Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Cefuroxime Glob Limited 125 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 150.36 mg cefuroxime axetil equivalent to 125 mg cefuroxime.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

White to off-white, capsule shaped tablets with ‘A32’ debossed on one side and plain on the other side. The size is 12.5 mm X 5.0 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Cefuroxime Glob Limited is indicated for the treatment of the following mild to moderately severe infections caused by micro-organisms susceptible to cefuroxime:

- upper respiratory tract infections: acute otitis media, sinusitis, tonsillitis and pharyngitis
- acute bacterial bronchitis, acute exacerbations of chronic bronchitis
- lower uncomplicated urinary tract infections: cystitis
- skin and soft tissue infections: furunculosis, pyoderma and impetigo
- treatment of early stage Lyme disease (stadium I) and subsequent prevention of late complications in adults and children above 12 years of age.

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

4.2 Posology and method of administration

Route of administration: oral
This medicinal product is available in three strengths:
125 mg, 250 mg and 500 mg

The usual duration of therapy is 7 days (ranging from 5 to 10 days). For treatment of pharyngotonsillitis caused by *Streptococcus pyogenes* a therapy duration of at least 10 days is indicated. The duration of treatment of early Lyme disease should be 20 days. In order to achieve optimum absorption cefuroxime Glob Limited tablets should be taken shortly after meals.

The dosage depends on the severity of the infection. For severe infections parenteral forms of cefuroxime are recommended. Where appropriate cefuroxime is effective when used following initial parenteral cefuroxime sodium in the treatment of pneumonia and acute exacerbations of chronic bronchitis. The dose may need to be revised when switching from parenteral to oral treatment

Dosage schedule for tablets:

Adults and children over 12 years of age	**Dosage**
Upper respiratory tract infections	250 (- 500) mg twice daily
Lower respiratory tract infections	500 mg twice daily

Lower uncomplicated urinary tract infections	125 – 250 mg twice daily
Skin and soft tissue infections	250 – 500 mg twice daily
Early Lyme disease	500 mg twice daily during 20 days
Children from 5 to 12 years of age*	
Above-mentioned indications, if relevant for this group of children	125 – 250 mg twice daily
Acute otitis media	250 mg twice daily

***** Cefuroxime Glob Limited tablets can be suitable for use in children above the age of 5 that can swallow whole tablets. The child's tolerance of the taste and tablet's size should be ascertained by the clinician and parent. The tablets should not be crushed.

Children under 5 years of age:
Cefuroxime Glob Limited tablets are not suitable for use in children under the age of 5. For patients in this age group it is advised to use an oral suspension. There is no experience in children under 3 months of age.

Dosage regimen in renal impairment, in dialysis patients and elderly:
No special precautions are necessary in patients with renal impairment or in elderly patients if the daily dosage does not exceed 1 gram. In patients with severe renal impairment (creatinine clearance < 20 ml/min) the dosage should be reduced to once daily in order to compensate for the slower elimination.

Patients undergoing haemodialysis will require a supplementary dose of cefuroxime at the end of each dialysis treatment.

4.3 Contraindications

Hypersensitivity to cefuroxime or to any of the excipients.

Hypersensitivity to any other cephalosporin antibacterial agent.

Severe hypersensitivity (eg anaphylactic reaction, severe skin reaction) to any other type of betalactam antibacterial agent (e.g. penicillins or carbapenems).

4.4 Special warnings and precautions for use

Before therapy with Cefuroxime axetil is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to cefuroxime, cephalosporins, penicillins, or other drugs. This product should be given with caution to penicillin-sensitive patients ***(for contraindications due to known hypersensitivity reactions see section 4.3)***.

Antibiotics should be administered with caution to any patient who has demonstrated some form of allergy, particularly to drugs. If an allergic reaction to Cefuroxime axetil occurs, discontinue the drug.

Serious hypersensitivity reactions may require epinephrine and other emergency measures.

Cefuroxime axetil should not be prescribed in the absence of a proven or strongly suspected bacterial infection.

Antibiotic-associated diarrhoea, colitis and pseudomembranous colitis linked to Clostridium Difficile can all be reported with the use of cefuroxime axetil. These diagnoses should be considered in any patient who develops diarrhoea during or shortly after treatment. A 20-day treatment of Lyme disease may cause the frequency of developing diarrhoea to increase. Cefuroxime Glob should be discontinued if severe and/or bloody diarrhoea occurs during treatment and appropriate therapy instituted. Anti-peristaltics are contraindicated.

As with other cephalosporins, prolonged use of cefuroxime may result in the overgrowth of nonsusceptible organisms *(e.g. perianal, oral or vaginal candidiasis; pseudomembranous colitis; superinfection.* In these cases, specific treatment should be initiated.

During long-treatment (>7 days) with high-dose cefuroxime, blood counts and liver/kidney function must be monitored.

Regular renal function monitoring is also indicated, if aminoglycosides or potent diuretics such as furosemide are administered concomitantly. If cefuroxime alone was given, neither nephrotoxicity nor ototoxicity was observed.

Cefuroxime Glob should be administered with caution in patients with renal insufficiency, and adjust the daily dose in terms of creatinine clearance ***(see section 4.2)***
The use of cefuroxime is not recommended in patients with severe intestinal tract disorders accompanied by vomiting and diarrhoea, since in these situations a sufficient absorption cannot be guaranteed.
Administration of a parenteral formulation of cefuroxime should be considered.

The Jarisch-Herxheimer reaction has been reported following cefuroxime axetil treatment of Lyme disease. The reaction results directly from the bactericidal activity of cefuroxime axetil on the spirochaete *Borrelia burgdorferi*. Patients should be informed of this common and usually self-limited reaction being a consequence of antibiotic treatment of Lyme disease.

Concomitant administration of medicinal products that elevate gastric pH levels (e.g. antiacid drugs) may impair absorption, independently from ingestion.

There is no clinical experience with the use of cefuroxime axetil in children under the age of 3 months. With respect to the treatment of early Lyme disease there is only clinical experience with children from the age of 12 and with adults.

Either the glucose oxidase or the hexokinase methods are recommended to determine the blood and plasma glucose levels in patients receiving cefuroxime. Cefuroxime does not interfere in the alkaline picrate assay for creatinine (see section 4.5).

Please refer to section 4.5 for information on the use of cefuroxime axetil in combination with oral contraceptives.

4.5 Interaction with other medicinal products and other forms of interaction

Simultaneous use of medicines enhancing the pH of the stomach decreases the bioavailability of cefuroxime. It is recommended to avoid this combination (see section 4.4).

Since bacteriostatic drugs may interfere with the bactericidal action of cephalosporins, it is advisable to avoid giving tetracyclines, macrolides, or chloramphenicol in conjunction with cefuroxime.

The concomitant administration of probenicid can produce higher and sustained concentrations of cefuroxime in the serum and in the bile.

Cefuroxime may interfere with the determination of glucose in urine with copper containing reagentia (Benedict- or Fehling-solution, Clinitest). For the determination of blood and plasma sugar levels in patients receiving cefuroxime, the glucose-oxidase- or hexokinase method is recommended (see section 4.4).

The use of cefuroxime may be accompanied by a false positive Coombs test. This may interfere with the performance of cross matching tests with blood (see section 4.8).

Cephalosporin antibiotics at high dosage should be given with caution to patients receiving potent diuretics, aminoglycosides, or amphotericin as these combinations increases the risk of nephrotoxicity.

The reliability of the contraceptive effect of oral contraceptives is in doubt when using cefuroxime axetil at the same time. For this reason, other non-hormonal contraceptive means should be used in addition to oral contraceptives during treatment with Cefuroxime.

Please refer to section 4.4 for information on other interactions.

4.6 Fertility, pregnancy and lactation

Pregnancy
Data on a limited number of exposed pregnancies indicate no adverse effects of cefuroxime on the pregnancy or on the health of the fetus/newborn child. To date no other relevant epidemiological data are available. Animal studies do not show any harmful effects on embryonal and fetal development (see section 5.3.). Cefuroxime reaches the embryo/fetus via the placenta. Due to the limited clinical experience cefuroxime should only be used during pregnancy after careful risk/benefit, especially during the first trimester.

Lactation
Small amounts of the drug are excreted in breast milk. Cefuroxime should only be used during periods of breastfeeding if the benefits outweigh the possible risk. Diarrhoea and fungus infections of the mucous membranes in the breast-fed infant cannot be excluded, so that nursing might have to be discontinued. The possibility of sensitisation should be borne in mind.

Fertility:
Reproductive studies revealed no impairment of fertility in animals (see section 5.3).

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. Since this medicinal product may cause dizziness, patients should be warned to be cautious when driving a vehicle or operating machinery.

4.8 Undesirable effects

Within each frequency class, undesirable effects are specified in order of decreasing severity.
The frequency is defined using the following conventions:
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), not known (cannot be estimated from the available data).

Infections and infestations
Rare: Pseudomembranous colitis
As with other antibiotics prolonged use may lead to secondary superinfections caused by insusceptible organisms, e.g. *Candida, Enterococci* and *Clostridium difficile* (see section 4.4).

Blood and the lymphatic system disorders
Common: eosinophilia
Uncommon: thrombocytopenia, lecocytopenia and/or neutrocytopenia (sometimes severe)
Very rare: Haemolytic anaemia

Immune system disorders
Common: Jarisch-Herxheimer reaction following cefuroxime axetil treatment of Lyme disease (see section 4.4)
Uncommon: rash
Rare: urticaria, pruritus
Very rare: fever, serum sickness, anaphylaxis

Nervous system disorders
Uncommon: Headache, dizziness
Very rare: Restlessness, nervousness, confusion

Gastrointestinal disorders
Common: Diarrhoea, nausea and vomiting. The frequency of diarrhoea is related to the administered dose and may range up to 10% with tablets. The incidence is even higher
(approx. 13%) after prolonged treatment of early Lyme disease for 20 days.

Hepato-biliary disorders
Rare: temporary increases of liver enzymes (AST, ALT and LDH)
Very rare: hepatitis, obstructive jaundice.

Skin and subcutaneous tissue disorders
Common: Skin rashes, urticaria, pruritus.
Very rare: Erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis

Renal and urinary disorders
Common: Increased levels of creatinine and urea in serum, especially in patients with impaired renal function.
Uncommon: Acute interstitial nephritis

General disorders and administration site conditions
Rare: Drug fever

Investigations
Depending on the method, false-positive or false-negative results may be observed in glucose testing of the blood or urine. This can be prevented by using enzymatic methods. During cephalosporin treatment, results of Coombs-testing may be false-positive. The alkaline Pikrad assay (Jaffé method) should be used for creatinine assessment.

4.9 Overdose

Limited information is available on the acute toxicity of cefuroxime axetil in humans. Overdosage of cephalosporins can cause CNS irritation leading to seizures. If acute overdosage of cefuroxime occurs, hemodialysis and/or peritoneal dialysis can be used to enhance elimination of the drug from the body.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other beta-lactam antibacterials, second-generation cephalosporin

ATC code: J01D C02

Mode of action
Cefuroxime axetil owes its *in vivo* bactericidal activity to the parent compound cefuroxime.
All cephalosporins (β-lactam antibiotics) inhibit cell wall production and are selective inhibitors of peptidoglycan synthesis. The initial step in drug action consists of binding of the drug to cell receptors, called Penicillin-Binding Proteins. After a β-lactam antibiotic has bound to these receptors, the transpeptidation reaction is inhibited and peptidoglycan synthesis is blocked. Bacterial lysis is the end result.
PK/PD relationship

For cephalosporins, the most important pharmacokinetic-pharmacodynamic index correlating with in vivo efficacy has been shown to be the duration that the unbound drug concentration remains above the minimum inhibitory concentration (MIC) as a percentage of the dosing interval (%T>MIC).

Mechanism of resistance
Bacterial resistance to cefuroxime may be due to one or more of the following mechanisms:
- hydrolysis by beta-lactamases. Cefuroxime may be efficiently hydrolysed by certain of the extended-spectrum beta-lactamases (ESBLs) and by the chromosomally-encoded (AmpC) enzyme that may be induced or stably derepressed in certain aerobic gram negative bacterial species
- reduced affinity of penicillin-binding proteins for cefuroxime
- outer membrane impermeability, which restricts access of cefuroxime to penicillin binding proteins in gram-negative organisms
- drug efflux pumps

Methicillin-resistant staphylococci (MRS) are resistant to all currently available β-lactam antibiotics including cefuroxime.

Penicillin-resistant *Streptococcus pneumoniae* are cross-resistant to cephalosporins such as cefuroxime through alteration of penicillin binding proteins.

Beta-lactamase negative, ampicillin resistant (BLNAR) strains of *H. influenzae* should be considered resistant to cefuroxime despite apparent in vitro susceptibility.
Strains of Enterobacteriaceae, in particular *Klebsiella* spp. and *Escherichia coli* that produce ESBLs (extended spectrum β-lactamase) may be clinically resistant to therapy with cephalosporins despite apparent in vitro susceptibility and should be considered as resistant.

Breakpoints:
According to the EUCAST 2009-05-25 (v 2.0) the following breakpoints have been defined for cefuroxime axetil:

BACTERIAL SPECIES	**MIC breakpoints**
	S≤ / R > (mg/L)
Enterobacteriaceae	8.0 / 8.0[1]
Haemophilus influenzae	0.12 / 1.0
Moraxella catarrhalis	0.12 / 2.0
Staphylococcus spp.	Note[2]
Streptococcus A, B, C, G	Note[3]
Streptococcus pneumoniae	0.25 / 0.5

[1] For uncomplicated urinary tract infections only.

[2] Susceptibility of staphylococci to cephalosporins is inferred from the methicillin susceptibility.

[3] The susceptibility of streptococcus groups A, B, C and G can be inferred from the susceptibility to benzylpenicillin.

Susceptibility:
The prevalence of 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 the agent in at least some types of infections is questionable.

Commonly susceptible species
Aerobes, Gram positive: *Staphylococcus aureus* (methicillin-susceptible) Coagulase-negative staphylococci (methicillin susceptible) *Streptococcus agalactiae* *Streptococcus pneumoniae* *Streptococcus pyogenes*
Aerobes, Gram negative: *Haemophilus influenzae* *Moraxella catarrhalis* *Proteus mirabilis*
Anaerobes, *Peptococcus* species *Peptostreptococcus* species
Other organisms: *Borrelia burgdorferi*.
Species for which resistance may be a problem

Acinetobacter species *Citrobacter* species *Enterobacter* species *Escherichia coli* *Klebsiella species* *Providencia rettgeri* *Streptococcus pneumoniae*
Inherantly resistant organisms
Bacteroides fragilis *Clostridium difficile* *Enterococcus spp* *Listeria monocytogenes* *Morganella morganii* *Proteus vulgaris* *Pseudomonas aeruginosa* *Serratia* species Others: *Legionella spp.* *Clamydophilia pneumoniae* *Mycoplasma pneumoniae*

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 causing the release of the active compound cefuroxime into the circulation. Optimum absorption occurs when cefuroxime axetil is taken shortly after a meal (50-60%). Under these circumstances maximum serum concentration is achieved after 2-3 hours.

Distribution: Cefuroxime is widely distributed in the body including pleural fluid, sputum, bone, synovial fluid, and aqueous humour, but only achieves therapeutic concentrations in the CSF when the meninges are inflamed. About 50% of cefuroxime in the circulation is bound to plasma proteins. It diffuses across the placenta and has been detected in breast milk.

Metabolism: Cefuroxime is not metabolised.

Elimination: Most of the dose of cefuroxime is excreted unchanged. About 50% is excreted by glomerular filtration and about 50% through renal tubular secretion within 24 hours, with the majority being eliminated within 6 hours; high concentrations are achieved in the urine.

Small amounts of cefuroxime are excreted in bile. Probenecid competes with cefuroxime for renal tubular secretion resulting in higher and more prolonged plasma concentrations of cefuroxime.
The plasma half-life ranges between 60 and 90 minutes and is prolonged in patients with renal impairment and in neonates.

Dialysis causes the decrease of cefuroxime serum levels.

5.3 Preclinical safety data

Cefuroxime sodium has a very low order of toxicity as demonstrated by acute toxicity studies.
Investigations of chronic toxicity in several animal species (rat, dog and monkey) yielded no indications of drug related toxicological effects. The most prominent treatment-related effect was tissue damage at the injection sites.
Preclinical nephrotoxicity studies showed the product can cause renal damage in some species when administered in very high doses. Its nephrotoxicity increases when administered in combination with glycerol and furosemide.
A cefuroxime ester did not show clinically relevant effects when tested in vitro and in vivo for genotoxic potential.
No long-term investigations for determination of tumorigenic potential were performed.

Investigations in rabbits and mice did not demonstrate reproductive toxicity or teratogeniceffects.
Cefuroxime has been shown to pass the placenta.
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 (E 460)
Croscarmellose sodium
Sodium lauril sulfate
Cottonseed oil, hydrogenated
Colloidal anhydrous silica

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions.
Store in the original package in order to protect from light.

6.5 Nature and contents of container

Polyamide/Aluminium/PVC/Aluminium blister
Pack sizes:
125mg: 8, 10, 12, 14 or 30 tablets
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

7 MARKETING AUTHORISATION HOLDER

Glob Limited
65 Delamere Road,
Hayes,
Middlesex UB 4 0NN,
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA 1675/002/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 30th September 2011

10 DATE OF REVISION OF THE TEXT