteus penneri
Proteus vulgaris
Pseudomonas spp. incl. P. aeruginosa
Serratia spp.
Stenotrophomonas maltophilia
Gram-positive anaerobes:
Clostridium difficile
Gram-negative anaerobes:
Bacteroides fragilis
Other microorganisms:
Chlamydia species
Mycoplasma species
Legionella species

It is recommended that a sensitivity test be carried out in infections caused by moderately sensitive microorganisms, so that possible resistance can be excluded. Sensitivity to cefuroxime can be determined via standardised procedures, as recommended for example by the Clinical and Laboratory Standards Institute (CLSI), using disc or dilution tests.

The following parameters are recommended by the CLSI as sensitivity criteria:

	Disc test (30 µg) diameter (mm)	Dilution test MIC (mg/L)
Sensitive	≥23	≤4
Intermediate	15-22	8-16
Resistant	≤14	≥32

Laboratory results in the dilution test or the standardised disc diffusion test should be interpreted according to the following criteria:

Moderately sensitive microorganisms are sensitive at high dosage or when the infection is restricted to tissues and fluids in which high antibiotic levels are achieved.

In vitro, synergistic or additive effects have been observed for cefuroxime with a number of bactericidal antibiotics, especially aminoglycosides.

Antagonism with cefoxitin, imipenem and chloramphenicol has been demonstrated in rare cases. The clinical significance of these *in vitro* results is not known.
As with other penicillins and cephalosporins, cross-resistance can occur within the same class of antibiotic.

5.1 Pharmacokinetics properties

Absorption

Following oral administration, cefuroxime axetil is absorbed from the gastrointestinal tract and rapidly hydrolysed in the intestinal mucosa. It enters the blood circulation as cefuroxime. Absorption is optimal when taken after meals.
The absolute bioavailability of the film-coated tablets is 40-60% when taken with meals and 30-40% when taken on an empty stomach. Peak blood levels are achieved after 2-3 hours, amounting to 2-3 mg/L after 125 mg, 4-6 mg/L after 250 mg, 5-8 mg/L after 500 mg and 9- 14 mg/L after 1 g when the film-coated tablets are taken with food.

Distribution

The apparent volume of distribution after an oral dose is 17.4 L. Protein binding is 33-50%, depending on the assay method used.
In pregnant women, small amounts of cefuroxime cross the placental barrier.
Small amounts of cefuroxime are excreted in human milk.

Metabolism

Following oral administration, cefuroxime axetil is rapidly hydrolysed by non-specific esterases in the intestines and blood. The axetil fraction is converted to acetaldehyde and acetic acid, while cefuroxime is excreted unchanged.

Elimination

The serum half-life is 1-1.5 h. Cefuroxime is not metabolised and is excreted by glomerular filtration and tubular secretion. Within 12 hours, approximately 50% of the active substance is found in the urine.

Kinetics of special patient groups

Probenecid

Concomitant administration of probenecid increases the area under the plasma level/time curve by 50%.

Renal impairment

The pharmacokinetics of cefuroxime have been studied in patients with various degrees of impaired renal function. The elimination half-life of cefuroxime increases with diminishing renal

function; based on this, the recommendations for dose adjustment in this patient group are made (see Posology/Administration). In patients receiving haemodialysis, at least 60% of the total baseline amount of cefuroxime present in the body is removed during a 4-hour dialysis session. For this reason, an additional single dose of cefuroxime should be administered upon completion of the haemodialysis session.

5.2 Preclinical safety data

General toxicology

In animal studies, cefuroxime axetil has been shown to have only very low toxicity. There were no indications of target organ toxicity in repeated-dose studies with rats and dogs at dosages exceeding those in therapeutic use.

Mutagenicity/carcinogenicity

Only negative findings were obtained for cefuroxime axetil in a standard series of *in vitro* tests and an *in vivo* micronucleus test in mice.

As expected, the substance induced chromosomal aberrations in human lymphocytes under *in vitro* conditions. However, this property can also be observed with other beta-lactam antibiotics and there is no evidence to suggest that this indicates a carcinogenic potential.

As cefuroxime axetil is used for short-term treatment only, no carcinogenicity studies have been conducted.

Reproductive toxicology

Cefuroxime axetil showed no adverse effects on the fertility or peri/postnatal development of rats, or on the embryofoetal development of mice or rats, at dosages significantly exceeding those in therapeutic use.

6. Pharmaceutical particulars

6.1 List of excipients

Table core: croscarmellose sodium, crospovidone, sodium laurilsulfate, castor oil, hydrogenated, methylcellulose, silica, precipitated.

Film-coating: hypromellose, cellulose, microcrystalline, macrogol 8 stearate, talcum, titanium dioxide.

6.2 Incompatibilities

Effect on diagnostic methods

During Zamur treatment, the direct Coombs' test can become temporarily positive. This can

affect serological cross-matching.
Enzymatic methods (glucose oxidase or hexokinase method) should be used for blood/plasma glucose determination, as interference has been observed in reduction tests. To determine creatinine, the alkaline picrate assay (Jaffé test) should be used.

6.3 Shelf life

36 months

Zamur may only be used until the date marked with “EXP” on the container.

6.4 Special precautions for storage

Do not store above 30 ºC.

6.5 Nature and contents of container

PVC/PVDC foil blisters or aluminium-foil / aluminium-foil blisters.

Presentations

Zamur 250 mg, film-coated tablets (with a score line): 14 and 10x14
Zamur 500 mg, film-coated tablets (with a score line): 14 and 10x14
Not all presentations may be marketed.

7. Marketing Authorisation Holder

Acino Pharma AG, Liesberg, Switzerland

8. Marketing Authorization Number

21-222-06
22-222-06

9. Date of first authorization/renewal of the authorization

December 2006

10. Date of revision of the text

Jan 2019