NEW ZEALAND DATA SHEET

1 PRODUCT NAME

Cefalexin 125 mg/5 mL Granules for oral suspension
Cefalexin 250 mg/5 mL Granules for oral suspension

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Cefalexin 125 mg/5 mL Granules for oral suspension:

When prepared as directed, each 5 mL of reconstituted suspension contains (as the active ingredient) cefalexin monohydrate equivalent to 125 mg of cefalexin base.

Excipients with known effect: contains 3.119 g of sucrose per 5 mL after reconstitution.

Cefalexin 250 mg/5 mL Granules for oral suspension:

When prepared as directed, each 5 mL of reconstituted suspension contains as the active ingredient, cefalexin monohydrate equivalent to 250 mg of cefalexin base.

Excipients with known effect: contains 2.972 g of sucrose per 5 mL after reconstitution.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Granules for oral suspension.

White granules.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Cefalexin is indicated for the treatment of the following infections when caused by susceptible strains of the designated microorganisms:

- bacterial sinusitis caused by streptococci, S. pneumoniae, and Staphylococcus aureus (methicillin-sensitive only);
- respiratory tract infections caused by S. pneumoniae and S. pyogenes (penicillin is the usual medicine of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever - cefalexin is generally effective in the eradication of streptococci from the nasopharynx; however, substantial data establishing the efficacy of cefalexin in the subsequent prevention of either rheumatic fever or bacterial endocarditis are not available at present);
- otitis media due to S. pneumoniae, H. influenzae, staphylococci, streptococci, and M. catarrhalis;
- skin and skin-structure infections caused by staphylococci and/or streptococci;
- bone infections caused by staphylococci and/or P. mirabilis;
- genitourinary tract infections, including acute prostatitis, caused by E. coli, P. mirabilis, and Klebsiella pneumoniae;
- dental infections caused by staphylococci and/or streptococci.

Note - Culture and susceptibility tests should be initiated prior to and during therapy. Renal

function studies should be performed when indicated.

4.2 Dose and method of administration

Dosage

Cefalexin is administered orally.

Adults

The adult dosage ranges from 1 to 4 g daily in divided doses. The usual adult dose is 250 mg every 6 hours. For the following infections, a dosage of 500 mg may be administered every 12 hours: streptococcal pharyngitis, skin and skin-structure infections, and uncomplicated cystitis in patients over 15 years of age. Cystitis therapy should be continued for 7 to 14 days. 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.

Children

The usual recommended daily dosage for children is 25 to 50 mg/kg in divided doses. For streptococcal pharyngitis in patients over 1 year of age, mild, uncomplicated urinary tract infections, and for skin and skin-structure infections, the total daily dose may be divided and administered every 12 hours.

Cefalexin granules for oral suspension 125 mg/5 mL

For a child weighing about 10 kg, give prepared suspension 2.5 to 5 mL four times a day or 5 to 10 mL twice a day.

For a child weighing about 20 kg, give prepared suspension 5 to 10 mL four times a day or 10 to 20 mL twice a day.

For a child weighing about 40 kg, give prepared suspension 10 to 20 mL four times a day or 20 to 40 mL twice a day.

Cefalexin granules for oral suspension 250 mg/5 mL

For a child weighing about 10 kg, give prepared suspension 1.25 to 2.5 mL four times a day or 2.5 to 5 mL twice a day.

For a child weighing about 20 kg, give prepared suspension 2.5 to 5 mL four times a day or 5 to 10 mL twice a day.

For a child weighing about 40 kg, give prepared suspension 5 to 10 mL four times a day or 10 to 20 mL twice a day.

In severe infections, the dosage may be doubled.

In the therapy of otitis media, clinical studies have shown that a dosage of 75 to 100 mg/kg/day in 4 divided doses is required.

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

Administration

Cefalexin granules for oral suspension were developed specially for paediatric use.

For instructions on reconstitution of Cefalexin granules for oral suspension, see section 6.6 Special precautions for disposal and other handling.

4.3 Contraindications

Cefalexin is contraindicated in patients who have had previous experience of a major allergy or anaphylaxis to a cephalosporin or penicillin.

Cefalexin is contraindicated in patients who have experienced hypersensitivity to any of the excipients listed in section 6.1.

Limitations

Cefalexin is not indicated in the management of bacterial infections of the brain or spinal column.

4.4 Special warnings and precautions for use

Cefalexin should not ordinarily be given to those allergic to cephalosporins or to penicillins, especially where an allergic or urticarial reaction has occurred. Before cefalexin therapy is instituted, careful inquiry should be made concerning previous hypersensitivity reactions to cephalosporins, penicillins or other medicines. Cephalosporin C derivatives should be given cautiously to penicillin-sensitive patients. Serious acute hypersensitivity reactions may require adrenaline or epinephrine and other emergency measures. There is some clinical and laboratory evidence of partial cross-allergenicity of the penicillins and the cephalosporins. Patients have been reported to have had severe reactions (including anaphylaxis) to both medicines. Any patient who has demonstrated some form of allergy, particularly to medicines, should receive antibiotics cautiously. No exception should be made with regard to cefalexin.

Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics (including macrolides, semisynthetic penicillins, and cephalosporins); therefore, it is important to consider its diagnosis in patients who develop diarrhoea in association with the use of antibiotics. Mild cases of pseudomembranous colitis usually respond to medicine discontinuance alone. In moderate to severe cases, appropriate measures should be taken.

Antibiotic associated pseudomembranous colitis has been reported with many antibiotics including cefalexin. A toxin produced with Clostridium difficile appears to be the primary cause. The severity of the colitis may range from mild to life threatening. It is important to consider this diagnosis in patient who develop diarrhoea or colitis in association with antibiotic use (this may occur up to several weeks after cessation of antibiotic therapy). Mild cases usually respond to medicine discontinuation alone. However, in moderate to severe cases appropriate therapy with a suitable oral antibacterial agent effective against Cl. difficile should be considered. Fluids, electrolytes and protein replacement therapy should be provided when indicated. Medicines that delay peristalsis e.g. opiates and diphenoxylate with atropine, may prolong and/or worsen the condition and should not be used.

Neurotoxicity:
Reports of neurotoxicity have been identified in association with cephalosporin treatment. Symptoms may include encephalopathy, myoclonus and seizures. Elderly patients, patients with severe renal impairment or central nervous system disorders are particularly at risk. If cefalexin associated neurotoxicity is suspected, discontinuation of cefalexin should be considered.

Prothrombin time: Prolonged prothrombin time may occur in patients receiving protracted antimicrobial therapy.

Patients should be followed carefully so that any side effects or unusual manifestations of medicine idiosyncrasy may be detected. If an allergic reaction to cefalexin occurs, the medicine

should be discontinued and the patient treated with the usual agents (e.g. adrenaline or epinephrine or other pressor amines, antihistamines, or corticosteroids).

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.

Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Indicated surgical procedures should be performed in conjunction with antibiotic therapy.

Impaired renal function: Cefalexin should be administered with caution in the presence of markedly impaired renal function. Under such conditions, careful clinical observation 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.

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

This product contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Also contains Allura Red AC (E129), which may cause allergic reactions.

This product contains less than 1 mmol sodium (23 mg) per 5ml, that is to say essentially 'sodium-free'.
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.

4.5 Interaction with other medicines and other forms of interaction

As with other beta-lactams, the renal excretion of cefalexin is inhibited by probenecid. As a result, cefalexin plasma levels are increased and sustained for longer periods.

A potential interaction between cefalexin and metformin may result in accumulation of metformin. In 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%. The interaction of cefalexin and metformin following multiple dose administration has not been studied. Administration of a cephalosporin to a metformin treated patient may result in increased metformin exposure. A potential interaction between cefalexin and metformin may result in accumulation of metformin.

As cephalosporins like cefalexin are only active against proliferating micro-organisms, they should not be combined with bacteriostatic antibiotics.

If associated with highly potent diuretics such as furosemide or other potentially nephrotoxic antibiotics (aminoglycosides, polymyxin, colistin), cephalosporins may show higher nephrotoxicity.

The combined use of cephalosporins and oral anticoagulants may prolong the prothrombin time.

Cephalosporins may reduce the effects of oral contraceptives.

Laboratory diagnostic tests

Positive direct Coombs' tests have been reported during treatment with the cephalosporin antibiotics. In haematologic 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 medicine.

Cefalexin may cause a false-positive glucose reaction in urine with Benedict's and Fehlings's solutions or with copper sulfate test tablets.

The quantitative determination of urinary protein excretion using strong acids is misleading during cefalexin therapy as precipitation of cefalexin in the urine may occur.

4.6 Fertility, pregnancy and lactation

Use in pregnancy

Category A

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. Note that the safety of cefalexin during pregnancy in humans has not been established. Cefalexin showed no enhanced toxicity in weanling and newborn rats as compared with adult animals.
Nevertheless, because the studies in humans cannot rule out the possibility of harm, cefalexin should be used during pregnancy only if clearly needed.

Use in lactation

The excretion of cefalexin in breast milk increased up to 4 hours after a 500 mg dose; the medicine reached a maximum level of 4 mg/l, then decreased gradually, and had disappeared 8 hours after administration. Caution should be exercised when cefalexin is administered to a nursing woman, since the neonate is presented with the risk of candidasis and CNS toxicity due to immaturity of the blood-brain barrier. There is a theoretical possibility of later sensitisation.

Fertility

Refer to section 5.3 Preclinical safety data.

4.7 Effects on ability to drive and use machines

During treatment with Cefalexin, undesirable effects may occur (e.g. dizziness), which may influence the ability to drive and use machines. Patients should be cautious when driving or operating machinery.

4.8 Undesirable effects

Gastrointestinal

Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment. The most frequent side effect has been diarrhoea. However, it was very rarely severe enough to warrant cessation of therapy. Nausea and vomiting have been reported rarely. Dyspepsia and abdominal pain have also occurred. As with some penicillins and some other cephalosporins, transient hepatitis and cholestatic jaundice have been reported rarely.

Hypersensitivity: Allergic reactions in the form of rash, urticaria, angioedema, and, rarely, erythema multiforme, Stevens-Johnson Syndrome, or toxic epidermal necrolysis have been observed. These reactions usually subsided upon discontinuation of the medicine. In some of the reactions, supportive therapy may be necessary. Anaphylaxis has also been reported.

Haemic and Lymphatic System: Eosinophilia, neutropenia, thrombocytopenia and haemolytic anaemia have been reported.

Skin and subcutaneous tissue disorders: Acute generalised exanthematous pustulosis (AGEP) has been reported with unknown frequency.

Other: Other reactions have included genital and anal pruritis, genital moniliasis, vaginitis and vaginal discharge, dizziness, fatigue, headache, agitation, confusion, hallucinations, arthralgia, arthritis, cutaneous vasculitis, and joint disorders. Reversible interstitial nephritis has been reported rarely. Eosinophilia, neutropenia, thrombocytopenia, haemolytic anaemia and slight elevations in AST and ALT have been reported. There have been reports of neurological sequelae including tremor, myoclonia, convulsions, encephalopathy with drugs belonging to the class of cephalosporins. Most cases occurred in patients with renal impairment who received doses that exceeded the recommended dose and resolved following discontinuation of treatment.

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/

4.9 Overdose

Signs and symptoms

There is no definite experience of poisoning or severe overdosage with cefalexin. However, clinical features of overdosage may be similar to those seen with other cephalosporins and penicillins, i.e. convulsions, hallucinations, hyperreflexia, electrolyte imbalance, nausea, vomiting, epigastric distress, diarrhoea, and haematuria. If other symptoms are present, it is probably secondary to an underlying disease state, an allergic reaction, or toxicity due to ingestion of a second medication. The oral median lethal dose of cefalexin in rats is 5,000 mg/kg.

Management

In the event of severe overdosage, general supportive care is recommended including close clinical and laboratory monitoring of haematological, renal, 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; however, it would be extremely unlikely that one of these procedures would be indicated.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:
Antibacterials for systemic use, first-generation cephalosporins, ATC code: J01DB01.

Antibiotic class

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

The nucleus of cephalexin is related to that of other cephalosporin antibiotics. The compound is a zwitterion; i.e. the molecule contains both a basic and an acidic group. The isoelectric point of cephalexin in water is approximately 4.5 to 5. The crystalline form of cephalexin, which is available, is a monohydrate. It is a white or almost white crystalline solid having a bitter taste. Solubility in water is about 1% at room temperature. It is practically insoluble in alcohol and in ether. The cephalosporins differ from penicillins in the structure of the bicyclic ring system. Cephalexin has a d-phenylglycyl group as substituent at the 7-amino position and an unsubstituted methyl group at the 3-position.

Antibiotic nature and mode of action

In vitro tests demonstrate that the cephalosporins are bactericidal because of their inhibition of cell-wall synthesis. Cefalexin has been shown to be active against most strains of the following microorganisms both in vitro and in clinical infections as described in section 4.1 Therapeutic Indications.

Aerobes, Gram-positive:
Staphylococcus aureus (including penicillinase-producing strains);
Staphylococcus epidermidis (penicillin-susceptible strains);
Streptococcus pneumoniae;
Streptococcus pyogenes.

Aerobes, Gram-negative:
Escherichia coli;
Haemophilus influenzae;
Klebsiella pneumoniae;
Moraxella catarrhalis;
Proteus mirabilis.

Susceptibility data and clinically relevant MIC ranges

Susceptibility Tests - Diffusion techniques

Quantitative methods that require measurement of zone diameters provide reproducible estimates of susceptibility of bacteria to antimicrobial compounds. One such standardised procedure has been recommended for use with discs to test the susceptibility of microorganisms to cefalexin and uses the 30 mcg cephalothin disc. Interpretation involves correlation of the diameter obtained in the disc test with the minimum inhibitory concentration (MIC) for cefalexin.

Reports from the laboratory providing results of the standard single-disc susceptibility test with a 30 mcg cephalothin disc should be interpreted according to the following criteria:

- a zone diameter NLT 18 mm is considered susceptible;
- a zone diameter between 15 and 17 mm is considered intermediate;
- a zone diameter NMT 14 mm is considered resistant.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited by usually achievable concentrations of the antimicrobial compound in blood.

A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible medicine, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of medicine can be used. This category also provides a buffer zone that prevents small uncontrolled technical factors from causing major discrepancies in interpretation.

A report of "Resistant" indicates that usually achievable concentrations of the antimicrobial compound in the blood are unlikely to be inhibitory and that other therapy should be selected.

Measurement of MIC or MBC and achieved antimicrobial compound concentrations may be appropriate to guide therapy in some infections (refer to section 5.2 Pharmacokinetic Properties, for information on drug concentrations achieved in infected body sites and other pharmacokinetic properties of this antimicrobial medicine.)

Standardised susceptibility test procedures require the use of laboratory control microorganisms. The 30 mcg cephalothin disc should provide the following zone diameters in these laboratory test quality control strains:

- for *E. coli* ATCC 25922, 15 to 21 mm;
- for *S. aureus* ATCC 25923, 29 to 37 mm.

Dilution techniques

Quantitative methods that are used to determine MICs provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardised procedure uses a standardised dilution method (broth, agar, microdilution) or equivalent with cephalothin powder. The MIC values obtained should be interpreted according to the following criteria:

- a MIC NMT 8 mcg/mL is considered susceptible;
- a MIC of 16 mcg/mL is considered intermediate;
- a MIC NLT 32 mcg/mL is considered resistant.

Interpretation should be as stated above for results using diffusion techniques.

As with standard diffusion techniques, dilution methods require the use of laboratory control microorganisms. Standard cephalothin powder should provide the following MIC values:

- for *E. coli* ATCC 25922, 4 to 16 mcg/mL;
- for *E. faecalis* ATCC 29212, 8 to 32 mcg/mL;
- for *S. aureus* ATCC 29213, 0.12 to 0.5 mcg/mL.

Resistance

Methicillin-resistant staphylococci and most strains of enterococci (*Enterococcus faecalis*) are resistant to cephalosporins including cefalexin. Penicillin-resistant *Streptococcus pneumoniae* is usually cross-resistant to beta-lactam antibiotics. It is not active against most strains of *Enterobacter spp., Morganella morganii* and *Proteus vulgaris*. It has no activity against *Pseudomonas spp*. or *Acinetobacter calcoaceticus*.

When tested by in vitro methods, Staphylococci exhibit cross-resistance between cefalexin and methicillin type antibiotics.

5.2 Pharmacokinetic properties

Pharmacokinetic

s <u>Absorption</u>

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 one hour. Measurable levels were present six hours after administration.

<u>Distribution</u>

Cefalexin readily diffuses into tissues, including bone, joints and the pericardial as well as pleural cavities. Only 10 to 15% of a dose is bound to plasma protein.

Biotransformation

Cefalexin is excreted in the urine by glomerular filtration and tubular secretion. Almost the entire dose recovered from the urine is therapeutically active.

Elimination

Elimination is mainly renal. The half-life is approximately 50 min and this increases with reduced renal function. Studies showed that over 90% of the medicine 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 1000, 2200, and 5000 mg/L respectively.

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

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

The granules contain the following excipients:

Sucrose
Imitation Guarana Flavour
Allura Red AC (E129)
Sodium Lauryl Sulphate
Methylcellulose 15
Dimeticone
Xanthan Gum
Pregelatinised Starch

6.2 Incompatibilities

None known.

6.3 Shelf life

Cefalexin 125 mg/5 mL Granules for oral suspension

Unopened product: 2 years

After reconstitution: to be used within 10 days.

Cefalexin 250 mg/5 mL Granules for oral suspension

Unopened product: 3 years

After reconstitution: to be used within 10 days

6.4 Special precautions for storage

Store at or below 25°C.

Reconstituted suspension should be stored in a refrigerator (2°C-8°C).

6.5 Nature and contents of container

100 mL HDPE bottles with screw caps.

6.6 Special precautions for disposal and other handling

Reconstitution of Cefalexin granules for oral suspension 125 mg/5 mL and 250 mg/5 mL

First invert the bottle and tap to loosen the powder then add a total of 60 mL water in two portions, shaking after each addition until suspended. The suspension is red.

Shake well before use.

No special requirements for disposal.

7 MEDICINE SCHEDULE

Prescription Medicine.

8 SPONSOR

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9 DATE OF FIRST APPROVAL

11 November 2021

10 DATE OF REVISION OF THE TEXT

19 July 2024

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.8	Additional information regarding neurological sequelae has been added under 'Other'. Updated link for reporting AEs to CARM.