PROFESSIONAL INFORMATION

SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

CEFTAZIDIME 500 mg FRESENIUS Powder for solution for Injection

CEFTAZIDIME 1 000 mg FRESENIUS Powder for solution for Injection

CEFTAZIDIME 2 000 mg FRESENIUS Powder for solution for Injection or Infusion

2. QUALITITATIVE AND QUANTITATIVE COMPOSITION

CEFTAZIDIME 500 mg FRESENIUS:

Each vial contains 500 mg ceftazidime (as ceftazidime.5H_2O)

Sodium content: 1,1 mmol (26 mg) sodium

CEFTAZIDIME 1 000 mg FRESENIUS:

Each vial contains 1000 mg ceftazidime (as ceftazidime.5H_2O)

Sodium content: 2,3 mmol (52 mg) sodium

CEFTAZIDIME 2 000 mg FRESENIUS:

Each infusion bottle contains 2000 mg ceftazidime (as ceftazidime.5H_2O)

Sodium content: 4,6 mmol (104 mg) sodium

Sugar free.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection

A white to yellowish powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

CEFTAZIDIME FRESENIUS is indicated for the treatment of the following infections when caused by susceptible organisms:

Severe infections including: septicaemia, bacteraemia, peritonitis, and in immunocompromised patients, caused by *Streptococcus pyogenes*, *Streptococcus* Group B, *Streptococcus pneumoniae*, *Streptococcus mitis*, *Streptococcus* spp., *Escherichia coli*, *Haemophilus influenzae*, *Klebsiella pneumoniae*, *Salmonella* spp., *Acinetobacter* spp., *Yersinia enterocolitica*, or *Pasteurella multocida*.

- **Respiratory tract infections such as pneumonia, bronchopneumonia, and bronchitis including lung infections in patients with cystic fibrosis**, caused by *Streptococcus pneumoniae*, *Haemophilus influenzae, Klebsiella pneumoniae, Haemophilus parainfluenzae, Escherichia coli, Streptococcus pyogenes, Proteus mirabilis, Serratia* spp., or *Enterobacter* spp.
- **Ear, nose and throat infections**, caused by *Streptococcus pneumoniae*, *Haemophilus influenzae, Klebsiella pneumoniae, Haemophilus parainfluenzae, Escherichia coli, Streptococcus pyogenes, Proteus mirabilis, Serratia* spp., or *Enterobacter* spp.
- **Urinary tract infections**, caused by *Neisseria gonorrhoeae, Escherichia coli, Proteus mirabilis, Klebsiella pneumoniae, Proteus vulgaris, Morganella morganii, Enterobacter* spp., or *Citrobacter* spp.
- **Skin and soft tissue infections**, caused by *Streptococcus pyogenes, Streptococcus* spp., *Escherichia coli, Enterobacter* spp., *Klebsiella pneumoniae, Proteus mirabilis*, or *Morganella morganii*.
- **Gastrointestinal, biliary and abdominal infections**, caused by *Escherichia coli, Klebsiella pneumoniae, Streptococcus* spp., *Salmonella* spp., *Shigella* spp., or *Yersinia enterocolitica*.

4.2 Posology and method of administration

Posology

General dosage recommendations:

CEFTAZIDIME FRESENIUS is to be used by the parenteral route, the dosage depends upon the severity, sensitivity and type of infection and the age, mass and renal function of the patient.

Adults:

The adult dosage range for CEFTAZIDIME FRESENIUS is 1 to 6 g per day: for instance, 1 g or 2 g given 12 or 8 hourly by IV or IM injection. In urinary tract infections and in many less serious infections, 500 mg or 1 g, 12 hourly is usually adequate. In the majority of infections, 1 g, 8 hourly or 2 g, 12 hourly should be given. In very severe infections, especially in immunocompromised patients, including those with neutropenia, 2 g, 8 or 12 hourly should be administered.

Special populations

Cystic fibrosis:

In fibrocystic adults with normal renal function who have pseudomonal lung infections, high doses of 100 to 150 mg/kg/day as three divided doses should be used. In adults with normal renal function 9 g/day has been used.

Use in elderly:

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.

Dosage in impaired renal function:

CEFTAZIDIME FRESENIUS is excreted by the kidneys almost exclusively by glomerular filtration. Therefore, in patients with impaired renal function it is recommended that the dosage of CEFTAZIDIME FRESENIUS should be reduced to compensate for its slower excretion, except in mild impairment, i.e. glomerular filtration rate (GFR) greater than 50 mL/min. In patients with suspected renal insufficiency, and initial loading dose of 1 g of CEFTAZIDIME

FRESENIUS may be given. An estimate of GFR should be made to determine the appropriate maintenance dose.

Recommended maintenance doses are shown below:

Recommended maintenance doses of CEFTAZIDIME FRESENIUS in renal insufficiency

Creatinine clearance mL/min**	**Approx. serum creatinine* µmol/l (mg/dl)**	**Recommended unit dose CEFTAZIDIME FRESENIUS (g)**	**Frequency of dosing (hourly)**
50 – 31	150 – 200 (1,7 – 2,3)	1	12
30 – 16	200 – 350 (2,3 – 4,0)	1	24
15 – 6	350 – 500 (4,0 – 5,6)	0,5	24
< 5	> 500 (> 5,6)	0,5	48

* The serum creatinine values are approximate values and do not indicate the same degree of impairment for all patients with impaired renal function; this applies especially to elderly patients in which the renal function is over-rated on the basis of the serum creatinine concentration.

** Relative to the body surface

Patients with severe infections, especially neutropenic patients, who would normally receive 6 g of CEFTAZIDIME FRESENIUS daily were it not for renal insufficiency, the unit dose given in the table above may be increased by 50 % or the dosing frequency increased appropriately. In such patients it is recommended that ceftazidime serum levels should be monitored and trough levels should not exceed 40 mg/l. When only serum creatinine is available, the following formula (Cockcroft's equation) may be used to estimate creatinine clearance. The serum creatinine should represent a steady state of renal function:

Creatinine clearance (mL/min) =

Males:

[140 – age] x mass (kg)

Scr($\mu mol/l$)

Females: multiply by 0,85

In children the creatinine clearance should be adjusted for body surface area or lean body mass and the dosing frequency reduced in cases of renal insufficiency as for adults. The serum half-life of ceftazidime during haemodialysis ranges from 3 to 5 hours. The appropriate maintenance dose of CEFTAZIDIME FRESENIUS should be repeated following each haemodialysis period.

Paediatric population

Infants and children (> 2 months):

The usual dosage range for children aged over two months is 30 to 100 mg/kg/day, given as two or three divided doses. The dosage for children over 2 months but under 1 year is generally 25 to 50 mg/kg twice daily. Doses up to 50 mg/kg three times per day, to a maximum of 6 g daily, may be given to infected immunocompromised or fibrocystic children.

Neonates (and children) up to 2 months of age:

Whilst clinical experience is limited, a dose of 60 mg/kg/day given as two divided doses has proved to be effective. In the neonate the serum half-life of ceftazidime can be three to four times that in adults.

Method of administration

CEFTAZIDIME FRESENIUS may be given intravenously or by deep intramuscular injection into a large muscle mass such as the upper outer quadrant of the gluteus maximus or lateral part of the thigh.

For single use only.

Any remaining solution must be discarded.

Only clear solutions practically free from particles should be used.

For instructions on reconstitution and dilution before administration of CEFTAZIDIME FRESENIUS, see section 6.6.

4.3 Contraindications

- Hypersensitivity to ceftazidime, cephalosporin antibiotics or to any of the excipients in CEFTAZIDIME FRESENIUS.
- Immediate and severe hypersensitivity (e.g. anaphylactic reaction) to any other type of β-lactam antibacterial medicine (e.g. penicillins, monobactams or carbapenems).

4.4 Special warnings and precautions for use

Antibiotic stewardship

Prescribers should adhere to the principles of antimicrobial stewardship.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of CEFTAZIDIME FRESENIUS, it should be used to treat only indicated infections that are proven or strongly suspected to be caused by susceptible bacteria. It is recommended that CEFTAZIDIME FRESENIUS be used only after consultation with a medical practitioner with appropriate experience in the management of infectious diseases.

Hypersensitivity reactions

Serious and occasionally fatal hypersensitivity reactions have been reported. In severe hypersensitivity reactions, treatment with CEFTAZIDIME FRESENIUS must be discontinued immediately and adequate emergency measures must be initiated.

Before beginning treatment, it should be established whether the patient has a history of severe hypersensitivity reactions to ceftazidime, to other cephalosporins or to any other type of β-lactam medicine. Caution should be used if CEFTAZIDIME FRESENIUS is given to patients with a history of non-severe hypersensitivity to other β-lactam medicines.

***Clostridium difficile*-associated diarrhoea**

Antibacterial medicine-associated colitis and pseudo-membranous colitis have been reported with CEFTAZIDIME FRESENIUS and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea during or subsequent to the administration of CEFTAZIDIME FRESENIUS (see section 4.8). Discontinuation of therapy with CEFTAZIDIME FRESENIUS and the administration of specific

treatment for Clostridium difficile should be considered. Medicines that inhibit peristalsis should not be given.

Patients with renal impairment

Ceftazidime is eliminated via the kidneys; therefore, the dose of CEFTAZIDIME FRESENIUS should be reduced according to the degree of renal impairment. Patients with renal impairment should be closely monitored for both safety and efficacy. Neurological sequelae, including tremor, myoclonus, non-convulsive status epilepticus, convulsion, encephalopathy and coma, have been reported with ceftazidime when the dose has not been reduced in patients with renal impairment (see section 4.2).

Concurrent treatment with high doses of cephalosporins and nephrotoxic medicines such as aminoglycosides or potent diuretics (e.g. furosemide) may adversely affect renal function.

Non-susceptible organisms

Prolonged use of CEFTAZIDIME FRESENIUS may result in the overgrowth of non-susceptible organisms (e.g. enterococci, fungi), which may require interruption of treatment or other appropriate measures.

Non-medicine interference

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

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

Direct antiglobulin test (DAGT or Coombs test) seroconversion and potential risk of haemolytic anaemia

Positive results to be direct antiglobulin test (DAGT, or Coombs test) have been found during treatment with CEFTAZIDIME FRESENIUS and these can interfere with blood cross matching and/or may cause medicine induced immune haemolytic anaemia.

While DAGT seroconversion in patients receiving CEFTAZIDIME FRESENIUS was frequent in clinical studies, there was no evidence of haemolysis in patients who developed a positive DAGT on treatment (see section 4.8). However, the possibility that haemolytic anaemia could

occur in association with CEFTAZIDIME FRESENIUS treatment cannot be ruled out. Patients experiencing anaemia during or after treatment with CEFTAZIDIME FRESENIUS should be investigated for this possibility.

Controlled sodium diet

The sodium content of the medicinal product (26 mg sodium for CEFTAZIDIME 500 mg FRESENIUS, 52 mg sodium for CEFTAZIDIME 1 000 mg FRESENIUS and 104 mg sodium for CEFTAZIDIME 2 000 mg FRESENIUS) should be considered for patients who are on a controlled sodium diet.

Paediatric population

There is a potential risk of overdosing, particularly for paediatric patients aged from 3 to less than 12 months of age. Care should be taken when calculating the volume of administration of the dose (see section 4.2).

4.5 Interaction with other medicines and other forms of interaction

The concomitant use of a nephrotoxic medicine such as the aminoglycoside gentamicin may increase the risk of kidney damage with CEFTAZIDIME FRESENIUS. There is also some evidence for enhanced nephrotoxicity with a loop diuretic like furosemide.

The renal excretion of CEFTAZIDIME FRESENIUS is inhibited by probenecid.

There may be antagonism between CEFTAZIDIME FRESENIUS and bacteriostatic antibacterial agents. Chloramphenicol is antagonistic *in vitro* with ceftazidime and other cephalosporins. The clinical relevance of this finding is unknown, but if concurrent administration of CEFTAZIDIME FRESENIUS with chloramphenicol is proposed, the possibility of antagonism should be considered.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety in pregnancy has not been established.

CEFTAZIDIME FRESENIUS should not be used during pregnancy unless clearly necessary.

Breastfeeding

Safety of breastfeeding has not been established.

Ceftazidime is excreted in human milk. Women receiving CEFTAZIDIME FRESENIUS should not breastfeed their infants.

Fertility

The effects of ceftazidime on fertility in humans have not been studied. Animal studies with ceftazidime do not indicate harmful effects with respect to fertility.

4.7 Effects on ability to drive or use machines

Undesirable effects may occur (e.g. dizziness), which may influence the ability to drive and use machines (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

The most frequent adverse reactions are eosinophilia, thrombocytosis, phlebitis or thrombophlebitis with intravenous administration, diarrhoea, transient increases in hepatic enzymes, maculopapular or urticarial rash, pain and/or inflammation following intramuscular injection and positive antiglobulin test (DAGT).

Tabulated list of adverse reactions

System organ class/frequency	**Adverse reaction**
Infections and infestations	
Frequent:	Candidiasis (including vulvovaginal candidiasis and oral candidiasis), vaginitis.
Less frequent:	*Clostridium difficile* colitis, pseudomembranous colitis
Blood and lymphatic system disorders	
Frequent:	Positive direct antiglobulin test (DAGT) (see section 4.4), eosinophilia, thrombocytosis, thrombocytopenia

Less frequent:	Neutropenia, leukopenia, lymphocytosis
Frequency unknown**:**	Agranulocytosis, haemolytic anaemia
Immune system disorders	
Frequent:	Hypersensitivity reactions
Frequency unknown:	Anaphylaxis
Nervous system disorders	
Frequent:	Headache, dizziness
Less frequent:	Paraesthesia
Frequency unknown:	Convulsions and other signs of CNS toxicity, especially in patients with severe renal impairment
Gastrointestinal disorders	
Frequent:	Diarrhoea, abdominal pain, nausea, vomiting
Less frequent:	Dysgeusia
Frequency unknown:	Prolonged use may result in overgrowth of non-susceptible organisms.
Hepatobiliary disorders	
Frequent:	Increased alanine aminotransferase, increased aspartate aminotransferase, increased blood alkaline phosphatase, increased Gamma-glutamyltransferase, increased blood lactate dehydrogenase
Frequency unknown:	Hepatitis and cholestatic jaundice
Skin and subcutaneous tissue disorders	
Frequent:	Maculopapular rash, urticaria, pruritus
Frequency unknown:	Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis, angioedema, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
Renal and urinary disorders	
Less frequent:	Increased blood creatinine, increased blood urea, acute

	kidney injury, tubulointerstitial nephritis
General disorders and administration site conditions	
Frequent:	Infusion site thrombosis, infusion site phlebitis, pyrexia
Frequency unknown:	Pain and/or inflammation at the injection site following intramuscular administration

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. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

Healthcare providers are asked to report any suspected adverse drug reactions to the Holder of the Certificate of Registration at the following email address: safety.fksa@fresenius-kabi.com and to the relevant medicine's regulatory authority in the country where the product is marketed.

4.9 Overdose

See section 4.8.

Overdosage can lead to neurological sequelae including encephalopathy, convulsions and coma.

Serum levels of CEFTAZIDIME FRESENIUS are reduced by dialysis.

Treatment is supportive and symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 20.1.1 – Broad and medium spectrum antibiotics

Pharmacotherapeutic group: Antibacterials for systemic use. Third-generation cephalosporins

ATC code: J01DD02

Ceftazidime is a bactericidal cephalosporin antibiotic.

Bacteriology:

Ceftazidime is bactericidal in action, exerting its effect on target cell wall proteins and causing inhibition of cell wall synthesis. A wide range of pathogenic strains and isolates associated with hospital acquired infections are susceptible to ceftazidime *in vitro*, including resistant strains and multi-resistant strains. It is stable to most clinically important beta-lactamases produced by both Gram-negative and Gram-positive organisms including multi-resistant strains. Ceftazidime has high intrinsic activity *in vitro* and acts with few changes in minimum inhibitory concentration (MIC) at varied inoculum levels.

Ceftazidime is not active against the following bacteria:

Methicillin-resistant staphylococci, *Enterococcus (Streptococcus) faecalis*, *Clostridium difficile, Listeria monocytogenes, Campylobacter* spp.

5.2 Pharmacokinetic properties

In healthy subjects, the serum half-life of ceftazidime is 1,8 hours (1,5 to 2 hours) and only slightly altered by dosage or route of administration. The half-life is prolonged in patients with impaired renal function. Ceftazidime has a low serum protein binding (10 %).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Anhydrous sodium carbonate

6.2 Incompatibilities

CEFTAZIDIME FRESENIUS is incompatible with vancomycin and is less stable in Sodium Bicarbonate Injection than in other intravenous fluids.

6.3 Shelf life

36 months

Reconstituted solution:

Chemical and physical in use stability has been demonstrated up to 6 hours at 25 ºC and 12 hours at 5 ºC after reconstitution of the product with water for injection, 1 % lidocaine (lignocaine) solution, 0,9 % sodium chloride solution, ringer lactate and 10 % glucose solution.

From a microbiological point of view, the product should be used immediately.

6.4 Special precautions for storage

Sterile powder:

Store at or below 25 °C. Keep the vials in outer carton to protect from light.

Reconstituted product:

For storage conditions after reconstitution of the product, see section 6.3.

6.5 Nature and contents of container

CEFTAZIDIME 500 mg FRESENIUS:

10 mL type II, clear colourless glass vial closed with red and dark grey rubber stoppers and green aluminium/plastic caps, in packs of 1 and 10.

CEFTAZIDIME 1 000 mg FRESENIUS:

10 mL type II, clear colourless glass vials closed with red and dark grey rubber stoppers and blue aluminium/plastic caps, in packs of 1 and 10.

CEFTAZIDIME 2 000 mg FRESENIUS:

50 mL type II, clear colourless glass infusion bottles closed with red and dark grey rubber stoppers and red aluminium/plastic caps, in packs of 1 and 10.

Packed in 1's or 10's in cardboard carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

This medicinal product is for single use only. Discard any remaining reconstituted solution.

Instructions for reconstitution:

See table for addition volumes and solution concentrations.

Preparation of solutions of CEFTAZIDIME FRESENIUS:

	AMOUNT OF SOLVENT TO BE ADDED (mL)	APPROXIMATE CEFTAZIDIME FRESENIUS CONCENTRATION (mg/mL)
500 mg		
Intramuscular	1,5	260
Intravenous	5,0	90
1 g		
Intramuscular	3,0	260
Intravenous	10,0	90
2 g		
IV bolus	10,0	170
Infusion	50,0*	40

* Addition should be in 2 stages (see below)

All sizes of vials as supplied are under reduced pressure. As the product dissolves carbon dioxide is released and a positive pressure develops. For ease of use, it is recommended that the following techniques of reconstitution are adopted.

500 mg IM/IV and 1 g IM/IV:

1. Inject the diluent and shake well to dissolve. The vial may contain a vacuum to assist injection of the diluent.
2. Carbon dioxide is released as the antibiotic dissolves, generating pressure. The solution will dissolve within 1-2 minutes.
3. Invert the vial and completely depress the syringe plunger prior to insertion.
4. Insert the needle through the stopper. Make sure the needle remains within the solution.
5. The withdrawn solution may contain carbon dioxide bubbles, which must be expelled before injection.

2 g infusion bottle:

1. Inject 10 mL of the diluent and shake well to dissolve. The vial may contain a vacuum to assist injection of the diluent.

2. Carbon dioxide is released as the antibiotic dissolves, generating pressure. The solution will dissolve within 1-2 minutes.
3. Insert a vent needle to release pressure before adding additional diluent to the infusion bottle. Add diluent and then remove the vent needle.
4. Additional pressure that may develop in the infusion bottle, especially after storage, should be relieved prior to administration.

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

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

Compatibility

CEFTAZIDIME FRESENIUS is compatible with the most commonly used intravenous fluids (see below).

At concentrations between 40 mg/mL and 333,3 mg/mL, CEFTAZIDIME FRESENIUS may be mixed in commonly used solutions for infusion:

- 0,9 % sodium chloride solution (physiological saline solution)
- Ringer lactate solution
- 10 % glucose solution

When reconstituted for intramuscular use, CEFTAZIDIME FRESENIUS can also be diluted with 1 % lidocaine (lignocaine) solution.

Only clear solutions practically free from particles should be used.

7. HOLDER OF CERTIFICATE OF REGISTRATION

FRESENIUS KABI SOUTH AFRICA (PTY) LIMITED

Stand 7, Growthpoint Business Park

162 Tonetti Street

Halfway House extension 7

Midrand, Gauteng

1685

SOUTH AFRICA

Telephone number: (011) 545 0000

8. REGISTRATION NUMBERS

CEFTAZIDIME 500 mg FRESENIUS: 43/20.1.1/0553

CEFTAZIDIME 1 000 mg FRESENIUS: 43/20.1.1/0554

CEFTAZIDIME 2 000 mg FRESENIUS: 43/20.1.1/0555

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15 August 2013

10. DATE OF REVISION OF THE TEXT

09 March 2023