

IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0577/045/001

Case No: 2051195

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

McDermott Laboratories Ltd t/a Gerard Laboratories

35/36 Baldoyle Industrial Estate, Grange Road, Dublin 13, Ireland

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

Cefager Powder for Oral Suspension 125 mg/5 ml

The particulars of which are set out in Part I and Part II of 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 **18/02/2009** until **12/12/2010**.

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

Cefager Powder for Oral Suspension 125 mg/5 ml.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

When reconstituted as directed in Section 6.6, each 5ml dose contains cefaclor (as monohydrate) 125 mg. Cefager powder for oral suspension also contains Sorbitol (E420).

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Powder for oral suspension.
An off-white, sugar-free, strawberry-flavoured product.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Cefaclor is indicated for the treatment of the following infections due to susceptible micro-organisms:

Respiratory tract infections, including pneumonia bronchitis, exacerbation of chronic bronchitis, pharyngitis and tonsillitis, and as part of the management of sinusitis.

Otitis media. Skin and soft tissue infections. Acute and chronic urinary tract infections, including pyelonephritis and cystitis.

Cefaclor is generally effective in the eradication of streptococci from the nasopharynx; however, data establishing efficacy in the subsequent prevention of either rheumatic fever or bacterial endocarditis are not available.

4.2 Posology and method of administration

Cefaclor is administered orally.

Adults:

The usual adult dosage is 250 mg every 8 hours.

For more severe infections this dose may be doubled to 500 mg every 8 hours. However, the maximum daily dose should not exceed 4 g, which has been administered safely to normal subjects for 28 days.

For patients undergoing regular haemodialysis a loading dose of 250 mg - 1 g should be administered preceding dialysis. A therapeutic dose of 250 mg - 500 mg should be given every 6 to 8 hours during interdialytic intervals.

Cefaclor may be administered in the presence of impaired renal function. Under such conditions dosage is usually unchanged (*see section 4.4, Special warnings and precautions for use*).

The elderly

As for adults.

Children:

The usual recommended daily dosage for children is 20 mg/kg/day in divided doses every eight hours. For bronchitis and pneumonia, the dosage is 20 mg/kg/day in divided doses administered three times daily. For otitis media and pharyngitis the total daily dosage may be divided and administered every 12 hours. Safety and efficacy have not been established for use in infants aged less than one month.

<u>Cefaclor for Oral Suspension</u>	<u>125 mg/5 ml</u>
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<1 year (9 kg)	2.5 ml t.i.d
1 – 5 years (9 – 18 kg)	5.0 ml t.i.d

In more serious infections, otitis media, sinusitis and infections caused by less susceptible organisms, 40 mg/kg/day in divided doses is recommended up to a daily maximum of 1 g.

In the treatment of beta-haemolytic streptococcal infections, therapy should be continued for at least 10 days.

4.3 Contraindications

- Patients with a history of hypersensitivity to Cefaclor or to any other cephalosporins.
- Patients with a history of hypersensitivity to the other constituents
- Patients with a history of severe allergy or asthma should be closely monitored.

4.4 Special warnings and precautions for use

Before therapy with Cefaclor is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to Cefaclor, cephalosporins or other drugs. If this product is to be given to penicillin-sensitive patients, caution should be exercised because cross-sensitivity among beta-lactam antibiotics has been clearly documented and may occur in up to 10% of patients with a history of penicillin allergy. If an allergic reaction to Cefaclor occurs, discontinue the drug. Serious acute hypersensitivity reactions may require emergency treatment measures.

Patients with severe renal impairment should be monitored closely although adjustment of the dose is not usually required. The half-life of Cefaclor in anuric patients is 2.3 to 2.8 hours compared to 0.6 to 0.9 hours in normal subjects.

Prolonged use of Cefaclor may encourage the growth of non-susceptible organisms. Appropriate measures should be taken if superinfection takes place during treatment with Cefaclor.

Pseudomembranous colitis is a common side effect of broad-spectrum antibiotic treatment. This should be considered when diagnosing cases of diarrhoea in patients taking Cefaclor. This type of colitis may range from mild to life-threatening. Mild colitis is usually alleviated by discontinuing the drug. More appropriate measures may be required in moderate to severe cases.

Caution should be exercised when prescribing broad spectrum antibiotics to persons with a history of gastrointestinal disease, especially colitis.

Each 5ml dose of Cefaclor Oral Suspension contains 786mg of sorbitol. It may therefore be unsuitable in hereditary fructose intolerance.

4.5 Interaction with other medicinal products and other forms of interaction

False positive Coombs' tests have been reported during treatment with cephalosporins. This should be taken into account when cross-matching for transfusion. False positives should also be considered when testing new-born infants' blood groups whose mothers were taking cephalosporin antibiotics prior to parturition.

False positives have also been reported for glucose in urine when using Benedict's or Fehling's solutions or with copper sulphate test tablets.

The renal excretion of Cefaclor is inhibited by probenecid.

In patients taking Cefaclor and warfarin concurrently there have been some rare cases of increased prothrombin time either with or without clinical bleeding. A dose adjustment may be necessary and such patients should be monitored closely.

The concomitant use of bacteriostatic antibiotics may interfere with the bactericidal effects of other antibiotics such as beta-lactams.

4.6 Pregnancy and lactation

Care should be taken when prescribing Cefaclor for pregnant women, in particular during the first three months. Animal studies have not shown any evidence of impaired fertility or teratogenicity although there are no adequate or well-controlled trials in human volunteers.

There have been small levels of Cefaclor detected in the breast milk of nursing mothers following single doses of 500 mg Cefaclor. Trace amounts are still detectable after 1 hour and the average amount of Cefaclor determined after 5 hours is 0.2 µg/ml. The effect of this residual Cefaclor on nursing infants is not known and consequently care should be taken when prescribing for nursing women.

4.7 Effects on ability to drive and use machines

It is unlikely that Cefaclor will affect the patient's ability to drive and/or operate machinery.

4.8 Undesirable effects

Gastro-intestinal

Diarrhoea is a common side-effect although it is not usually severe enough to discontinue therapy. Colitis and rare cases of pseudo-membranous colitis have also been reported. Nausea and vomiting have likewise been described. Transient hepatitis and cholestatic jaundice are infrequently found as with some penicillins and other cephalosporins.

Hypersensitivity:

Hypersensitivity reactions have occurred in patients including morbilliform rashes. Pruritus, urticaria and a positive Coombs' test are found in less than 1 in 200 treated patients.

There have been reports of generalised reactions similar to serum sickness with the use of Cefaclor. These are characterised by the presence of erythema, multiform rash and other signs affecting the skin, accompanied by arthritis/arthralgia, with or without fever. They may be distinguished from classical serum sickness in that lymphadenopathy and proteinuria are rarely found, no circulating immune complexes are present and there is to date no evidence of sequelae from the reaction.

While studies on this are underway, the "serum sickness like" reaction appears to be due to hypersensitivity and occurs more often in a second or subsequent treatment cycle with Cefaclor. These reactions have been reported with greater frequency in children compared with adults with an incidence of 1 in 200 (0.5%) in a clinical study, in 2 out of 8346 (0.024%) in other clinical studies (with an incidence in children of 0.055%) and finally in 1 in 38,000 (0.0003%) as spontaneous events. The signs and symptoms are evident a few days after the start of treatment and cease a few days after its conclusion. These reactions have only occasionally necessitated hospitalisation which is generally short (on average from 2 to 3 days according to the "Post-Marketing Surveillance" studies).

The symptoms at the time of hospital admission ranged from mild to severe and were more severe in children. Anti-histamines and glucocorticoids resolve the signs and symptoms. Serious sequelae have not been reported. More severe hypersensitivity reactions, including the Steven's-Johnson syndrome, toxic epidermal necrolysis and anaphylaxis, may be more readily seen in patients allergic to penicillins. Symptoms of anaphylactoid reactions can appear as individual symptoms including angioedema, asthenia, oedema (face and joints), dyspnoea, or vasodilation. In rare cases the symptoms of hypersensitivity can recur over a number of months.

Other:

Events related to treatment with Cefaclor include eosinophilia, genital pruritis and vaginitis; and rarely, thrombocytopenia and reversible interstitial nephritis, paraesthesias, syncope, vaginal moniliasis, nervousness, dizziness, hallucinations. There have been reports of cases of haemolytic anaemia following treatment with cephalosporins.

Central Nervous System: reversible hyperactivity, insomnia, mental confusion, hypertonia, a feeling of instability and staggering, and somnolence have been reported occasionally. These were reversible on cessation of treatment and the causal relationship to treatment is not certain.

Transient changes in biochemical values have also been reported and the causal relationship to treatment is not certain.

Changes in liver function: there have been reports of mild increases in SGOT and SGPT or alkaline phosphatase and the causal relationship to treatment is not certain.

Haematological changes: as with other beta-lactam antibiotics, there have been reports of transient lymphocytosis, leucopenia and, rarely, haemolytic anaemia and reversible neutropenia of possible clinical significance. There have been infrequent reports of an increase in the prothrombin time with or without clinical bleeding in patients who were taking Cefaclor and warfarin sodium at the same time.

Renal changes: there have been reports of mild increases in serum urea and creatinine or changes in urinalysis.

4.9 Overdose

Symptoms:

Symptoms of toxicity following an overdose may include nausea, vomiting, epigastric distress and diarrhoea. The severity of the epigastric distress and the diarrhoea is proportional to the dose taken. If other symptoms are noted they are probably secondary to the underlying pathology, to an allergic reaction or to another intoxication.

Treatment:

Gastrointestinal decontamination is not required unless 5 times the normal total daily dose has been consumed. Intestinal absorption may be reduced by giving activated charcoal which may, in many cases, be more effective than induced vomiting or gastric lavage. Activated charcoal should therefore be considered either as an alternative treatment or in conjunction with gastric emptying. The patient's airway should be carefully monitored if the stomach is being emptied when activated charcoal is utilised.

The patient's ventilation and pulmonary perfusion, vital signs, blood gas analysis, serum electrolysis, etc., should also be conscientiously monitored.

The benefit of forced diuresis, peritoneal dialysis, haemodialysis or haemoperfusion with charcoal has not been established for overdoses of Cefaclor.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

The cephalosporin mode of action is similar to penicillin in that there is inhibition of cell wall synthesis. The last stage of peptidoglycan synthesis in the bacterial cell wall is a cross-linking reaction effected by a transpeptidase enzyme. It is probable that cephalosporins inhibit this transpeptidase enzyme by acylating it in the same way as penicillins

Breakpoints

The following MIC breakpoints separating susceptible from intermediately/moderately susceptible from resistant organisms are suggested:

S is less than or equal to 8 mg/L and **R** is greater than or equal to 32 mg/L for all bacterial isolates.

<i>Susceptible</i>
Gram positive aerobes <i>Staphylococcus</i> spp. (including methicillin - susceptible) <i>Streptococcus pneumoniae</i> <i>Streptococcus pyogenes</i> (group A β haemolytic streptococci
Gram-negative aerobes <i>Moraxella catarrhalis</i> <i>Escherichia coli</i> <i>Haemophilus influenzae</i> <i>Klebsiella</i> spp. <i>Proteus mirabilis</i>

<i>Resistant</i>
Gram-positive aerobes <i>Staphylococcus</i> spp. (methicillin resistant) <i>Enterococcus</i> spp.
Gram-negative aerobes <i>Acinetobacter</i> spp. <i>Enterobacter</i> spp. <i>Morganella morganii</i> <i>Proteus vulgaris</i> <i>Providencia rettgeri</i> <i>Pseudomonas</i> spp. <i>Serratia</i> spp.

5.2 Pharmacokinetic properties

Cefaclor is rapidly absorbed from the gastrointestinal tract, plasma levels of 18-33 mg/l being found after a 1 g dose and 13-19 mg/l after 500 mg. It is unstable in serum at 37°C, less than 10% of activity remaining at six hours and activity in serum may thus be underestimated.

There was no evidence of accumulation after 10 days in multiple dose volunteer studies. The presence of food may arrest Cefaclor absorption temporarily but the total amount absorbed should remain the same. In normal fasting subjects, a mean peak value of 16.5 mg/l was reduced to 10.8 mg/l at 48 min when the drug was administered with food. Furthermore these values greatly exceed the MIC for susceptible organisms and the urinary excretion in the first six hours is not affected. The plasma half life is 29 - 60 min (mean 48 min). The volume of distribution is 0.37 ± 0.11 L/kg. Plasma protein binding is $24.6 \pm 3.5\%$.

In children aged four months to five years (average 1.9 years) doses of 10 mg/kg produced levels at 13 minutes in the serum of 10.8 mg/l in fasting patients and 6.7 mg/l in patients who received food. Very little of the drug reaches the CSF. In two patients given a single dose of 250 mg, peak levels in breast milk were 1.8 and 0.5 mg after two and four hours respectively. Peak levels detected in aqueous humor, interstitial fluid, middle ear aspirate and saliva have been found to be between 0.5 and 1 mg/l. Lower levels in sputum (around 0.5 mg/l) have been found.

Excretion in urine is the main elimination path with between 43 and 97% of the administered dose is excreted in the first 8 hours. 38 - 54% of excretion takes place in the first two hours, producing peak values in excess of 900 mg/l. Most of the drug is eliminated unchanged in the urine. A small proportion of the dose, up to 15%, is metabolised or otherwise degraded. In patients with severely impaired renal function receiving a single dose of 500 mg Cefaclor by mouth while fasting, peak plasma levels ranged from 12 to 23 mg/l and the plasma half life from 1.9 to 3.5 hours.

The minimum bactericidal concentration (MBC), depending on the organism tested, is usually two to eight times the minimum inhibitory concentration (MIC). There is no evidence that measuring plasma concentrations of Cefaclor is of any relevance in routine clinical practice.

5.3 Preclinical safety data

Cefaclor has shown low toxicity in mice, rats, dogs and monkeys. Subacute and chronic toxicity studies in rodents and dogs demonstrate that the drug is well tolerated. Cefaclor is not teratogenic to mice in doses as high as 1 mg/kg nor to rats in doses up to 1000 mg/kg daily. No carcinogenic effects have been observed in chronic one year toxicity studies in rats.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sorbitol (E420)
Simethicone
Xanthan gum
Strawberry flavour
Sodium lauryl sulphate
Mannitol

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

Shelf life for the product as packaged for sale:

2 years.

Shelf life after reconstitution according to directions:

14 days.

6.4 Special precautions for storage

For the product as packaged for sale:

Do not store above 25°C. Keep container in the outer carton. Keep container tightly closed.

After reconstitution:

Store in a refrigerator (2-8°C).

6.5 Nature and contents of container

This product is supplied in a 60 ml, 75ml, 100 ml or a 150 ml High Density Polyethylene (HDPE) bottle with a child-proof polypropylene/polyethylene (PP/PE) screw-cap.
The inside of the cap is lined with a saran disc (PVdC).

A 5 ml, CE certified, graduated polypropylene oral syringe for dosing is supplied.

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

The reconstitution is usually performed by the dispensing pharmacist.

1. Shake the bottle well before adding any water to loosen the powder.

2. For the 150 ml bottle size:

Add 116 ml water in two portions, shaking well between additions to ensure a homogenous suspension.

For the 100 ml bottle size:

Add 77 ml water in two portions, shaking well between additions to ensure a homogenous suspension.

For the 75 ml bottle size:

Add 58 ml water in two portions, shaking well between additions to ensure a homogenous suspension.

For the 60 ml bottle size

Add 47 ml water in two portions, shaking well between additions to ensure a homogenous suspension.

3. The reconstituted suspension should be stored in a refrigerator. Discard any remaining solution after 14 days.
The reconstituted suspension is in the form of an off-white suspension.

4. Shake the bottle thoroughly before use.

Instruction for use by the patient are included in the patient Information Leaflet and pertain to the use of an oral dosing device only.

7 MARKETING AUTHORISATION HOLDER

McDermott Laboratories Limited
T/A Gerard Laboratories
35/36 Baldoyle Industrial Estate
Grange Road
Dublin 13
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8 MARKETING AUTHORISATION NUMBER

PA 0577/045/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 8 March 2002

Date of last renewal: 13 December 2005

10 DATE OF REVISION OF THE TEXT

January 2009