NEW ZEALAND DATA SHEET

1. PRODUCT NAME

CEFTAZIDIME KABI ceftazidime (as pentahydrate) 1 g or 2 g powder for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

CEFTAZIDIME KABI powder for injection contains either 1 g or 2 g of ceftazidime (as pentahydrate).

For the full list of excipients, see section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Powder for injection.

Supplied as a white to pale yellow powder. On the addition of Water for Injections, Ceftazidime Kabi dissolves with effervescence to produce a solution for injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

CEFTAZIDIME KABI is indicated for the treatment of adults and children including neonates with single or multiple infections caused by susceptible organisms.

May be used alone as first choice medicine before the results of sensitivity tests are available.

May be used in combination with an aminoglycoside or most other beta-lactam antibiotics.

May be used with an antibiotic against anaerobes when the presence of *Bacteroides fragilis* is suspected.

Susceptibility to ceftazidime will vary with geography and time and local susceptibility data should be consulted where available (see section 5.1 Pharmacodynamic properties).

Indications include:

- Severe infections e.g.
  -septicaemia, bacteraemia, peritonitis, meningitis.

  -infections in immunosuppressed patients.

  -infections in patients in intensive care, e.g. infected burns.

- Respiratory tract infections including lung infections in cystic fibrosis.

- Ear, nose and throat infections.

- Urinary tract infections.

- Skin and soft tissue infections.

- Gastrointestinal, biliary and abdominal infections.

- Bone and joint infections.

- Infections associated with haemo- and peritoneal dialysis and with continuous ambulatory peritoneal dialysis (CAPD).

4.2 Dose and method of administration

Dose

Dosage depends upon the severity, sensitivity, site and type of infection and upon the age and renal function of the patient.

Adults:
1-6 g/day in 2 or 3 divided doses by intravenous (i.v.) or intramuscular (i.m.) injection.

Urinary tract and less severe infections:
500 mg or 1 g every 12 hours.

Most infections:
1 g every 8 hours or 2 g every 12 hours.

Very severe infections particularly in immunocompromised patients including those with neutropenia:
2 g every 8 or 12 hours, or 3 g every 12 hours.

Fibrocystic adults with pseudomonal lung infections:
100 to 150 mg/kg/day in three divided doses.

In adults with normal renal function 9 g/day has been used without ill effect.

Special Populations
Paediatric population

Infants and children (> 2 months):
30 to 100 mg/kg/day in two or three divided doses.

Doses up to 150 mg/kg/day (maximum 6 g/day) in three divided doses may be given to infected immunocompromised or fibrocystic children or children with meningitis.

Neonates (0 - 2 months):
25 to 60 mg/kg/day in two divided doses.

In neonates the serum half life of ceftazidime can be three to four times that in adults.

Elderly population

In view of the reduced clearance of ceftazidime in acutely ill elderly patients, the daily dosage should not normally exceed 3 g, especially in those over 80 years of age.

Renal Impairment

Ceftazidime is excreted unchanged by the kidneys. Therefore, in patients with impaired renal function the dosage should be reduced.

An initial loading dose of 1 g should be given. Maintenance doses should be based on creatinine clearance as shown in Table 1:

Table 1: Recommended maintenance doses of ceftazidime in renal insufficiency

Creatinine Clearance (mL/min)	**Approx. Serum creatinine (micromol/L) (mg/ dL)**	**Recommended unit dose of ceftazidime (g)**	**Frequency of dosing (hourly)**
> 50	< 150 (< 1.7)	Normal dosage	
50 to 31	150 to 200 (1.7 - 2.3)	1.0	12
30 to 16	200 to 350 (2.3 - 4.0)	1.0	24
15 to 6	350 to 500 (4.0 - 5.6)	0.5	24
< 5	> 500 (> 5.6)	0.5	48

In patients with severe infections the unit dose should be increased by 50% or the dosing frequency increased. In such patients the ceftazidime serum levels should be monitored and trough levels should not exceed 40 mg/L.

In children the creatinine clearance should be adjusted for body surface area or lean body mass.

Haemodialysis

The serum half-life during haemodialysis ranges from 3 to 5 hours.

Following each haemodialysis period the maintenance dose of ceftazidime recommended in the above table should be repeated.

Peritoneal dialysis

Ceftazidime may be used in peritoneal dialysis and continuous ambulatory peritoneal dialysis (CAPD).

In addition to intravenous use, ceftazidime can be incorporated into the dialysis fluid (usually 125 to 250 mg for 2 litres of dialysis solution).

For patients in renal failure on continuous arteriovenous haemodialysis or high-flux haemofiltration in intensive therapy units; 1 g daily either as a single dose or in

divided doses. For low-flux haemofiltration follow the dosage recommended under impaired renal function.

For patients on venovenous haemofiltration and venovenous haemodialysis, follow the dosage recommendations in table 2 and 3 below:

Table 2: Continuous venovenous haemofiltration dosage guidelines for ceftazidime

Residual renal function (creatinine clearance in mL/min)	Maintenance dose (mg) for an ultrafiltration rate (mL/min) of[a]:			
	5	16.7	33.3	50
0	250	250	500	500
5	250	250	500	500
10	250	500	500	750
15	250	500	500	750
20	500	500	500	750

[a]Maintenance dose to be administered every 12 hours.

Table 3: Ceftazidime dosage guidelines during continuous venovenous haemodialysis

Residual renal function (creatinine clearance in mL/min)	Maintenance dose (mg) for a dialysate inflow rate of[a]:					
	1.0 litres/h			2.0 litres/h		
	Ultrafiltration rate (litres/h)			Ultrafiltration rate (litres/h)		
	0.5	1.0	2.0	0.5	1.0	2.0
0	500	500	500	500	500	750
5	500	500	750	500	500	750
10	500	500	750	500	750	1000
15	500	750	750	750	750	1000
20	750	750	1000	750	750	1000

[a]Maintenance dose to be administered every 12 hours.

Method of Administration

Use CEFTAZIDIME KABI Injection intravenously or by deep intramuscular injection. Recommended i.m. injection sites are the upper outer quadrant of the gluteus maximus or lateral part of the thigh.

Ceftazidime solutions may be given directly into the vein or introduced into the tubing of a giving set if the patient is receiving parenteral fluids.

On the addition of Water for Injection, CEFTAZIDIME KABI dissolves with effervescence to produce a clear solution for injection or infusion.

For instructions on reconstitution of the medicine before administration, see section 6.6 Special precautions for disposal and other handling.

4.3 Contraindications

Patients with known hypersensitivity to cephalosporin antibiotics. Hypersensitivity to ceftazidime pentahydrate or to any of the excipients.

4.4 Special warnings and precautions for use

Before beginning treatment establish whether the patient has a history of hypersensitivity reactions to ceftazidime, cephalosporins, penicillins or other medicines. Special care is indicated in patients who have experienced an allergic reaction to penicillins or other beta-lactams. If an allergic reaction to ceftazidime occurs discontinue the medicine. Serious hypersensitivity reactions may require epinephrine (adrenaline), hydrocortisone, antihistamine or other emergency measures.

Concurrent treatment with high doses of cephalosporins and nephrotoxic medicines such as aminoglycosides or potent diuretics (e.g. frusemide) may adversely affect renal function. Clinical experience has shown that this is not likely to be a problem with ceftazidime at the recommended dose levels. There is no evidence that ceftazidime adversely affects renal function at normal therapeutic doses.

Ceftazidime is eliminated via the kidneys, therefore the dosage should be reduced according to the degree of renal impairment. Neurological sequelae have occasionally been reported when the dose has not been reduced in patients with renal impairment (see section 4.2 Dose and method of administration and section 4.8 Undesirable effects).

As with other broad spectrum antibiotics, prolonged use may result in the overgrowth of non-susceptible organisms (e.g. Candida, enterococci) which may require interruption of treatment or appropriate measures. Repeated evaluation of the patient's condition is essential.

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 diarrhoea during or after antibiotic use. If prolonged or significant diarrhoea occurs or the patient experiences abdominal cramps, treatment should be discontinued immediately and the patient investigated further.

As with other extended-spectrum cephalosporins and penicillins, some initially susceptible strains of Enterobacter spp. and Serratia spp. may develop resistance during ceftazidime therapy. When clinically appropriate during therapy of such infections, periodic susceptibility testing should be considered.

Neurotoxicity

There have been reports of neurotoxicity associated with cephalosporin treatment. Symptoms of neurotoxicity include encephalopathy, seizures and/or myoclonus. Risk factors for developing neurotoxicity with cephalosporin treatment include being elderly, renal impairment, central nervous system disorders and intravenous administration. Withdrawal of the medicine should be considered if there are signs of neurotoxicity.

Each 1 g of ceftazidime contains 52 mg of sodium. The sodium content must be taken into account in patients requiring sodium restriction.

4.5 Interaction with other medicines and other forms of interaction

Concurrent use of high doses with nephrotoxic medicines may adversely affect renal function (see section 4.4 Special warnings and precautions for use).

Chloramphenicol is antagonistic in vitro with ceftazidime and other cephalosporins. The clinical relevance of this finding is unknown, but if concurrent administration of ceftazidime with chloramphenicol is proposed, the possibility of antagonism should be considered.

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

Ceftazidime does not interfere with enzyme-based tests for glycosuria but slight interference may occur with copper reduction methods (Benedict's, Fehling's, Clinitest).

Ceftazidime does not interfere in the alkaline picrate assay for creatinine.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is no experimental evidence of embryopathic or teratogenic effects, but as with all medicines, ceftazidime should be administered with caution during the early months of pregnancy and early infancy.

Breast-feeding

Ceftazidime is excreted in human milk in small quantities and should be used with caution in breast feeding.

Fertility

No data available.

4.7 Effect on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, undesirable effects may occur (e.g. dizziness), which may influence the ability to drive and use machines.

4.8 Undesirable effects

Data from large clinical trials (internal and published) were used to determine the frequency of very common to uncommon undesirable effects. The frequencies assigned to all other undesirable effects 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 ≥1/10,000 to <1/1000,
very rare <1/10,000.

Infections and infestations

Uncommon: Candidiasis (including vaginitis and oral thrush).

Blood and lymphatic system disorders

Common: Eosinophilia and thrombocytosis.

Uncommon: Leucopenia, neutropenia, and thrombocytopenia.

Very Rare: Lymphocytosis, haemolytic anaemia, and agranulocytosis.

Immune system disorders

Very Rare: Anaphylaxis (including bronchospasm and/or hypotension).

Nervous system disorders
Uncommon: Headache and dizziness.

Very Rare: Paraesthesia.

There have been reports of neurological sequelae including tremor, myoclonia, convulsions, encephalopathy, and coma in patients with renal impairment in whom the dose of ceftazidime has not been appropriately reduced.

Vascular disorders

Common: Phlebitis or thrombophlebitis with i.v. administration.

Gastrointestinal disorders

Common: Diarrhoea.

Uncommon: Nausea, vomiting, abdominal pain, and colitis.

Very Rare: Bad taste.

As with other cephalosporins, colitis may be associated with Clostridium difficile and may present as pseudomembranous colitis (see section 4.4 Special warnings and precautions for use).

Hepatobiliary disorders

Common: Transient elevations in one or more of the hepatic enzymes, ALT (SGPT), AST (SOGT), LDH, GGT and alkaline phosphatase

Very Rare: Jaundice

Skin and subcutaneous tissue disorders

Common: Maculopapular or urticarial rash.

Uncommon: Pruritus.

Very Rare: Angioedema, erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis.

General disorders and administration site conditions

Common: Pain and/or inflammation after i.m. injection.

Uncommon: Fever.

Investigations

Common: Positive Coombs test.

Uncommon: As with some other cephalosporins, transient elevations of blood urea, blood urea nitrogen and/or serum creatinine have been observed.

A positive Coombs test develops in about 5% of patients and may interfere with blood cross-matching.

Reporting of suspected adverse reactions

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 via: https://nzphvc.otago.ac.nz/reporting.

4.9 Overdose

Overdosage can lead to neurological sequelae including encephalopathy, convulsions and coma. Serum levels of ceftazidime can be reduced by haemodialysis 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: Anti-bacterials for systemic use. Third-generation cephalosporins, ATC code: J01DD02.

The prevalence of acquired resistance is geographically and time dependent and for select species may be very high. Local information on resistance and prevalence of extended spectrum beta lactamase (ESBLs) producing organisms is desirable, particularly when treating severe infections.

***In vitro* susceptibility of micro-organisms to Ceftazidime** Where clinical efficacy of ceftazidime has been demonstrated in clinical trials this is indicated with an asterisk (*).
Commonly Susceptible Species
Gram-positive aerobes:
Beta-hemolytic streptococci* *Staphylococcus aureus* (methicillin susceptible)* *Coagulase negative staphylococcus* (methicillin susceptible)
Gram-negative aerobes:
*Haemophilus influenzae** including ampicillin-resistant strains *Haemophilus parainfluenzae* *Neisseria gonorrhoeae* *Neisseria meningitidis** *Pasteurella multocida Proteus* spp.* *Providencia* spp. *Salmonella* spp. *Shigella* spp.
Species for which acquired resistance may be a problem
Gram-negative aerobes:
Acinetobacter spp. *Burkholderia cepacian* *Citrobacter* spp.* *Enterobacter* spp.* *Escherichia coli** *Klebsiella* spp. including *K. pneumoniae** *Pseudomonas* spp. including *P. aeruginosa** *Serratia* spp.* *Morganella morganii* *Yersinia enterocolitica*
Gram-positive aerobes:
*Streptococcus pneumoniae** Viridans group streptococcus
Gram-positive anaerobes:
Clostridium spp. not including *C. difficile* *Peptostreptococcus* spp. *Propionibacterium* spp.
Gram-negative anaerobes:
Fusobacterium spp.
Inherently resistant organisms
Gram-positive aerobes:
Enterococcus spp. including *E. faecalis* and *E. faecium Listeria* spp.
Gram-negative aerobes:
Campylobacter spp.
Gram-positive anaerobes:
Clostridium difficile
Gram-negative anaerobes:
Bacteroides spp. including *B. fragilis*
Others:
Chlamydia spp. *Mycoplasma* spp. *Legionella* spp.

5.2 Pharmacokinetic Properties

Absorption

After i.m. administration of 500 mg and 1 g, peak levels of 18 and 37 mg/L respectively are rapidly achieved and 5 minutes after i.v. bolus injection of 500 mg, 1 g or 2 g, serum levels are respectively 46, 87 and 170 mg/L.

Distribution

Therapeutically effective concentrations are still present in the serum 8 to 12 hours after either i.v. or i.m. administration. Serum protein binding is about 10%.
Concentrations in excess of the MIC for common pathogens can be achieved in tissues such as bone, heart, bile, sputum, aqueous humour, synovial, pleural and peritoneal fluids. Ceftazidime crosses the placenta readily, and is excreted in the breast milk. Penetration of the intact blood-brain barrier is poor resulting in low levels of ceftazidime in the cerebral spinal fluid (CSF) in the absence of inflammation.
However, therapeutic levels of 4 to 20 mg/L or more are achieved in the CSF when the meninges are inflamed.

Biotransformation

Ceftazidime is not metabolised in the body.

Elimination
Parenteral administration produces high and prolonged serum levels which decrease with a half-life of about 2 hours. Ceftazidime is excreted unchanged, in active form into the urine by glomerular filtration; approximately 80 to 90% of the dose is recovered in the urine within 24 hours. Elimination of ceftazidime is decreased in patients with impaired renal function and the dose should be reduced (see section 4.2 Dose and method of administration - Renal impairment). Less than 1% is excreted via the bile, which limits the amount entering the bowel.

5.3 Preclinical Safety Data

Non-clinical data reveal no special hazard for humans based on studies of safety pharmacology, repeat dose toxicity, genotoxicity, toxicity to reproduction.
Carcinogenicity studies have not been performed with ceftazidime.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Sodium carbonate (anhydrous) (121.2 mg sodium carbonate per gram of ceftazidime).

6.2 Incompatibilities

Ceftazidime is less stable in Sodium Bicarbonate Injection than in other i.v. fluids. It is not recommended as a diluent. Ceftazidime and aminoglycosides should not be mixed in the same giving set or syringe. Precipitation has been reported when vancomycin has been added to ceftazidime in solution. Therefore, it would be prudent to flush giving sets and intravenous lines between administration of these two agents.

6.3 Shelf Life

30 months

6.4 Special Precautions for Storage

Vials of CEFTAZIDIME KABI for Injection should be stored at room temperature below 25ºC.

Protect from light.

6.5 Nature and contents of container

Each vial of unreconstituted Ceftazidime Kabi contains a white or pale yellow powder containing 1 g or 2 g ceftazidime (as pentahydrate).

Packs of 1, 5 and 10.

Not all strengths and/or pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Ceftazidime is compatible with most commonly used i.v. fluids. However, Sodium Bicarbonate Injection is not recommended as a diluent (see section 6.2 Incompatibilities).

All sizes of vials of CEFTAZIDIME KABI for Injection are supplied under reduced pressure. As the product dissolves, carbon dioxide is released and a positive pressure develops. Small bubbles of carbon dioxide in the constituted solution may be ignored.

Instructions for reconstitution

Table 4: Instructions for reconstitution

Vial Size		Amount of Diluent to be added (mL)	Approximate Concentration (mg/mL)
500 mg	Intramuscular	1.5 mL	260
	Intravenous	5 mL	90
1 g	Intramuscular	3 mL	260
	Intravenous bolus	10 mL	90
	Intravenous infusion	50 mL #	20
2 g	Intravenous bolus	10 mL	170
	Intravenous infusion	50 mL #	40

NOTE: Addition should be in two stages (see text).

Solutions range from light yellow to amber depending on concentration, diluent and storage conditions used. Within the stated recommendations, product potency is not adversely affected by such colour variations.

Ceftazidime at concentrations between 1 mg/mL and 40 mg/mL is compatible with:

- 0.9% Sodium Chloride Injection.

- M/6 Sodium Lactate Injection.

- Compound Sodium Lactate Injection (Hartmann's Solution).
- 5% Dextrose Injection.
- 0.225% Sodium Chloride and 5% Dextrose Injection.
- 0.45% Sodium Chloride and 5% Dextrose Injection.
- 0.9% Sodium Chloride and 5% Dextrose Injection.
- 0.18% Sodium Chloride and 4% Dextrose Injection.
- 10% Dextrose Injection.
- Dextran 40 Injection 10% in 0.9% Sodium Chloride Injection.
- Dextran 40 Injection 10% in 5% Dextrose Injection.
- Dextran 70 Injection 6% in 0.9% Sodium Chloride Injection.
- Dextran 70 Injection 6% in 5% Dextrose Injection.

Ceftazidime at concentrations between 0.05 mg/mL and 0.25 mg/mL is compatible with Intra-peritoneal Dialysis Fluid (Lactate).

Ceftazidime may be constituted for intramuscular use with 0.5% or 1% Lignocaine Hydrochloride Injection.

Both components retain satisfactory potency when ceftazidime at 4 mg/mL is admixed with:

- Hydrocortisone (hydrocortisone sodium phosphate) 1 mg/mL in 0.9% Sodium Chloride Injection or 5% Dextrose Injection.
- Cefuroxime (cefuroxime sodium) 3 mg/mL in 0.9% Sodium Chloride Injection.
- Cloxacillin (cloxacillin sodium) 4 mg/mL in 0.9% Sodium Chloride Injection.
- Heparin 10 IU/mL or 50 IU/mL in 0.9% Sodium Chloride Injection.
- Potassium Chloride 10 mEq/L or 40 mEq/L in 0.9% Sodium Chloride Injection.

<u>Preparation of solutions for i.m. or i.v. bolus injection:</u>

1. Introduce the syringe needle through the vial closure and inject the recommended volume of diluent.
2. Withdraw the needle and shake the vial to give a clear solution.
3. Invert the vial. With the syringe piston fully depressed insert the needle into the solution. Withdraw the total volume of solution into the syringe ensuring that the needle remains in the solution. Small bubbles of carbon dioxide may be disregarded.

Preparation of solutions for i.v. infusion from CEFTAZIDIME KABI Injection (mini-bag or burette- type set):

Prepare using a total of 50 mL of compatible diluent, added in TWO stages as

below: 1 g and 2 g vials for i.v. infusion-

1. Introduce the syringe needle through the vial closure and inject 10 mL of diluent for the 1 g and 2 g vials.

2. Withdraw the needle and shake the vial to give a clear solution.

3. Do not insert a gas relief needle until the product has dissolved. Insert a gas relief needle through the vial closure to relieve the internal pressure.

4. Transfer the reconstituted solution to final delivery vehicle (e.g. mini-bag or burette-type set) making up a total volume of at least 50 ml and administer by intravenous infusion over 15-30 minutes.

NOTE: To preserve product sterility, it is important that the gas relief needle is not inserted through the vial closure before the product has dissolved.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Fresenius Kabi New Zealand Limited
C/o GNZCC, HSBC Tower, Level 14, 188 Quay street Auckland 1010.
New Zealand

Freecall: 0800 144 892

9. DATE OF FIRST APPROVAL

21 May 2019

10. DATE OF REVISION OF THE TEXT

17June 2024

Summary table of changes:

Section Changed	Summary of new information
4.4	Addition of neurotoxicity warning section