IRISH MEDICINES BOARD ACT 1995, as amended

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

PA1380/041/001
Case No: 2084272

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

Actavis Group PTC ehf

Reykjavikurvegi 76-78, **220 Hafnarfjordur**, **Iceland**

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

Cefalexin 250mg hard capsules

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 **19/08/2010** until **02/04/2014**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Cefalexin 250mg hard capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains, as active ingredient, cefalexin monohydrate equivalent to 250 mg of cefalexin base.

Excipients: Brilliant blue (E133) and sunset yellow (E110).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule, hard

Green coloured opaque cap and white coloured opaque body size 2 hard gelatin capsules imprinted with black “CEF” on cap and “250” on body, filled with white to off white granular powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Cefalexin is a semi-synthetic cephalosporin antibiotic for oral administration.

Cefalexin is indicated for the treatment of the following infections (see also sections 4.4 and 5.1).

Exacerbation of chronic bronchitis
Mild to moderate community-acquired pneumonia
Uncomplicated upper and lower urinary tract infections
Skin and soft tissue infections

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

4.2 Posology and method of administration

Posology
The recommended dose for adults is 1-4 g daily in divided doses. Most infections will respond to a dosage of 500 mg every 8 hours. For skin and soft tissue infections and mild, uncomplicated urinary tract infections, the usual dosage is 250 mg every 6 hours or 500 mg every 12 hours.

For more severe infections or those caused by less susceptible organisms, larger doses may be needed. If daily doses of cefalexin greater than 4 g are required, parenteral cephalosporins, in appropriate doses, should be considered.

Patients with impaired renal function
Reduce dosage if renal function is markedly impaired (section 4.4).

Elderly patients
The recommended dose for adults should be used in elderly patients except those with impaired renal function (see section 4.4).

Children
The recommended daily dosage for children is 25-50 mg/kg body weight divided in 3 doses.

In severe infections, the dosage may be doubled.

In the treatment of beta-haemolytic streptococcal infections, a therapeutic dose should be administered for at least 10 days.

Method of administration

Cefalexin is administered orally.

4.3 Contraindications

Hypersensitivity to the cephalosporin group of antibiotics or to any of the excipients.

4.4 Special warnings and precautions for use

Before instituting therapy with Cefalexin, every effort should be made to determine whether the patient has had previous hypersensitivity reactions to the cephalosporins, penicillins or other medicinal products. Cefalexin should be given cautiously to penicillin-sensitive patients. There is some clinical and laboratory evidence of partial cross-allergenicity of the penicillins and cephalosporins. Patients have had severe reactions (including anaphylaxis) to both medicinal products.

Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics, including macrolides, semi-synthetic penicillins, and cephalosporins. It is important, therefore, to consider its diagnosis in patients who develop diarrhoea in association with the use of antibiotics. Such colitis may range in severity from mild to life-threatening. Mild cases of pseudomembranous colitis usually respond to drug discontinuance alone. In moderate to severe cases, appropriate measures should be taken.

If an allergic reaction to Cefalexin occurs, the drug should be discontinued and the patient treated with the appropriate agents.

Prolonged use of Cefalexin may result in the overgrowth of non-susceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Cefalexin should not be used in infections in which *Haemophilus influenzae* is, or is likely to be, implicated.

Cefalexin should be administered with caution in the presence of markedly impaired renal function. Careful clinical and laboratory studies should be made because safe dosage may be lower than that usually recommended. If dialysis is required for renal failure, the daily dose of cefalexin should not exceed 500 mg.

Positive direct Coombs' tests have been reported during treatment with the cephalosporin antibiotics. In haematological studies, or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side, or in Coombs' testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognised that a positive Coombs' test may be due to the medicinal product.

A false positive reaction for glucose in the urine may occur with Benedict's or Fehling's solutions, or with copper sulphate test tablets.

Cefalexin capsules, hard contain colouring agents brilliant blue (E133) and sunset yellow (E110), which may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

As with other beta-lactam medicinal products, renal excretion of Cefalexin is inhibited by probenecid.

Concurrent administration with certain other drug substances, such as aminoglycosides, other cephalosporins, or furosemide, and similar potent diuretics, may increase the risk of nephrotoxicity.

In a single study of 12 healthy subjects given single 500 mg doses of Cefalexin and metformin, plasma metformin C_{max} and AUC increased by an average of 34% and 24%, respectively, and metformin renal clearance decreased by an average of 14%. No side effects were reported in 12 healthy subjects in this study. No information is available about the interaction of Cefalexin and metformin following multiple dose administration. The clinical significance of this study is unclear, particularly as no cases of “lactic acidosis” have been reported in association with concomitant metformin and Cefalexin treatment.

4.6 Pregnancy and lactation

Pregnancy
There are no adequate and well controlled studies in pregnant women. Although animal studies have shown no evidence of teratogenicity, caution should be exercised when prescribing cefalexin during pregnancy (see section 5.3).

Lactation
Cefalexin is excreted in human milk. Caution should be exercised when cefalexin is administered to a nursing woman.

4.7 Effects on ability to drive and use machines

There are no known effects of cephalexin on a patient's ability to drive or use machinery. However when driving vehicles or operating machines it should be taken into account that occasionally dizziness or confusion may occur.

4.8 Undesirable effects

Adverse events that have been reported in cefalexin trials are categorised below, according to system organ class and frequency.

Frequencies are defined as:
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),
not known (cannot be estimated from the available data).

Undesirable effects for cefalexin occur at a frequency of 3-6%.

Investigations
Uncommon: Increase in ASAT and ALAT (reversible)
Frequency not known: Positive direct Coombs test. False positive reaction to glucose in the urine

Blood and lymphatic system disorders
Uncommon: Eosinophilia
Rare: Neutropenia, thrombocytopenia, haemolytic anaemia

Nervous system disorders
Rare: Headache, dizziness

Gastrointestinal disorders
Common: Diarrhoea, nausea.
Rare: Abdominal pain, vomiting, dyspepsia, pseudomembranous colitis

Renal and urinary disorders
Rare: Reversible interstitial nephritis

Skin and subcutaneous tissue disorders
Uncommon: Rash, urticaria, pruritus
Rare: Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis (Lyell's syndrome), angioedema

Musculoskeletal and connective tissue disorders
Frequency not known: Arthralgia, arthritis

Infections and infestations
Rare: Genital and anal pruritus, vaginitis
Frequency not known: Vaginal candidiasis

General disorders and administration site conditions
Rare: Tiredness
Frequency not known: Fever

Immune system disorders
Rare: Anaphylactic reaction

Hepatobiliary disorders
Rare: Hepatitis, cholestatic icterus

Psychiatric disorders
Frequency not known: Hallucinations, agitation, confusion

4.9 Overdose

Symptoms of oral overdose may include nausea, vomiting, epigastric distress, diarrhoea, and haematuria.

In the event of severe overdosage, general supportive care is recommended, including close clinical and laboratory monitoring of haematological, renal and hepatic functions, and coagulation status until the patient is stable. Forced diuresis, peritoneal dialysis, haemodialysis, or charcoal haemoperfusion have not been established as beneficial for an overdose of Cefalexin. It would be extremely unlikely that one of these procedures would be indicated.

Unless 5 to 10 times the normal total daily dose has been ingested, gastro-intestinal decontamination should not be necessary.

There have been reports of haematuria, without impairment of renal function, in children accidentally ingesting more than 3.5 g of cefalexin in a day. Treatment has been supportive (fluids) and no sequelae have been reported.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: First generation cephalosporin, ATC code: J01DB01.

Mode of Action
Cefalexin is an antibacterial agent of the cephalosporin class.

Like other cephalosporins cefalexin exerts antibacterial activity by binding to and inhibiting the action of penicillin-binding proteins involved in the synthesis of bacterial cell walls. This leads to bacterial cell lysis and cell death.

Mechanisms of resistance
Bacterial resistance to cefalexin may be due to one or more of the following mechanisms:

- Hydrolysis by extended-spectrum beta-lactamases and / or by chromosomally-encoded (AmpC) enzymes that may be induced or de-repressed in certain aerobic gram-negative bacterial species.
- Reduced affinity of penicillin-binding proteins.
- Reduced permeability of the outer membrane of certain gram-negative organisms restricting access to penicillin-binding proteins
- Drug efflux pumps

More than one of these mechanisms of resistance may co-exist in a single bacterial cell. Depending on the mechanism (s) present, bacteria may express cross-resistance to several or all other beta-lactams and/ or antibacterial medicinal products of other classes.

Breakpoints
Minimum inhibitory concentration (MIC) breakpoints established by the British Society of Antimicrobial Chemotherapy for beta-haemolytic Streptococci and *Streptococcus pneumoniae* are: susceptible ≤ 2mg /l, resistant ≥ 2.5 mg/l.

Susceptibility
The prevalence of resistance may vary geographically and over 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)
Streptococcus agalactiae
Streptococcus pneumoniae
Streptococcus pyogenes

Aerobes, Gram negative:
Escherichia coli
Moraxella catarrhalis

Anaerobes:
Peptostreptococcus species

Species for which resistance may be a problem

Gram-negative aerobes:
Citrobacter species
Enterobacter species
Morganella morganii.

Inherently resistant species

Gram-negative aerobes:
Haemophilus influenzae

5.2 Pharmacokinetic properties

Cefalexin is acid stable and may be given without regard to meals. It is rapidly absorbed after oral administration. Following doses of 250 mg, 500 mg, and 1 g, average peak serum levels of approximately 9, 18, and 32 mg/l, respectively, were obtained at 1 hour. Measurable levels were present 6 hours after administration. Cefalexin is excreted in the urine by glomerular filtration and tubular secretion. Studies showed that over 90% of the medicinal product was excreted unchanged in the urine within 8 hours. During this period, peak urine concentrations following the 250 mg, 500 mg, and 1 g doses were approximately 1,000, 2,200, and 5,000 mg/l, respectively.

Cefalexin is almost completely absorbed from the gastro-intestinal tract, and 75-100% is rapidly excreted in active form in the urine. Absorption is slightly reduced if the drug is administered with food. The half-life is approximately 60 minutes in patients with normal renal function. Haemodialysis and peritoneal dialysis will remove cefalexin from the blood.

Peak blood levels are achieved one hour after administration, and therapeutic levels are maintained for 6-8 hours. Approximately 80% of the active drug is excreted in the urine within 6 hours. No accumulation is seen with dosages above the therapeutic maximum of 4 g/day.

The half-life may be increased in neonates due to their renal immaturity, but there is no accumulation when given at up to 50 mg/kg/day.

5.3 Preclinical safety data

The daily oral administration of cefalexin to rats in doses of 250 or 500 mg/kg prior to and during pregnancy, or to rats and mice during the period of organogenesis only, had no adverse effect on fertility, foetal viability, foetal weight, or litter size.

Cefalexin showed no enhanced toxicity in weanling and newborn rats as compared with adult animals.

The oral LD_{50} of cefalexin in rats is 5,000 mg/kg.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content
Cellulose microcrystalline
Croscarmellose sodium
Magnesium stearate

Capsule shell
Sodium laurilsulfate
Sunset yellow (E110)
Brilliant blue (E133)
Titanium dioxide (E171)
Gelatin
Black printing ink (containing shellac, propylene glycol, potassium hydroxide and iron oxide, black (E172))

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Blister strips consisting of PVC/Aclar/Aluminium blister film.

Pack sizes:

14 and 28 capsules, hard.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements

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

7 MARKETING AUTHORISATION HOLDER

Actavis Group PTC ehf
Reykjavikurvegi 76-78
220 Hafnarfjordur
Iceland

8 MARKETING AUTHORISATION NUMBER

PA 1380/41/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 3rd April 2009

10 DATE OF REVISION OF THE TEXT

February 2010