SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ceporex Tablets 500 mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Cefalexin Ph.Eur 500mg per tablet

3 PHARMACEUTICAL FORM

Tablet

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Ceporex is a bactericidal antibiotic of the cephalosporin group which is active against a wide range of Gram-positive and Gram-negative organisms. It is indicated for treatment of the following conditions, when caused by susceptible bacteria.

Respiratory tract infections: Acute and chronic bronchitis and infected bronchiectasis.

Ear, nose and throat infections: Otitis media, mastoiditis, sinusitis, follicular tonsillitis and pharyngitis.

Urinary tract infections: Acute and chronic pyelonephritis, cystitis and prostatitis. Prophylaxis of recurrent urinary tract infection.

Gynaecological and obstetric infections.
Skin, soft-tissue and bone infections.
Gonorrhoea (when penicillin is unsuitable).
Dental procedures: Treatment of dental infections.

4.2 Posology and method of administration

Route of administration: oral

Many infections in adults will respond to oral dosage of 1 gram to 2 grams per day in divided doses; however, for most infections, the following simple dosage scheme will be found satisfactory:

Adults and children over 12 years: 1 g b.d.

The following additional information should also be considered:

Adults: For severe or deep-seated infections, especially when less sensitive organisms are involved, the dosage should be increased to 1g t.d.s. or 3g b.d.

For prophylaxis of recurrent urinary tract infections in adults, a dose of 125mg each night is recommended and may be continued for several months (the 125mg/5ml Suspension is suitable for this purpose).

Children: Ideally, dosage should be calculated on a body-weight basis, particularly in infants. The following dosage recommendations for children are derived from a normal dosage of 25 to 60mg/kg/day. For chronic, severe or deep-seated infections, this should be increased to 100mg/kg/day (maximum 4g/day).

Children under 1 year (25 to 60mg/kg/day)	
	62.5 to 125mg b.d.
Children 1-6 years	250mg - 500mg b.d.
Children 7-12 years	500mg - 1g b.d.

Notes: For most acute infections, treatment should continue for at least two days after signs have returned to normal and symptoms have subsided, but in chronic, recurrent or complicated urinary tract infections, treatment for two weeks (giving 1g b.d.) is recommended. For gonorrhoea, a single dose of 3g with 1g probenecid for males or 2g with 0.5g probenecid for females is usually effective. Concurrent administration of probenecid delays excretion of cefalexin and raises the serum levels by 50 to 100%.

Ceporex has not been shown to have a toxic effect on the kidney, but as with other antibiotics which are excreted mainly by the kidneys, unnecessary accumulation may occur in the body when renal function is below about half of normal. Therefore, the maximum recommended dosages (i.e. Adults 6g/day, children 4 g/day) should be reduced proportionately in these patients. In elderly patients, the possibility of renal impairment should be considered.

Adult patients receiving intermittent dialysis should be given an additional 500mg Ceporex after each dialysis, i.e., a total dosage of up to lg on that day. Children should receive an additional 8mg per kg.

4.3 Contraindications

Cefalexin is contra-indicated in patients with known allergy to the cephalosporin group of antibiotics.

4.4 Special warnings and precautions for use

Acute generalised exanthematous pustulosis (AGEP) has been reported in association with cefalexin treatment. At the time of prescription patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of these reactions appear, cefalexin should be withdrawn immediately and an alternative treatment considered. Most of these reactions occurred most likely in the first week during treatment.

Cefalexin should be given cautiously to patients who have shown hypersensitivity to other drugs. Cephalosporins should be given with caution to penicillin-sensitive patients, as there is some evidence of partial cross-allergenicity between the penicillins and cephalosporins. Patients have had severe reactions (including anaphylaxis) to both drugs.

Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics, including macrolides, semisynthetic 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 the patient experiences an allergic reaction cefalexin should be discontinued and treatment with the appropriate agents initiated.

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 be administered with caution in the presence of markedly impaired renal function as it is excreted mainly by the kidneys. Careful clinical and laboratory studies should be made because the safe dosage may be lower than that usually recommended.

In patients receiving Ceporex, a false-positive reaction for glucose in the urine may be given, with Benedict's or Fehling's solution, or with 'Clinitest' tablets, but not with enzyme-based tests.

Positive direct Coombs' tests have been reported during treatment with cephalosporin antibiotics. For 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.

4.5 Interaction with other medicinal products and other forms of interaction

As cephalosporins like cefalexin are only active against proliferating microorganisms they should not be combined with bacteriostatic antibiotics.

If associated with highly potent diuretics (furosemide, ethacrynic acid) or other potentially nephrotoxic antibiotics (aminoglycoside, polymyxin, colistin) Cephalosporins may show higher nephrotoxicity.

Combined use of cephalosporins and oral anticoagulants may prolong prothrombin time.

Hypokalaemia has been described in patients taking cytotoxic drugs for leukaemia when they were given gentamicin and cefalexin.

Cefalexin may reduce the effects of oral contraceptives.

Concomitant use of uricrosuric drugs (e.g.Probenecid) suppresses renal drug elimination. As a result, cefalexin plasma levels are increased and sustained for longer.

A potential interaction between cefalexin and metformin may result in an accumulation of metformin and could result in fatal lactic acidosis.

4.6 Fertility, pregnancy and lactation

Pregnancy

Laboratory experiments and clinical experience show no evidence of teratogenicity, but it would be wise to proceed with caution during the early months of pregnancy, as with all drugs.

Breast-feeding

The excretion of cefalexin in human breast milk increased up to 4 hours following a 500mg dose. The drug reached a maximum level of 4 micrograms/ml, then decreased gradually and had disappeared 8 hours after administration. 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 effects on ability to drive or operate machinery.

4.8 Undesirable effects

Blood and Lymphatic System Disorders:

Adverse effects common to the cephalosporin group are the blood and lymphatic system disorders: eosinophilia, thrombocytopenia, leucopenia, neutropenia to agranulocytosis, and aplastic anaemia. Haemolytic anaemia has been reported but rarely occurs.

Cefalexin does not contain an N-methylthiotetrazole side chain and therefore the risk of bleeding complications due to impaired vitamin-K dependent clotting factor synthesis is low.

Nervous System Disorders:

Nervous system disorders that have been reported are headache, dizziness, confusion, hallucinations, hyperactivity, nervousness, sleep disturbances. Patients should be advised not to drive or use machinery if they feel dizzy after taking Ceporex, see Section 4.7.

There are some reports of patients suffering from hypertonia after cephalosporin treatment.

Gastrointestinal Disorders:

Gastrointestinal adverse effects such as nausea, vomiting, abdominal discomfort and diarrhoea have been reported. Dyspepsia has also occurred. As with other broad-spectrum antibiotics, prolonged use may result in the overgrowth of non-susceptible organisms and pseudomembranous colitis may develop. There has been some evidence from clinical trials of some cephalosporins that the incidence of diarrhoea and pseudomembranous colitis are dose related and therefore the Committee for the Safety of Medicines has recommended that higher doses should be reserved for severe infections and that in any case, treatment should be discontinued if symptoms suggestive of pseudomembranous colitis arise.

Cephalosporins may cause disturbances in liver enzymes, transient hepatitis and cholestatic jaundice. Normal liver function should return following discontinuation of the medication.

Renal and Urinary Disorders:
Reversible interstitial nephritis has occurred in a few patients but this is very rare. Acute renal tubular necrosis has followed excessive dosage and has also been associated with use in older patients and in patients with renal impairment, See Section 4.2.

As with other antibiotics, prolonged use may result in the overgrowth of non-susceptible organisms, e.g., Candida. This may present as vulvo-vaginitis.

Hypersensitivity Reactions:
Hypersensitivity reactions have been associated with the use of all cephalosporins, including cefalexin. These reactions include: urticarial and maculopapular rashes, erythema multiforme and allergic pruritus, toxic epidermal necrolysis, Stevens-Johnson syndrome, angioedema and anaphylaxis, serum-sickness-like reactions e.g. skin rash, hives, itching, joint pain, fever, malaise, enlarged lymph nodes.

Skin and subcutaneous tissue disorders
Genital and anal pruritus
Acute generalised exanthematous pustulosis (AGEP) (frequency: not known)

Infections and infestations
Genital candidiasis, vaginitis

Reproductive system and breast disorders
Vaginal discharge

General disorders and administration site conditions
Fatigue

Psychiatric disorders
Agitation

Musculoskeletal and connective tissue disorders
Arthralgia, arthritis and joint disorders

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product, Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme: www.mhra.gov.uk/yellowcard

4.9 Overdose

Symptoms of oral overdose may include nausea, vomiting, epigastric distress, diarrhoea and haematuria. General management consists of close clinical and laboratory monitoring of haematological, renal and hepatic functions and coagulation status until the patient is stable.

Serum levels of cefalexin can be considerably reduced by peritoneal dialysis or haemodialysis.

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

Bacteriology:

Cefalexin is a bactericidal antibiotic of the cephalosporin group which is active against a wide range of Gram-positive and Gram-negative organisms. The bactericidal activity is due to inhibition of bacterial wall synthesis of actively dividing cells by binding to essential target proteins, penicillin binding proteins (PBPs). Cefalexin also decreases the availability of murein hydrolase, an enzyme essential for cell division, and therefore preventing bacterial cell division.

Breakpoints:

The following MIC breakpoints for cefalexin 500mg oral dose, separating susceptible (S) from resistant(R) micro-organisms have been provided by a report from the British Society of Antimicrobial Chemotherapy Working Party (J Antimicrob Chemo 1991; Suppl D to Vol 27):

Staphylococcus aureus: S<=8mcg/ml, R >8mcg/ml
Streptococci: S<=2mcg/ml, R >2mcg/ml
Enterobacteriacae: S<=8mcg/ml, R >8mcg/ml

Susceptibility:
The prevalence of resistance may vary geographically and with time for selected species. Local information on resistance is desirable, particularly when treating severe infections. This information gives only an approximate guidance on the probabilities whether micro-organisms will be susceptible to cefalexin or not. The following table lists the susceptibilities of various bacteria:

Susceptible	*Range of acquired resistance in UK*
Aerobic Gram-positive micro-organisms	
Staphylococcus aureus-methicillin susceptible strains	<1%
Staphylococcus epidermidis (methicillin susceptible)	<1%
Streptococcus agalactiae	0%
Streptococcus pneumoniae	4%
Streptococcus pyogenes	0%
Viridans group Streptococcus	Not known
Aerobic Gram-negative micro-organisms	
Escherichia coli	3%
Haemophilus influenzae	Not known
Klebsiella species	7%
Neisseria gonorrhoeae	Not known
Proteus mirabilis	5%
Resistant	
Aerobic Gram-positive micro-organisms	
Staphylococcus aureus-methicillin resistant	100%
Aerobic Gram-negative micro-organisms	
Citrobacter freundii	>50%
Enterobacter aerogenes	>50%
Enterobacter cloacae	>50%
Enterococcus faecalis	100%
Morganella morganii	>50%
Pseudomonas aeruginosa	100%

Other information:

Certain micro-organisms which are resistant to first and second generation cephalosporins and to other beta-lactam antibiotics may exhibit resistance to cefalexin.

5.2 Pharmacokinetic properties

Absorption

Cefalexin is almost completely absorbed in the upper portions of the gastrointestinal tract. Following oral administration, absorption is rapid and peak serum levels (4.5µg/ml for a 125mg dose, 9µg/ml for 250mg dose, 18µg/ml for a 500mg dose and 32µg/ml for a 1000mg dose) are usually reached at one hour. In patients with normal renal function, serum levels persist for 4 to 6 hours and disappear within 8 hours. Absorption is delayed when cefalexin is given with or shortly after food, but the total amount absorbed is not altered.

Absorption of cefalexin is not adversely affected by coeliac disease, partial gastrectomy, achlorhydria, jaundice or diverticulosis (duodenal or jejunal).

The serum half-life is normally about one hour, but is longer in the newborn (see Dosage and Administration).

In patients with impaired renal function, an increase in serum half-life of cefalexin occurs. Clinical practice indicates that in view of the wide therapeutic window of cefalexin, the standard recommended doses should be halved only in those patients with creatinine clearance ≤ 50ml/min. The maximum recommended dose (i.e. adults 6g/day, children 4g/day) should be reduced to 50% in mild (40 - ≤ 50ml/min), 25% in moderate (>10 - < 40 ml/min) and 12.5% in severe renal impairment (≤ 10ml/min).

Distribution
Cefalexin is widely distributed in body tissues and high concentrations are found in all organs, particularly the liver and kidneys. Cefalexin reaches therapeutic levels in the blood, urine, bile, synovial fluid, tonsillar tissue, amniotic fluid, cord blood and foetal blood.

Metabolism and Elimination
Cefalexin is not metabolised in the body and is rapidly excreted unchanged in the urine. High concentrations (80-100%) of an orally administered dose are recoverable in the urine within 6 to 8 hours. Cefalexin is excreted in human milk in low concentrations.

Concurrent administration of probenecid delays excretion of cefalexin and raises serum levels by 50 to 100% (see Sections 4.2 and 4.5 of this SPC).

5.3 Preclinical safety data
Cefalexin is not anticipated to cause any genotoxic or carcinogenic effects, although no specific studies have been performed to determine this.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline Cellulose	EP
Magnesium Stearate	EP

Film-Coating:

Hydroxypropyl methylcellulose	EP
Macrogol 400	EP
Opadry OY-S-6927	In-House
Purified Water	BP

6.2 Incompatibilities

No incompatibilities have been reported.

6.3 Shelf life

36 months

6.4 Special precautions for storage

The product is stored at a temperature not exceeding 30°C, protected from light.

6.5 Nature and contents of container

1) Tubular glass vial with polyethene snap-plug closure.

2) Tamper evident polypropylene container with low density polyethylene lid. One or more cartridges of activated charcoal according to pack size are included.

3) Tablets are sealed into individual pockets in an aluminium polyethylene/ foil laminate (30 and 38 micrometres respectively).

4) Tablets are sealed into individual pockets in an aluminium foil blister with an aluminium lid (43 and 20 micrometres respectively).

All container presentations contain 20, 28, 100 or 500 tablets.

6.6 Special precautions for disposal

None stated

7 MARKETING AUTHORISATION HOLDER

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Trading as: Co-pharma

8 MARKETING AUTHORISATION NUMBER(S)

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9 DATE OF FIRST AUTHORISATION

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