Cefalexin 250 mg Capsules
Cefalexin 500 mg Capsules
(cefalexin)
PL 35507/0104-5

UK Public Assessment Report

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Cefalexin 250 mg Capsules
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LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Lupin (Europe) Limited Marketing Authorisations (licences) for the medicinal products Cefalexin 250 mg and 500 mg Capsules (PL 20092/0064-5) on 15th July 2011. These licences underwent Change of Ownership on 7th September 2011 and are still held by Lupin (Europe) Limited (PL 35507/0104-5). These are prescription-only medicines (POM).

Cefalexin 250 mg and 500 mg Capsules contain the active ingredient cefalexin, which is an antibiotic. Antibiotics work by killing the bacteria (germs) that can cause an infection.

Cefalexin Capsules are used to treat infections of:

- the lungs and breathing airways (bronchitis and mild to moderate pneumonia)
- the skin and soft tissue (such as wound infection)

The test products were considered to be generic versions of the UK reference products Keflex / Cefalexin 250 mg and 500 mg Capsules (PL 13621/0025 and 0021, Flynn Pharma Limited) based on the data submitted by Lupin (Europe) Limited.

No new or unexpected safety concerns arose from these applications. It has been judged that the benefits of Cefalexin 250 mg and 500 mg Capsules outweigh the risks; hence Marketing Authorisations have been granted.
Cefalexin 250 mg Capsules
Cefalexin 500 mg Capsules

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SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Lupin (Europe) Limited Marketing Authorisations for the medicinal products Cefalexin 250 mg and 500 mg Capsules (PL 20092/0064-5) on 15th July 2011. These licences subsequently underwent Change of Ownership on 7th September 2011 and are still held by Lupin (Europe) Limited (PL 35507/0104-5). These are prescription-only medicines (POM).

These are generic applications for Cefalexin 250 mg and 500 mg Capsules, submitted under Article 10.1 of Directive 2001/83 EC, as amended. The applications refer to the UK products, Keflex / Cefalexin 250 mg and 500 mg Capsules, originally awarded default conversion licences to Eli Lilly and Company Limited (PLs 00006/5103 and 0076) in 1985. These licences underwent Change of Ownership (CoA) procedures in October 2005 and are currently authorised to Flynn Pharma Limited (PL 13621/0025 and 0021). The reference products have been authorised in the UK for more than 10 years, thus the period of data exclusivity has expired.

Cefalexin is a semi-synthetic cephalosporin antibiotic (ATC code – J01D B01) for oral administration. It is indicated in the treatment of the following infections due to susceptible micro-organisms:

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

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.

No new pre-clinical or clinical efficacy studies were conducted for these applications, which is acceptable given that the applications were for generic versions of products that have been licensed for over 10 years.

The applications are supported by a bioequivalence study comparing the pharmacokinetic profile of the test product, Cefalexin 500 mg Capsules, to that of the clinical reference product, Keflex 500 mg Capsules (Flynn Pharma Limited). The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture and assembly of these products. Evidence of compliance with GMP has been provided for the named manufacturing and assembly sites.

The MHRA considers that the pharmacovigilance system as described by the Marketing Authorisation Holder (MAH) fulfils the requirements and provides adequate evidence that the MAH has the services of a Qualified Person (QP)
responsible for pharmacovigilance and has the necessary means for the notification of
any adverse reaction suspected of occurring either in the Community or in a third
country.

The MAH has provided adequate justification for not submitting a Risk Management
Plan (RMP). As the applications are for generic versions of already authorised
reference products, for which safety concerns requiring additional risk minimisation
have not been identified, routine pharmacovigilance activities are proposed and a risk
minimisation system is not considered necessary. The reference products have been in
use for many years and the safety profile of the active is well-established.

The MAH has provided adequate justification for not submitting a detailed
Environmental Risk Assessment (ERA). These were applications for generic products
and there is no reason to conclude that marketing of these products will change the
overall use pattern of the existing market. There are no environmental concerns
associated with the method of manufacture or formulation of the products.
PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE

Cefalexin

Nomenclature:

INN: Cefalexin monohydrate

Chemical name: \((6R,7R)-7-[[2R]2\text{-Amino}-2\text{-phenylacetyl}]\text{amino}]3\text{-methyl}-8\text{-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid monohydrate}\)

Structure:

![Structure of Cefalexin monohydrate]

Molecular formula: \(\text{C}_{16}\text{H}_{17}\text{N}_{3}\text{O}_{4}\text{S} \cdot \text{H}_{2}\text{O}\)

Molecular weight: 365.4 g/mol

CAS No: 23325-78-2

Physical form: A white or almost white crystalline powder

Solubility: Sparingly soluble in water, practically insoluble in alcohol

The active substance, cefalexin monohydrate, is the subject of a European Pharmacopeia (Ph. Eur.) monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis. Confirmation has been provided that the raw materials, intermediates and auxiliary agents used in synthesis of the active are not of animal, biological or genetically modified origin.

Appropriate specifications have been provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specifications. Satisfactory Certificates of Analysis have been provided for any reference standards used by the active substance manufacturer during validation studies.

The active substance is stored in appropriate packaging. Specifications and Certificates of Analysis have been provided for the packaging materials used. The primary packaging in direct contact with the active substance complies with relevant Ph. Eur. requirements and satisfies Directive 2002/72/EC (as amended); it is suitable for contact with foodstuffs.
Appropriate stability data have been generated for the active substance stored in the proposed commercial packaging. These data demonstrate the stability of the active substance and support the 48-month shelf-life period that has been applied.

**MEDICINAL PRODUCT**

**Description and Composition**

Cefalexin 250 mg and 500 mg Capsules are presented as hard, gelatin capsules containing white to yellowish-white granular powder. Each capsule contains 250 mg or 500 mg of the active ingredient, cefalexin. The 250 mg strength capsules have a dark green cap, imprinted with ‘250’, and white body. The 500 mg strength capsules have a dark green cap, imprinted with ‘500’, and light green body. Full descriptions of the individual capsules may be found by referring to the Summary of Product Characteristics or patient information leaflet.

Other ingredients consist of pharmaceutical excipients, namely microcrystalline cellulose, magnesium stearate and water making up the cores; and gelatin, sodium lauryl sulphate, sunset yellow FCF (E110), quinoline yellow (E104), titanium dioxide (E171), patent blue V (E131) and black printing ink making up the capsule shells. The black printing ink is constituted of shellac, propylene glycol, potassium hydroxide and black iron oxide (E172). Appropriate justification for the inclusion of each excipient has been provided.

The excipients of the granular cores comply with their respective European Pharmacopoeia monographs. The hard gelatin capsule shells comply with satisfactory in-house specifications. Satisfactory Certificates of Analysis have been provided for all excipients.

The magnesium stearate has been confirmed as being of vegetable origin. The only excipient used that contains material of animal or human origin is gelatin. Satisfactory documentation has been provided by the gelatin suppliers stating that the gelatin they provide complies with the criteria described in the current version of the monograph ‘Products with risk of transmitting agents of animal spongiform encephalopathies’. None of the excipients are sourced from genetically modified organisms.

There were no novel excipients used.

**Pharmaceutical development**

Details of the pharmaceutical development of the medicinal products have been supplied and are satisfactory. The objective was to develop stable, generic, capsule formulations, bioequivalent to the reference products, Keflex / Cefalexin 250 mg and 500 mg Capsules (PL 13621/0025 and 0021, Flynn Pharma Limited).

Comparative dissolution and impurity data were provided for batches of the test products and appropriate reference products. The dissolution and impurity profiles were satisfactory.

**Manufacture**

A description and flow-chart of the manufacturing method has been provided.
In-process controls have been provided and are appropriate considering the nature of the products and the method of manufacture. Process validation studies were conducted and the results were satisfactory.

**Finished product specification**

Finished product specifications are provided for both release and shelf-life and are satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Satisfactory batch analysis data are provided and accepted. The data demonstrate that the batches are compliant with the proposed specifications. Certificates of Analysis have been provided for any reference standards used.

**Container Closure System**

Cefalexin 250 mg and 500 mg Capsules are licensed for marketing in polyvinylchloride (PVC) / polyvinylidene chloride (PVdC) - aluminium foil blister strips, which are packaged with the Patient Information Leaflet (PIL) into cardboard outer cartons in pack sizes of 4, 10, 12, 16, 20, 21, 24, 28, 30, 100 or 112 capsules (250 mg strength) and 8, 10, 12, 14, 15, 16, 20, 21, 28, 30, 40 or 100 capsules (500 mg strength). The MAH has stated that not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis for all packaging components used have been provided. All primary product packaging complies with EU legislation, Directive 2002/72/EC (as amended), and is suitable for contact with foodstuffs.

**Stability**

Finished product stability studies have been conducted in accordance with current guidelines, using product stored in the packaging proposed for marketing. These data support the applied shelf-life of 24 months, with the storage instructions ‘Store below 30°C. Store in the original package’.

**Quality Overall Summary**

A satisfactory quality overview is provided and has been prepared by an appropriately qualified expert. The CV of the expert has been supplied.

**Product Information**

The approved Summaries of Product Characteristics (SmPCs), Patient Information Leaflets (PIL) and labelling are satisfactory. Mock-ups of the PIL and labelling have been provided. The PIL user-testing report has been evaluated and is accepted. The labelling text fulfils the statutory requirements for Braille.

The MAH has stated that not all licensed pack sizes may be marketed. They have committed to submitting mock-ups for unmarketed pack sizes to the MHRA for approval before those packs are commercially marketed.

**Conclusion**

All pharmaceutical issues have been resolved and the quality grounds for these applications are considered adequate. There are no objections to approval of Cefalexin 250 mg and 500 mg Capsules from a pharmaceutical point of view.
PRE-CLINICAL ASSESSMENT

These abridged applications, submitted under Article 10.1 of Directive 2001/83/EC, as amended, are for Cefalexin 250 mg and 500 mg Capsules, products claiming to be generic medicinal products of Keflex / Cefalexin 250 mg and 500 mg Capsules (PL 13621/0025 and 0021; Flynn Pharma Limited).

No new pre-clinical data have been supplied with these applications and none are required for applications of this type. A pre-clinical overview has been written by a suitably qualified person and is satisfactory. The CV of the expert has been supplied.

The MAH has provided adequate justification for not submitting an Environmental Risk Assessment (ERA).

There are no objections to approval of these products from a non-clinical point of view.
CLINICAL ASSESSMENT

INDICATIONS
Cefalexin 250 mg and 500 mg Capsules are indicated in the treatment of the following infections due to susceptible micro-organisms:

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

The indications are consistent with those for the UK reference products and are satisfactory.

POSOLOGY AND METHOD OF ADMINISTRATION
Full details concerning the posology are provided in the SmPCs. The posology is consistent with that for the UK reference products and is satisfactory.

TOXICOLOGY
The toxicology of cefalexin is well-known. No new data have been submitted and none are required for applications of this type.

CLINICAL PHARMACOLOGY
Pharmacodynamics
The clinical pharmacology of cefalexin is well-known. With the exception of the bioequivalence study, no new pharmacodynamic or pharmacokinetic data are supplied and none are required for these applications.

Pharmacokinetics - Bioequivalence study
The applications are supported by the bioequivalence study comparing the pharmacokinetic profiles of Cefalexin 500 mg Capsules (test) and Keflex 500 mg Capsules - Flynn Pharma Limited (reference). The bioequivalence study was of an appropriate design and was conducted to principles of Good Clinical Practice (GCP). Certificates of Analysis were provided for the test and reference products.

This was an open-label, randomised, two-treatment, two-way, two-period, single dose crossover bioequivalence study conducted in 28 healthy adult male human subjects under fasting conditions. Following an overnight fast, a single dose of the investigational products was administered orally, with 240 ml of water, to each subject in each period. A satisfactory washout period of 4 days was maintained between the two dosing days in each group.

Blood samples were taken pre-dose (0.0) and at specified time points up to 10.0 hours after administration of test or reference product. Plasma levels of cefalexin were quantified by a validated HPLC method.
The primary pharmacokinetic parameters for this study were $C_{\text{max}}$, $\text{AUC}_{0\text{-}t}$, and $\text{AUC}_{0\text{-}\infty}$. Bioequivalence of the test product versus the reference product was concluded if the 90% Confidence Intervals (CI) fell within the acceptance range, 0.80-1.25 (80.00%-125.00%), for log-transformed $C_{\text{max}}$, $\text{AUC}_{0\text{-}t}$, and $\text{AUC}_{0\text{-}\infty}$.

**Biostudy outcome and results:**

28 subjects were enrolled in the study; 27 of these completed the study and were included in the pharmacokinetic evaluation and statistical analysis. The discontinuation, and non-inclusion in the pharmacokinetic analysis, of 1 subject was satisfactorily justified.

*Safety* - A total of 7 adverse events were reported by 5 subjects. There were no deaths or serious or significant adverse events reported in the study.

The summary of the results of the bioequivalence study are tabulated below:

Pharmacokinetic results for cefalexin for a randomised, two-way, two-period, single-dose crossover bioequivalence study between the 500 mg strength test and reference products; n=27 healthy subjects, dosed fasted; t=10 hours; washout period: 4 days.

<table>
<thead>
<tr>
<th>Parameters (Units)</th>
<th>(In-transformed) Geometric Least Squares Mean</th>
<th>90% Confidence Interval (Parametric)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Test Product-B</td>
<td>Reference Product-A</td>
</tr>
<tr>
<td>$C_{\text{max}}$ (mcg / mL)</td>
<td>25.985</td>
<td>25.879</td>
</tr>
<tr>
<td>$\text{AUC}_{0\text{-}t}$ (mcg.h / mL)</td>
<td>54.400</td>
<td>54.144</td>
</tr>
<tr>
<td>$\text{AUC}_{0\text{-}\infty}$ (mcg.h / mL)</td>
<td>55.442</td>
<td>55.185</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>$C_{\text{max}}$</th>
<th>maximum plasma concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{AUC}_{0\text{-}t}$</td>
<td>area under the plasma concentration-time curve from time zero to t hours</td>
</tr>
<tr>
<td>$\text{AUC}_{0\text{-}\infty}$</td>
<td>area under the plasma concentration-time curve from time zero to infinity</td>
</tr>
</tbody>
</table>

**Conclusion on Bioequivalence**

The results of the bioequivalence study show that the test and reference products are bioequivalent under fasting conditions, as the confidence intervals for $C_{\text{max}}$, $\text{AUC}_{0\text{-}t}$ and $\text{AUC}_{0\text{-}\infty}$ for cefalexin fall within the acceptance criteria ranges of 80.00-125.00%, in line with current guidelines.

Satisfactory justification is provided for a bio-waiver for Cefalexin 250 mg Capsules. As Cefalexin 250 mg and 500 mg Capsules meet the criteria specified in the “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 500 mg strength can be extrapolated to the 250 mg strength capsules.

**EFFICACY**

No new data have been submitted and none are required. The reference products are established and the applications depend upon the ability to demonstrate bioequivalence. Efficacy is reviewed in the clinical overview. The efficacy of cefalexin is well-established from its extensive use in clinical practice.
SAFETY
No new data have been submitted and none are required for applications of this type. No new or unexpected safety concerns arose from these applications. Safety is reviewed in the clinical overview. The safety profile of cefalexin is well-known.

PRODUCT INFORMATION:

Summary of Product Characteristics
The approved SmPCs are consistent with those for the UK reference products and are acceptable.

Patient Information Leaflet
The final PIL is in line with the approved SmPCs and is satisfactory. The PIL user-testing has been evaluated and is accepted.

Labelling
The labelling is satisfactory.

Clinical overview
A satisfactory clinical overview is provided, and has been prepared by an appropriately qualified expert. The CV of the clinical expert has been supplied.

CONCLUSIONS
Sufficient clinical information has been submitted to support these applications. The risk-benefit of the products is considered favourable from a clinical perspective.
OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Cefalexin 250 mg and 500 mg Capsules are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRE-CLINICAL
No new pre-clinical data were submitted and none are required for applications of this type.

CLINICAL
Bioequivalence has been demonstrated between the applicant’s Cefalexin 500 mg Capsules and the UK reference product, Keflex 500 mg Capsules (Flynn Pharma Limited).

As the proposed products, Cefalexin 250 mg and 500 mg Capsules, meet the criteria specified in the “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 500 mg strength were extrapolated to the 250 mg strength capsules, and omission of further bioequivalence studies on the lower strength can be accepted.

No new or unexpected safety concerns arise from these applications.

PRODUCT LITERATURE
The approved SmPCs are consistent with those for the UK reference products and are satisfactory.

A mock-up PIL has been provided. The package leaflet is in line with the SmPCs and is satisfactory. It has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

The approved labelling artwork complies with statutory requirements. In line with current legislation, the name of the product in Braille appears on the outer packaging and sufficient space has been included for a standard UK pharmacy dispensing label. The MAH has stated that not all licensed pack sizes may be marketed. They have committed to submitting mock-ups for unmarketed pack sizes to the MHRA for approval before those packs are marketed.

BENEFIT-RISK ASSESSMENT
The quality of the products is acceptable and no new pre-clinical or clinical safety concerns have been identified. The bioequivalence study and its conclusions support the claim that the applicant’s Cefalexin 250 mg and 500 mg Capsules are generic versions of the reference products, Keflex / Cefalexin 250 mg and 500 mg Capsules (Flynn Pharma Limited). Extensive clinical experience with cefalexin is considered to have demonstrated the therapeutic value of the active substance. The benefit: risk ratio is considered to be positive.
Cefalexin 250 mg Capsules
Cefalexin 500 mg Capsules

(cefalexin)

PL 35507/0104-5

STEPS TAKEN FOR ASSESSMENT

1. The MHRA received the marketing authorisation applications for PLs 20092/0064-5 on 8th December 2008.

2. Following standard checks and communication with the applicant the MHRA considered the applications valid on 29th December 2008.

3. Following assessment of the applications the MHRA requested further information relating to the quality dossier on 11th March 2009, 29th June 2009, 7th October 2010 and 4th February 2011; and further information relating to the clinical dossier on 1st May 2009.

4. The applicant responded to the MHRA’s requests, providing further information for the quality sections on 16th June 2009, 10th May 2010, 24th November 2010 and 14th February 2011 respectively; and further information for the clinical sections on 22nd July 2009.

5. The applications were determined on 15th July 2011.

6. The MAs 20092/0064-5 (Lupin (Europe) Limited) underwent Change of Ownership to MAs 35507/0104-5 (Lupin (Europe) Limited) on 7th September 2011.
Cefalexin 250 mg Capsules
Cefalexin 500 mg Capsules

(cefalexin)

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STEPS TAKEN AFTER AUTHORISATION

Not applicable
SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SmPC) for Cefalexin 250 mg and 500 mg Capsules (PL 35507/0104-5) is as follows. Differences between the individual SmPCs are highlighted:

1 NAME OF THE MEDICINAL PRODUCT

Cefalexin 250 / 500 mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains Cefalexin monohydrate equivalent to 250 / 500 mg Cefalexin. Excipients: Sunset yellow (E110), Quinoline yellow (E104) and Patent Blue V (E131).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule.

Cefalexin 250 mg Capsules are size ‘2’ capsules with dark green cap and white body imprinted with ‘250’ in black ink on cap, containing white to yellowish-white granular powder.

Cefalexin 500 mg Capsules are size ‘0’ capsules with dark green cap and light green body imprinted with ‘500’ in black ink on cap, containing white to yellowish-white granular powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Cefalexin is indicated in the treatment of the following infections due to susceptible micro-organisms (see also section 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

Cefalexin is administered orally.

Adults: The adult dosage ranges from 1-4g daily in divided doses; most infections will respond to a dosage of 500mg every 8 hours. For skin and soft tissue infections, streptococcal pharyngitis, and mild, uncomplicated urinary tract infections, the usual dosage is 250mg 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 4g are required, parenteral cephalosporins, in appropriate doses, should be considered.

Patients with impaired renal function: Reduce dosage if renal function is markedly impaired (see section 4.4).
**Elderly patients:**
The recommended dose for adults should be used in elderly patients except those with impaired renal function.

**Children:**
The recommended daily dosage for children is 25-50mg/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.

### 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 500mg.

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 drug.

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 contain colouring agents, sunset yellow (E110), quinoline yellow (E104) and patent blue V (E131) which may cause allergic reactions.
4.5 Interaction with other medicinal products and other forms of interaction

As with other beta-lactam drugs, 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 500mg 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 the 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,<1/10);
uncommon (≥1/1,000, <1/100);
rare (≥1/10,000, <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: Dizziness, headache

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), anaphylaxis

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 3.5g 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 ≥2.5mg/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 acquired resistance may be a problem

**Gram-negative aerobes:**
- *Citrobacter* species
- *Enterobacter* species
- *Morganella morgani*.

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 250mg, 500mg, and 1g, average peak serum levels of approximately 9, 18, and 32mg/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 250mg, 500mg, and 1g doses were approximately 1,000, 2,200, and 5,000mg/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 4g/day.

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

5.3 Preclinical safety data
The daily oral administration of cefalexin to rats in doses of 250 or 500mg/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 LD₅₀ of cefalexin in rats is 5,000mg/kg.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Core:
- Microcrystalline cellulose
- Magnesium stearate
- Water

Capsule shell:
- Gelatin
- Sodium lauryl sulphate
- Sunset yellow FCF (E110)
- Quinoline yellow (E104)
- Titanium dioxide (E171)
- Patent Blue V (E131)
- and
- Printing ink

Black Ink (SW – 9008) components:
- Shellac
- Propylene Glycol
- Potassium Hydroxide
- Black Iron Oxide (E172)

6.2 Incompatibilities
Not applicable

6.3 Shelf life
24 months

6.4 Special precautions for storage
Store below 30°C. Store in the original package.
6.5 Nature and contents of container

Cefalexin 250 mg Capsules are packed in:
PVC/PVdC/Aluminium blisters of 4, 10, 12, 16, 20, 21, 24, 28, 30, 100 and 112 capsules. Not all pack sizes may be marketed.

Cefalexin 500 mg Capsules are packed in:
PVC/PVdC/Aluminium blisters of 8, 10, 12, 14, 15, 16, 20, 21, 28, 30, 40, and 100 capsules. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

Lupin (Europe) Limited,
Victoria Court,
Bexton Road,
Knutsford,
Cheshire WA16 OPF
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 35507/0104
PL 35507/0105

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15/07/2011

10 DATE OF REVISION OF THE TEXT

07/09/2011
PATIENT INFORMATION LEAFLET

CEFALEXIN 250 mg AND 500 mg CAPSULES

CEFALEXIN

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What these capsules are and what are they used for
2. Before you take these capsules
3. How to take these capsules
4. Possible side effects
5. How to store these capsules
6. Further information

1. WHAT THESE CAPSULES ARE AND WHAT ARE THEY USED FOR
Cefalexin capsules contain the active ingredient cefalexin, which is an antibiotic.
Antibiotics work by killing the bacteria (germs) that can cause an infection.
Cefalexin capsules are used to treat the following infections:
- the lungs and breathing passages (bronchitis and mild to moderate pneumonia)
- the skin and soft tissue (such as wound infection)

2. BEFORE YOU TAKE THESE CAPSULES
Do not take these capsules if:
- you are allergic (hypersensitive) to cefalexin or other cephalosporins (similar antibiotics) or any of the other ingredients of these capsules (see list of ingredients in section 6)
An allergic reaction may include rash, itching, difficulty breathing or swelling of the face, lips, throat or tongue.

Take special care with these capsules if you:
- have had an allergic reaction to cefalexin, cephalosporins, penicillins or other drugs
- develop diarrhoea
- have a severe kidney disorder (you may need a reduced dose)
If any of the above applies to you, speak to your doctor.

Taking other medicines:
Please tell your doctor or pharmacist if you are taking or have recently taken any of the following medicines, including medicines obtained without a prescription, as they may interact with your Cefalexin capsules.
This is especially true of:
- probenecid (a treatment for gout)
- metformin (a treatment for diabetes)
- aminoglycosides and other cephalosporins (a treatment for infections)
- furosemide (drug to increase urine output)
It may still be all right for you to be given Cefalexin capsules and your doctor will be able to decide what is suitable for you.

Effects on laboratory tests
Tell your doctor if you are taking Cefalexin capsules and you are having blood or urine tests as Cefalexin capsules may interfere with the results of these tests.

Pregnancy and breast feeding:
You should tell your doctor if you are pregnant or breast-feeding and he/she will decide if it is OK for you to take Cefalexin Capsules. Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines:
Cefalexin capsules should not affect your ability to drive or use machines. Use with caution when driving or operating heavy machinery until you are aware of how this drug affects you.

Important information about some of the ingredients of this medicine:
This medicine contains Sunset Yellow (E110), Quinoline yellow (E104) and Patent Blue V (E131) which may cause allergic reactions.

3. HOW TO TAKE THESE CAPSULES
Always take these capsules exactly as your doctor has told you to. You should check with your doctor or pharmacist if you are not sure.

Dosage in adults:
The recommended adult dose is 1-4 g to be taken orally daily in divided doses. Most infections can be treated by 500mg every 8 hours (1.5g/day).
- For skin and soft tissue infections, sore throat, and mild, uncomplicated urinary tract infections, the usual dose is 250mg every 6 hours or 500mg every 12 hours.
- For more severe infections, larger doses may be needed.
- A reduced dose is needed for patients with severe kidney disorders.

Dosage in children:
The usual dose in children is 25-50mg/kg (body weight) in 3 divided doses. In severe infections the dosage may be doubled.
In the treatment of beta-haemolytic streptococcal infections (a type of bacteria) treatment should be given for at least 10 days.

If you take more capsules than you should:
Do not take more capsules than your doctor tells you to. If you ever take too many capsules, go to your nearest hospital casualty department or call your doctor immediately.
If you forget to take these capsules:
If you forget to take a dose, take it as soon as you remember. If you have missed several doses, tell your doctor or pharmacist. Do not take a double dose to make up for a forgotten dose.

4. POSSIBLE SIDE EFFECTS
Like all medicines, Cefalexin Capsules can cause side effects, although not everybody gets them.

If any of the following serious side effects occur, stop taking this medicine and tell your doctor or pharmacist immediately, or go to your nearest hospital accident and emergency department taking your medicine with you:
- swelling of your face, lips, tongue or throat (angioedema)
- a sudden allergic reaction with shortness of breath, rash, wheezing and drop of blood pressure
- itchy spots or rash on the arms and legs or severe, extensive, blistering skin rash (erythema multiforme, Steven-Johnson syndrome)

Tell your doctor if you experience the following:
- Diarrhoea (which may be bloody or have mucus in it)

The following side effects have also been reported:
Common: (affecting at least 1 in 100 patients but less than 1 in 10 patients)
- Diarrhoea, nausea

Uncommon: (affecting at least 1 in 1,000 patients but less than 1 in 100 patients)
- Changes in blood tests that check how well your liver is working
- Increase in some types of white blood cells (eosinophilia)
- Skin rash, hives or itching

Rare (affecting at least 1 in 10,000 patients but less than 1 in 1,000 patients)
- Blood problems: change in the number of cells in the body responsible for combating infections (symptoms may include infections and abnormal bruising or bleeding), increase in the number of cells responsible for blood clotting; haemolytic anaemia, a type of anaemia caused by the breakdown of red blood cells.
- Dizziness and headache
- Abdominal pain, vomiting, indigestion, inflammation of the intestinal tract (pseudomembranous colitis)
- Reversible kidney inflammation (interstitial nephritis)
- Genital and anal itching, and inflammation of the vagina
- Tiredness
- Inflammation of the liver (hepatitis), yellowing of the skin and eyes (cholestatic icterus)

Other side effects: (Frequency not known)
- Pain or inflammation in the joints (arthralgia, arthritis)
- Vaginal thrush (candidiasis)
- Fever
- Hallucinations, confusion and agitation

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE THESE CAPSULES
- Keep out of the reach and sight of children.
- Do not use these capsules after the expiry date which is stated on the carton.
- The expiry date refers to the last day of the month.
- Store below 30°C. Store in the original package.

Disposal
Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION
Cefalexin 250mg Capsules: Each capsule contains 250mg Cefalexin (as monohydrate).
Cefalexin 500mg Capsules: Each capsule contains 500mg Cefalexin (as monohydrate).

What these capsules contain
The active substance is Cefalexin (as monohydrate).

The other ingredients are:
- Capsule content: Microcrystalline cellulose, Magnesium Stearate and water. Capsule Shell: Gelatin, sodium lauryl sulphate, sunset yellow (E110), quinoline yellow (E104), titanium dioxide (E171), patent blue (E131) and black imprinting ink (containing shellac, propylene glycol, water, potassium hydroxide and black iron oxide).

What Cefalexin Capsules look like and contents of the pack
Cefalexin Capsules are available in two strengths.

Cefalexin 250mg Capsules are size 2’ capsules with dark green cap and white body imprinted with ‘250’ in black ink on cap containing white to yellowish-white granular powder.

Cefalexin 500mg Capsules are size 0’ capsules with dark green cap and light green body imprinted with ‘500’ in black ink on cap containing white to yellowish-white granular powder.

Cefalexin 250mg Capsules are packed in blisters of 4, 10, 12, 15, 20, 21, 24, 28, 30, 100 and 112 capsules.

Cefalexin 500mg Capsules are packed in blisters of 8, 10, 12, 14, 15, 16, 20, 21, 28, 30, 40 and 100 capsules.

Not all pack sizes may be marketed.

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LABELLING

Cefalexin 250 mg Capsules

Carton for blisters, with braille
Blister foil
Cefalexin 500 mg Capsules

Carton for blisters, with braille

Braille translation

Cefalexin #500 mg Capsules
Blister foil