IRISH MEDICINES BOARD ACT 1995, as amended

Medicinal Products (Control of Placing on the Market) Regulations, 2007, as amended

PA0711/101/001
Case No: 2082950

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Rowex Ltd

Bantry, **Co. Cork**, **Ireland**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Ceftal 125mg coated tablets

the particulars of which are set out in the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **28/07/2010**.

Signed on behalf of the Irish Medicines Board this

_____

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ceftal 125mg coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Ceftal 125 mg contains 150.36 mg cefuroxime axetil which is equivalent to 125 mg cefuroxime per tablet

Excipients: aspartame (E951) 0.2mg

For a full list of excipients: see section 6.1.

3 PHARMACEUTICAL FORM

Coated tablets
White to slightly yellowish, biconvex, oblong tablets

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Cefuroxime axetil is indicated for the treatment of mild to moderately severe infections caused by micro-organisms susceptible to cefuroxime, such as:

- upper respiratory tract infections: acute otitis media, sinusitis, tonsillitis and pharyngitis
- acute 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

Ceftal Tablets are coated to mask their taste: they should not be chewed.
The usual duration of therapy is 7 days (ranging from 5 to 10 days). In case 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 Ceftal 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 axetil is effective when used following initial parenteral cefuroxime sodium in the treatment of pneumonia and acute exacerbations of chronic bronchitis.

Dosage schedule for tablets:

Adults and children over 12years 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

Children under 5 years of age:
Ceftal 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 renal impairment and creatinine clearance below 20 ml/min Ceftal Tablets should be dosed carefully. Patients undergoing haemodialysis will require a supplementary dose of cefuroxime at the end of each dialysis treatment.

4.3 Contraindications

Hypersensitivity to cefuroxime, other cephalosporins or to any of the excipients.
Previous immediate and /or severe hypersensitivity reaction to a penicillin or to any other type of beta-lactam medicinal products.

4.4 Special warnings and precautions for use

If after administration of cefuroxime axetil sensitivity reactions occur, the use should be discontinued immediately and an appropriate treatment should be established.
Special care is indicated in patients who have experienced an allergic reaction to penicillins or other beta-lactams.

As with other broad spectrum antibiotics, prolonged use of cefuroxime axetil may result in the overgrowth of non-susceptible organisms (e.g., candida, enterococci and clostridium difficile, which may require interruption of treatment.
In patients who develop severe diarrhoea during or after use of cefuroxime axetil, the risk of life threatening pseudomembranous colitis should be taken into account. The use of cefuroxime axetil should be discontinued and the appropriate treatment established. The use of preparations inhibiting the intestinal peristaltism is contra-indicated (see section 4.8).
A 20-day treatment of Lyme disease may cause the frequency of developing diarrhoea to increase.

Long term use of cefuroxime axetil may lead to an excess of pathogens resistant to cefuroxime axetil. It is of high importance that the patient is carefully checked. If a superinfection occurs during treatment, appropriate measures should be taken (see section 4.8).

The use of cefuroxime axetil is not recommended in patients with severe intestinal tract disorders accompanied by vomiting and diarrhoea, since in these situations a sufficient absorption can not 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.

Simultaneous use of medicines enhancing the pH of the stomach is not recommended (see section 4.5).

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.

Special care should be taken with phenylketonuric patients because of the aspartame containing coating.

Ceftal 125mg Coated Tablets contain 0,2 mg aspartame per tablet

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

During the treatment with cefuroxime sodium, some children have experienced slight to moderate hearing loss.

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 axetil. 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 axetil.

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 axetil, the glucose-oxidase- or hexokinase method is recommended (see section 4.4).

The use of cefuroxime axetil 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.

4.6 Pregnancy and lactation

Use in pregnancy
There are not sufficient data on the use of cefuroxime axetil during pregnancy to assess its possible harmfulness. So far, animal tests have not yielded evidence of harmfulness. Cefuroxime crosses the placenta. Cefuroxime axetil should not be used during pregnancy unless considered essential by the physician.

Use during lactation
Cefuroxime is excreted to a small degree in human milk; breast feeding should be avoided in women using cefuroxime axetil.

4.7 Effects on ability to drive and use machines

There are no studies of the effect of cefuroxime axetil on the ability to drive and to handle machines.
However, any effects are not to be expected.

4.8 Undesirable effects

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)

<u>Infections and infestations:</u>
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
Rare
Decreased haemoglobin concentration, eosinophilia, leucopenia, neutropenia and thrombocytopenia
Very rare
Haemolytic anemia

Immune system disorders:
Common
Jarisch-Herxheimer reaction following cefuroxime axetil treatment of Lyme disease (see section 4.4).
Rare
Serum sickness
Very rare
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 rate up to 10% with tablets. The incidence is even higher (approx. 13%) at prolonged treatment of 20 days of early Lyme disease.

Hepato-biliary disorders:
Rare
Transient increases of hepatic enzyme levels (AST, ALT and LDH) and serum bilirubin.
Very rare
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
The use of cefuroxime axetil may be accompanied by a false positive Coombstest. This may interfere with the performance of cross matching tests with blood (see section 4.5).

4.9 Overdose

Overdose of cephalosporins may cause cerebral irritancy leading to convulsions. In case of overdose cefuroxime serum

levels can be reduced by haemodialysis and peritoneal dialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

General properties:
ATC classification
Pharmacotherapeutic group: cephalosporins and related substances
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.

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 NCCLS (National Committee on Clinical Laboratory Standards) in 2001 the following breakpoints have been defined for cefuroxime axetil:

Enterobacteriaceae: ≤ 4 µg/ml susceptible, ≥ 32 µg/ml resistant

Staphylococcus spp.: ≤ 4 µg/ml susceptible, ≥ 32 µg/ml resistant

Haemophilus spp.: ≤ 4 µg/ml susceptible; ≥ 16 µg/ml resistant

Streptococcus pneumoniae: ≤ 1 µg/ml susceptible, ≥ 4 µg/ml resistant

Streptococcus spp. other than *S. pneumoniae*:
Streptococcal isolates susceptible to penicillin (MIC_{90} ≤ 0.12 µg/ml) may be considered susceptible to cefuroxime.

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: ***Escherichia coli*** ***Haemophilus influenzae*** **Klebsiella species** ***Moraxella catarrhalis*** ***Proteus mirabilis*** ***Proteus rettgeri***
Anaerobes, **Peptococcus species** **Peptostreptococcus species**
Other organisms: ***Borrelia burgdorferi*.**
Species for which resistance may be a problem
Acinetobacter species **Citrobacter species** **Enterobacter species** ***Morganella morganii***
Resistant ***Bacteroides fragilis*** ***Clostridium difficile*** Enterococci ***Listeria monocytogenes*** ***Proteus vulgaris*** Pseudomonas **species** **Serratia species**

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 Cefuroximaxetil 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

Preclinical effects were observed in dosages far above the maximal human dosage which are therefore hardly relevant for the clinical use of cefuroxime axetil.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core
Sodium laurilsulfate,
Copovidone,
Croscarmellose sodium (E468),
Magnesium stearate (E 470B),
Colloidal anhydrous silica (E551),
Granulated mannitol (E421),
Microcrystalline cellulose (E460),
Crospovidone (E1202),
Talc (E553B).
Coating
Mannitol (E421),
Soluble starch (potato),
Talc (E553B),
Titanium dioxide (E171),
Aspartame (E951)

6.2 Incompatibilities

Not applicable

6.3 Shelf Life

Al/Al strip: 3 years
Al/Al blister: 3 years

6.4 Special precautions for storage

Al/Al strip: Store in the original packaging in order to protect from moisture
Al/Al blister: Store in the original packaging in order to protect from moisture
This medicinal product does not require any special temperature storage conditions

6.5 Nature and contents of container

Al/Al strip packaging
Al/Al blister packaging

Pack sizes:
8, 10, 12, 14, 24 tablets
Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Rowex Ltd
Bantry
Co Cork
Ireland

8 MARKETING AUTHORISATION NUMBER

PA 711/101/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 13 October 2006

Last date of renewal: 26 January 2010

10 DATE OF REVISION OF THE TEXT

June 2010