1.3.1
Summary Of Product Characteristics (SPC)

1.3.1 Summary of Product Characteristics (SPC)

1.3.1.1. Invented Name of the Medicinal Product

G-ROXIM 500

Cefuroxime Axetil Tablets USP 500mg

1.3.1.2 Strength

Cefuroxime Axetil USP 500mg

1.3.1.3 Dosage Form

Solid Dosage Form

1.3.1.4 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Film coated tablet contains:

Cefuroxime Axetil……USP

Equivalent…….500mg

Excipients .....q.s.

Colour: Titanium Dioxide

1.3.1.5 PHARMACEUTICAL FORM

Film Coated Tablet.

White coloured capsule shaped biconvex film coated Tablet plain on both side.

1.3.1.6 CLINICAL PARTICULARS

1.3.1.6.1 Therapeutic indications

To reduce the development of drug-resistant bacteria and maintain the effectiveness of cefuroxime axetil and other antibacterial drugs, cefuroxime axetil should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be

considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

• 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.

1.3.1.6.2 POSOLOGY AND METHOD OF ADMINISTRATION

Posology:

He 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	15 mg/kg twice daily to a maximum of 250 mg twice daily

severe infections	
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)

Table 3. Recommended doses for G-ROXIM 500 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

Method of administration

For oral administration.

1.3.1.6.3 CONTRAINDICATIONS

Patients with known hypersensitivity to cephalosporin antibiotics.

History of severe hypersensitivity (e.g. anaphylactic reaction) to any other type of beta lactam antibacterial agent (penicillins, monobactams and carbapenems).

1.3.1.6.4 WARNING AND PRECAUTION

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.

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.

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

G-ROXIM 500 tablets contain parabens which may cause allergic reactions (possibly delayed).

1.3.1.6.5 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.

1.3.1.6.6 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. **G-ROXIM 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.

1.3.1.6.7 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.

1.3.1.6.8 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.

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 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.

1.3.1.6.9 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.

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

1.3.1.7 PHARMACOLOGICAL PROPERTIES

1.3.1.7.1 Pharmacodynamic properties

Pharmacotherapeutic group: antibacterial 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.

1.3.1.7.2 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.

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.

1.3.1.7.3 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.

1.3.1.8 PHARMACEUTICAL PARTICULARS

1.3.1.8.1 None

1.3.1.8.2 Incompatibilities

Not applicable.

1.3.1.8.3 Shelf life

Two years.

1.3.1.8.4 Special precautions for storage

Store below 30°C. Protected from light.

1.3.1.8.5 Nature and contents of container

Available as blister of 01 x 10 tablets in mono carton.

1.3.1.8.6 Special precautions for disposal and other Special handling

As with other broad-spectrum antibiotics, prolonged administration of cefuroxime axetil may result in overgrowth of nonsusceptible microorganisms. If superinfection occurs during therapy, appropriate measures should be taken.

Cephalosporins, including cefuroxime axetil, should be given with caution to patients

receiving concurrent treatment with potent diuretics because these diuretics are suspected of adversely affecting renal function.

Cefuroxime axetil, as with other broad-spectrum antibiotics, should be prescribed with caution in individuals with a history of colitis. The safety and effectiveness of cefuroxime axetil have not been established in patients with gastrointestinal malabsorption. Patients with gastrointestinal malabsorption were excluded from participating in clinical trials of cefuroxime axetil.

Cephalosporins may be associated with a fall in prothrombin activity. Those at risk include patients with renal or hepatic impairment or poor nutritional state, as well as patients receiving a protracted course of antimicrobial therapy, and patients previously stabilized on anticoagulant therapy. Prothrombin time should be monitored in patients at risk and exogenous Vitamin K administered as indicated.

Prescribing cefuroxime axetil in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.

1.3.1.9 Marketed by:

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