NEW ZEALAND DATA SHEET

1. PRODUCT NAME

CEFUROXIME DEVATIS 250 mg, 750 mg & 1.5 g Powder for Injection/Infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:
Each 250 mg vial contains cefuroxime sodium equivalent to 250 mg cefuroxime.
Each 750 mg vial contains cefuroxime sodium equivalent to 750 mg cefuroxime.
Each 1.5 g vial contains cefuroxime sodium equivalent to 1.5 g cefuroxime.

Excipient with known effect:

Each 250 mg vial contains	13.55 mg sodium.
Each 750 mg vial contains	40.65 mg sodium.
Each 1.5 g vial contains	81.38 mg sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for injection/ infusion.
Cefuroxime is a white to faintly yellow powder to which appropriate amounts of water are added to prepare an off-white suspension for intramuscular use or a yellow solution of intravenous administration.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Cefuroxime is a bactericidal cephalosporin antibiotic which is resistant to most ß-lactamases and is active against a wide range of Gram-positive and Gram-negative organisms.
It is indicated for the treatment of infections before the infecting organism has been identified or when caused by sensitive bacteria. Susceptibility to cefuroxime sodium will vary with geography and time and local susceptibility data should be consulted where available (see section 5.1).

Indications include

- Respiratory tract infections for example, acute and chronic bronchitis, infected bronchiectasis, bacterial pneumonia, lung abscess and post-operative chest infections.
- Ear, nose and throat infections for example, sinusitis, tonsillitis, pharyngitis and otitis media.
- Urinary tract infections for example, acute and chronic pyelonephritis, cystitis and asymptomatic bacteriuria.
- Soft-tissue infections for example, cellulitis, erysipelas and wound infections.
- Bone and joint infections for example, osteomyelitis and septic arthritis.
- Obstetric and gynecological infections, pelvic inflammatory diseases.
- Gonorrhea particularly when penicillin is unsuitable.
- Other infections including septicemia, meningitis and peritonitis.
- Prophylaxis against infection in abdominal, pelvic, orthopedic, cardiac, pulmonary, esophageal and vascular surgery where there is increased risk from infection.

Usually Cefuroxime Devatis will be effective alone, but when appropriate it may be used in combination

with an aminoglycoside antibiotic, or in conjunction with metronidazole (orally or by suppository or injection), especially for prophylaxis in colonic or gynecological surgery (see section 4.4).

Where appropriate Cefuroxime Devatis is effective when used prior to oral therapy with cefuroxime axetil in the treatment of pneumonia and acute exacerbations of chronic bronchitis.

4.2 Dose and method of administration

Posology/duration and frequency of administration

Adults:
Many infections respond to 750 mg three times daily by intramuscular or intravenous injection. For more severe infections the dose should be increased to 1.5 g three times daily given intravenously. The frequency of administration may be increased to 6-hourly if necessary, giving total daily doses of 3 to 6 g. Where clinically indicated, some infections respond to 750 mg or 1.5 g twice daily (intravenously or intramuscularly) followed by oral therapy with Cefuroxime.

Infants and Children: 30 to 100 mg/kg/day given as 3 or 4 divided doses. A dose of 60 mg/kg/day is appropriate for most infections.

Neonates: 30 to 100 mg/kg/day given as 2 or 3 divided doses (see section 5.2).

Gonorrhea
Adults:
1.5 g as a single dose (as 2 x 750 mg injections given intramuscularly with different sites, e.g. each buttock).

Meningitis
Cefuroxime Devatis is suitable for sole therapy of bacterial meningitis due to sensitive strains.

Adults: 3 g given intravenously every eight hours.

Infants and Children: 150 to 250 mg/kg/day given intravenously in 3 or 4 divided doses.

Neonates: The dosage should be 100 mg/kg/day given intravenously.

Prophylaxis
Adults
The usual dose is 1.5 g given intravenously with induction of anesthesia for abdominal, pelvic and orthopedic operations. This may be supplemented with two 750 mg intramuscular doses eight and sixteen hours later.
In cardiac, pulmonary, esophageal and vascular operations, the usual dose is 1.5 g given intravenously with induction of anesthesia, continuing with 750 mg given intramuscularly three times daily for a further 24 to 48 hours.
In total joint replacement, 1.5 g cefuroxime powder may be mixed dry with each pack of methyl methacrylate cement polymer before adding the liquid monomer.

Sequential therapy
Adults:
Duration of both parenteral and oral therapy is determined by the severity of the infection and the clinical status of the patient.

Pneumonia: 1.5 g Cefuroxime Devatis 3 times daily or twice daily (given intravenously or intramuscularly) for 48 to 72 hours, followed by 500 mg twice daily cefuroxime axetil oral therapy for 7 to 10 days.

Acute exacerbations of chronic bronchitis: 750 mg Cefuroxime Devatis 3 times daily or twice daily (given intravenously or intramuscularly) for 48 to 72 hours, followed by 500 mg twice daily cefuroxime axetil oral therapy for 5 to 10 days.

Method of administration
Cefuroxime Injection is for intravenous (IV) and/or intramuscular (IM) administration.
No more than 750 mg should be injected at one intramuscular site.

Additional information on special populations

Renal Impairment
Cefuroxime is excreted by the kidneys. Therefore, as with all such antibiotics, in patients with markedly impaired renal function it is recommended that the dosage of Cefuroxime Devatis should be reduced to compensate for its slower excretion.
It is not necessary to reduce the standard dose (750 mg to 1.5 g 3 times daily) until the creatinine clearance falls to 20 ml/min or below.
In adults with marked impairment (creatinine clearance 10-20 ml/min) 750 mg twice daily is recommended and with severe impairment (creatinine clearance <10 ml/min) 750 mg once daily is adequate.
For patients on hemodialysis a further 750 mg dose should be given intravenously or intramuscularly at the end of each dialysis. In addition to parenteral use, cefuroxime can be incorporated into the peritoneal dialysis fluid (usually 250 mg for every 2 liters of dialysis fluid).
For patients in renal failure on continuous arteriovenous hemodialysis or high-flux hemofiltration in intensive therapy units a suitable dosage is 750 mg twice daily. For low-flux hemofiltration follow the dosage recommended under impaired renal function.
Cefuroxime is also available as the axetil ester for oral administration. This permits parenteral therapy with cefuroxime to be followed by oral therapy in situations where a change from parenteral to oral is clinically indicated.

Hepatic Impairment
Cefuroxime is primarily eliminated by the kidney. In patients with hepatic dysfunction this is not expected to affect the pharmacokinetics of cefuroxime.

Pediatric population
Appropriate dosages have been given above

Geriatric population
No adjustment of dosage is required in the elderly.

4.3 Contraindications
Hypersensitivity to cefuroxime or to any of the excipients listed in section 6.1.
Patients with known hypersensitivity to cephalosporin antibiotics.
History of severe hypersensitivity (e.g. anaphylactic reaction) to any other type of beta-lactam antibacterial agent (penicillins, monobactams and carbapenems).

4.4 Special warning and precautions for use
Special care is indicated in patients who have experienced an allergic reaction to penicillins or other beta-lactams.

Cephalosporin antibiotics at high dosage should be given with caution to patients receiving concurrent treatment with potent diuretics such as furosemide or aminoglycosides, as renal impairment has been reported with these combinations. Renal function should be monitored in these patients, the elderly, and those with pre-existing renal impairment (see section 4.2).

As with other therapeutic regimens used in the treatment of meningitis, mild-to-moderate hearing loss has been reported in a few pediatric patients treated with cefuroxime sodium. Persistence of positive cerebral spinal fluid (CSF) cultures of Haemophilus influenzae at 18 to 36 hours has also been noted with cefuroxime sodium injection, as well as with other antibiotic therapies; however, the clinical relevance of this is unknown.

As with other antibiotics, use of cefuroxime may result in the overgrowth of Candida. Prolonged use may also result in the overgrowth of other non-susceptible organisms (e.g. enterococci and Clostridium difficile), which may require interruption of treatment.

Pseudomembranous colitis has been reported with the use of antibiotics and may range in severity from mild to life-threatening. Therefore, it is important to consider its diagnosis in patients who develop diarrhea during or after antibiotic use. If prolonged or significant diarrhea occurs or the patient experiences abdominal cramps, treatment should be discontinued immediately and the patient investigated further.

With a sequential therapy regime the timing of change to oral therapy is determined by severity of the infection, clinical status of the patient and susceptibility of the pathogens involved. If there is no clinical improvement within 72 hours, then the parenteral course of treatment must be continued.

Refer to the relevant prescribing information for cefuroxime axetil before initiating sequential therapy.

Cefuroxime powder for solution for injection and infusion contains sodium. This should be considered for patients who are on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

In common with other antibiotics Cefuroxime Devatis may affect the gut flora, leading to lower estrogen reabsorption and reduced efficacy of combined oral contraceptives.

Cefuroxime Devatis does not interfere in enzyme-based tests for glycosuria.

Slight interference with copper reduction methods (Benedict's, Fehling's, Clinitest) may be observed. However, this should not lead to false-positive results, as may be experienced with some other cephalosporins.

It is recommended that either the glucose oxidase or hexokinase methods are used to determine blood/plasma glucose levels in patients receiving Cefuroxime Devatis.

This antibiotic does not interfere in the alkaline picrate assay for creatinine.

4.6 Fertility, pregnancy and lactation

General properties:
Pregnancy category is B

Pregnancy
There is no experimental evidence of embryopathic or teratogenic effects attributable to cefuroxime, but, as with all medicines, it should be administered with caution during the early months of pregnancy.

Breast-feeding
Cefuroxime is excreted in human milk, and consequently caution should be exercised when Cefuroxime Devatis is administered to a nursing mother.

Fertility
There are no data on the effects of cefuroxime sodium on fertility in humans. Reproductive studies in animals have shown no effects on fertility.

4.7 Effects on ability to drive and use machines
No studies on the effects on the ability to drive and use machines have been performed. However, based on known adverse reactions, cefuroxime is unlikely to have an effect on the ability to drive and use machines.

4.8 Undesirable effects
Adverse drug reactions are very rare (<1/10,000) and are generally mild and transient in nature.
The frequency categories assigned to the adverse reactions below are estimates, as for most reactions suitable data for calculating incidence are not available. In addition the incidence of adverse reactions associated with cefuroxime sodium may vary according to the indication.
Data from clinical trials were used to determine the frequency of very common to rare undesirable effects. The frequencies assigned to all other undesirable effects (i.e., those occurring at <1/10,000) were mainly determined using post-marketing data, and refer to a reporting rate rather than a true frequency.
The following convention has been used for the classification of frequency:

Very common	≥1/10
Common	≥1/100 to <1/10
Uncommon	≥1/1000 to <1/100
Rare	≥1/10000 to <1/1000
Very rare	<1/10000
Unknown	cannot be estimated based on available data

Infections and infestations
Rare: Candida overgrowth.

Blood and lymphatic system disorders
Common: Neutropenia, eosinophilia.
Uncommon: Leucopenia, decreased hemoglobin concentration, positive Coomb's test.
Rare: Thrombocytopenia.
Very rare: Hemolytic anemia.
Cephalosporins as a class tend to be absorbed onto the surface of red cell membranes and react with antibodies directed against the medicine to produce a positive Coomb's Test (which can interfere with cross matching of blood) and very rarely hemolytic anemia.

Immune system disorders
Hypersensitivity reactions including:
Uncommon: Skin rash, urticaria and pruritus.
Rare: Drug fever.
Very rare: Interstitial nephritis, anaphylaxis, cutaneous vasculitis.
See also Skin and subcutaneous tissue disorders and Renal and urinary disorders.

Vascular disorders
Common: Thrombophlebitis may follow intravenous injection.

Gastrointestinal disorders
Uncommon: Gastrointestinal disturbance.
Very rare: Pseudomembranous colitis (see section 4.4).

Hepatobiliary disorders
Common: Transient rise in liver enzymes.

Uncommon: Transient rise in bilirubin.
Transient rises in serum liver enzymes or bilirubin occur, particularly in patients with pre-existing liver disease, but there is no evidence of harm to the liver.

Skin and subcutaneous tissue disorders
Very rare: Erythema multiforme, toxic epidermal necrolysis and Stevens Johnson Syndrome.
See also Immune system disorders.

Renal and urinary disorders
Very rare: Elevations in serum creatinine, elevations in blood urea nitrogen and decreased creatinine clearance (see section 4.4).
See also Immune system disorders.

General disorders and administration site conditions
Common: Injection site reactions which may include pain and thrombophlebitis
Pain at the intramuscular injection site is more likely at higher doses. However it is unlikely to be a cause for discontinuation of treatment.

Reporting of suspected adverse reactions:
Reporting suspected adverse reactions after authorization 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://nzphvc.otago.ac.nz/reporting/.

4.9 Overdose
Overdosage of cephalosporins can cause cerebral irritation leading to convulsions. Serum levels of cefuroxime can be reduced by hemodialysis or peritoneal dialysis.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Antibacterials for systemic use, second-generation cephalosporins
ATC code: J01DC02

Mechanism of Action
Cefuroxime is a well characterized and effective antibacterial agent which has bactericidal activity against a wide range of common pathogens, including ß-lactamase producing strains.
Cefuroxime has good stability to bacterial ß-lactamase, and consequently is active against many ampicillin-resistant or amoxycillin-resistant strains.
The bactericidal action of cefuroxime results from inhibition of cell wall synthesis by binding to essential target proteins.

Pharmacodynamic Effects:
The prevalence of acquired resistance is geographically and time dependent and for select species may be very high. Local information on resistance is desirable, particularly when treating severe infections.

In vitro susceptibility of micro-organisms to Cefuroxime
Where clinical efficacy of cefuroxime has been demonstrated in clinical trials this is indicated with an asterisk (*).

Commonly Susceptible Species
Gram-Positive Aerobes Staphylococcus aureus (methicillin susceptible)* Coagulase negative staphylococcus (methicillin susceptible) Streptococcus pyogenes* Beta-hemolytic streptococci
Gram-Negative Aerobes Haemophilus influenzae including ampicillin resistant strains* Haemophilus parainfluenzae* Moraxella catarrhalis* Neisseria gonorrhoea* including penicillinase and non-penicillinase producing strains Neisseria meningitidis Shigella spp.
Gram-Positive Anaerobes: Peptostreptococcus spp. Propionibacterium spp.
Spirochetes: Borrelia burgdorferi*
Organisms for which acquired resistance may be a problem
Gram-Positive Aerobes: Streptococcus pneumoniae* Viridans group streptococcus
Gram-Negative Aerobes: Bordetella pertussis Citrobacter spp. not including C. freundii Enterobacter spp. not including E. aerogenes and E. cloacae Escherichia coli* Klebsiella spp. including K. pneumoniae* Proteus mirabilis Proteus spp. not including P. penneri and P. vulgaris Providencia spp. Salmonella spp.
Gram-Positive Anaerobes: Clostridium spp. not including C. difficile
Gram-Negative Anaerobes: Bacteroides spp. not including B. fragilis Fusobacterium spp.
Inherently resistant organisms
Gram-Positive Aerobes: Enterococcus spp. including E. faecalis and E. faecium Listeria monocytogenes
Gram-Negative Aerobes: Acinetobacter spp. Burkholderia cepacia Campylobacter spp. Citrobacter freundii Enterobacter aerogenes Enterobacter cloacae Morganella morganii Proteus penneri Proteus vulgaris Pseudomonas spp. including P. aeruginosa

Serratia spp. Stenotrophomonas maltophilia
Gram-Positive Anaerobes: Clostridium difficile
Gram-Negative Anaerobes: Bacteroides fragilis
Others: Chlamydia species Mycoplasma species Legionella species

5.2. Pharmacokinetic properties

Absorption:
Peak levels of cefuroxime are achieved within 30 to 45 minutes after intramuscular administration.

Distribution:
Protein binding has been variously stated as 33 to 50% depending on the methodology used.
Concentrations of cefuroxime in excess of the minimum inhibitory levels for common pathogens can be achieved in bone, synovial fluid and aqueous humor. Cefuroxime passes the blood-brain barrier when the meninges are inflamed.

Metabolism:
Cefuroxime is not metabolized and is excreted by glomerular filtration and tubular secretion.

Elimination:
The serum half-life after either intramuscular or intravenous injection is approximately 70 minutes.
In the first weeks of life the serum half-life of cefuroxime can be 3 to 5 times that in the adult.
Concurrent administration of probenecid prolongs the excretion of the antibiotic and produces an elevated peak serum level. There is an almost complete recovery (85-90%) of unchanged cefuroxime in urine within 24 hours of administration. The major part is excreted in the first six hours. Serum levels of cefuroxime are reduced by dialysis.

Special patient populations

Gender:
No differences in the pharmacokinetics of cefuroxime were observed between males and females following a single IV bolus injection of 1000 mg of cefuroxime as the sodium salt.

Elderly:
Following IM or IV administration, the absorption, distribution and excretion of cefuroxime in elderly patients are similar to younger patients with equivalent renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in cefuroxime dose selection, and it may be useful to monitor renal function (see section 4.2).

Pediatrics:
The serum half-life of cefuroxime has been shown to be substantially prolonged in neonates according to gestational age. However, in older infants (aged >3 weeks) and in children, the serum half-life of 60 to 90 minutes is similar to that observed in adults.

Renal impairment:
Cefuroxime is primarily excreted by the kidneys. As with all such antibiotics, in patients with markedly impaired renal function (i.e. Clcr <20 ml/minute) it is recommended that the dosage of cefuroxime should be

reduced to compensate for its slower excretion (see section 4.2). Cefuroxime is effectively removed by hemodialysis and peritoneal dialysis.

Hepatic impairment:
Since cefuroxime is primarily eliminated by the kidney, hepatic dysfunction is not expected to have an effect on the pharmacokinetics of cefuroxime.

PK/PD relationship:
For cephalosporins, the most important pharmacokinetic-pharmacodynamic index correlating with *in vivo* efficacy has been shown to be the percentage of the dosing interval (%T) that the unbound concentration remains above the minimum inhibitory concentration (MIC) of cefuroxime for individual target species (i.e. %T>MIC).

5.3 Preclinical safety data
Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and toxicity to reproduction and development. No carcinogenicity studies have been performed; however, there is no evidence to suggest carcinogenic potential.
Gamma glutamyl transpeptidase activity in rat urine is inhibited by various cephalosporins; however, the level of inhibition is less with cefuroxime. This may have significance in the interference in clinical laboratory tests in humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
None.

6.2 Incompatibilities
Cefuroxime Devatis should not be mixed in the syringe with aminoglycoside antibiotics.
The pH of 2.74% w/v Sodium Bicarbonate Injection BP considerably affects the color of the solution and therefore this solution is not recommended for the dilution of cefuroxime. However, if required, for patients receiving Sodium Bicarbonate Injection by infusion the cefuroxime may be introduced into the tube of the giving set.

6.3 Shelf life
Dry Powder: 36 months

Reconstituted Suspension and Solution:
After constitution, *Cefuroxime Devatis Powder for Injection/Infusion* should be stored at 25°C for 5 hours and 2-8°C for no longer than 24 hours.

6.4 Special precautions for storage
Store at or below 25°C in the original package and protect from light.

6.5 Nature and contents of container
CEFUROXIME DEVATIS 250 mg Powder for Injection/Infusion is provided in a glass vial (8 ml) with grey bromobutyl rubber plug and aluminum cap with its accompanying leaflet in a carton box of 1, 5 or 10 vials.

CEFUROXIME DEVATIS 750 mg Powder for Injection/Infusion is provided in a glass vial (15 ml) with grey bromobutyl rubber plug and aluminum cap with its accompanying leaflet in a carton box of 1, 5 or 10 vials.

CEFUROXIME DEVATIS 1.5 g Powder for Injection/Infusion is provided in a glass vial (25 ml) with grey bromobutyl rubber plug and aluminum cap with its accompanying leaflet in a carton box of 1, 5 or 10 vials.

6.6. Special precautions for disposal and other handling

No special requirements for disposal.
Any unused product or waste material should be disposed of in accordance with local requirements.

Instructions for constitution

Vial size	Routes of administration	Amount of water to be added (m)
250 mg	Intramuscular	1 ml
	Intravenous bolus	at least 2 ml
	Intravenous infusion	at least 2 ml*
750 mg	Intramuscular	3 ml
	Intravenous bolus	at least 6 ml
	Intravenous infusion	at least 6 ml*
1.5 g	Intramuscular	6 ml
	Intravenous bolus	at least 15 ml
	Intravenous infusion	15 ml*

* Reconstituted solution to be added to 50 or 100 ml of compatible infusion fluid (see information on compatibility, below)

Compatibility

Cefuroxime Devatis (5 mg/ml) in 5% w/v or 10% w/v xylitol injection may be stored for up to 5 hours at 25°C, 24 hours when stored at 2–8°C.

Cefuroxime Devatis is compatible with the more commonly used intravenous infusion fluids. It will retain potency for up to 5 hours at 25°C, 24 hours when stored at 2–8°C in:

- 0.9% w/v Sodium Chloride Injection BP
- 5% Dextrose Injection BP
- 0.18% w/v Sodium Chloride plus 4% Dextrose Injection BP
- 5% Dextrose and 0.9% w/v Sodium Chloride Injection BP
- 5% Dextrose and 0.45% Sodium Chloride Injection
- 5% Dextrose and 0.225% Sodium Chloride Injection
- 10% Dextrose Injection
- Ringer's Injection USP
- Lactated Ringer's Injection USP

7. MEDICINE SCHEDULE

Prescription Only Medicine

8. SPONSOR

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9. DATE OF FIRST APPROVAL

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