FRESENIUS KABI

CÓDIGO: *Code*	XXXXXX	**DESIGNAÇÃO:** *Name*	LIT.CEFTAZIDIME FKSG	**ELABORADO POR:** *Made by*	José Duarte
VERSÃO: *Version*	/XX	**PROVA:** *Proof*	02	**DATA:** *Date*	28 Jul. 2016
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CORES: *Colours*
- Black
- *Cut*

Anexo 6.00 do PT.G.087

PACKAGE INSERT
- INSTRUCTIONS FOR USE - READ CAREFULLY!

Ceftazidime Kabi
Powder for Solution for Injection 1g/vial

Ceftazidime Kabi
Powder for Solution for Injection 2g/vial

Composition

Ceftazidime Kabi 500 mg powder for solution for injection
Each vial contains 500 mg of ceftazidime (as Ceftazidime pentahydrate with sodium carbonate for injection)
Excipient: This medicinal product contains 1.1 mmol (26 mg) sodium for 500 mg Ceftazidime.

Ceftazidime Kabi 1000 mg powder for solution for injection
Each vial contains 1000 mg of ceftazidime (as Ceftazidime pentahydrate with sodium carbonate for injection)
Excipient: This medicinal product contains 2.3 mmol (52 mg) sodium for 1000 mg Ceftazidime.

Ceftazidime Kabi 2000 mg powder for solution for injection or infusion
Each vial contains 2000 mg of ceftazidime (as Ceftazidime pentahydrate with sodium carbonate for injection)
Excipient: This medicinal product contains 4.6 mmol (104 mg) sodium for 2000 mg Ceftazidime.

Pharmaceutical form

Powder for solution for injection.
Powder for solution for injection or infusion.

White to yellowish powder

Address of the pharmaceutical company

Fresenius Kabi Deutschland GmbH
D-61346 Bad Homburg v.d.H.
Germany

Manufacturers:
Labesfal Laboratorios Almiro S.A.
Fresenius Kabi Group
3465-157 Santiago de Besteiros
Portugal

Therapeutic indications

Ceftazidime is indicated for the treatment of single or multiple infections caused by susceptible organisms.
May be used alone as first choice drug 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.

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)
- Prophylaxis: prostatic surgery (transurethral resection).

Contraindications

Hypersensitivity to ceftazidime, to any other cephalosporin or to any of the excipients.

History of severe hypersensitivity (e.g. anaphylactic reaction) to any other type of beta-lactam antibacterial agent (penicillins, monobactams and carbapenems).

Fertility, pregnancy and lactation

Pregnancy

There are limited amounts of data from the use of ceftazidime in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/ foetal development, parturition or postnatal development.

Ceftazidime should be prescribed to pregnant women only if the benefit outweighs the risk.
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 are available.

Special warnings and precautions for use

As with all beta-lactam antibacterial agents, serious and occasionally fatal hypersensitivity reactions have been reported. In case of severe hypersensitivity reactions, treatment with ceftazidime 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 beta-lactam agent. Caution should be used if ceftazidime is given to patients with a history of non-severe hypersensitivity to other beta-lactam agents.

Ceftazidime has a limited spectrum of antibacterial activity. It is not suitable for use as a single agent for the treatment of some types of infections unless the pathogen is already documented and known to be susceptible or there is a very high suspicion that the most likely pathogen(s) would be suitable for treatment with ceftazidime. This particularly applies when considering the treatment of patients with bacteraemia and when treating bacterial meningitis, skin and soft tissue infections and bone and joint infections. In addition, ceftazidime is susceptible to hydrolysis by several of the extended spectrum beta lactamases (ESBLs). Therefore information on the prevalence of ESBL producing organisms should be taken into account when selecting ceftazidime for treatment.

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.

Antibacterial agent-associated colitis and pseudo-membranous colitis have been reported with nearly all anti-bacterial agents, including ceftazidime, and may range in severity from mild to lifethreatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea during or subsequent to the administration of ceftazidime (see section Undesirable Effects). Discontinuation of therapy with ceftazidime and the administration of specific treatment for *Clostridium difficile* should be considered. Medicinal products that inhibit peristalsis should not be given.

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

Ceftazidime is eliminated via the kidneys, therefore the dose 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 have occasionally been reported when the dose has not been reduced in patients with renal impairment (see sections Posology and method of administration and Undesirable Effects).

Prolonged use may result in the overgrowth of non-susceptible organisms (e.g. Enterococci, fungi) which may require interruption of treatment or other appropriate measures. Repeated evaluation of the patient's condition is essential.

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

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

The development of a positive Coombs' test associated with the use of ceftazidime in about 5% of patients may interfere with the cross-matching of blood.

Important information about one of the ingredients of Ceftazidime Kabi:

The sodium content of the medicinal product (26 mg sodium for 500 mg Ceftazidime, 52 mg sodium for 1.0 g Ceftazidime and 104 mg sodium for 2.0 g Ceftazidime) should be considered for patients who are on a controlled sodium diet.

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

Interaction with other medicinal products and other forms of interaction

Interaction studies have only been conducted with probenecid and furosemide.

Concurrent use of high doses with nephrotoxic medicinal products may adversely affect renal function (see section 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.

Incompatibilities

Ceftazidime should not be mixed with solutions with a pH above 7.5 for example sodium bicarbonate solution for injection. Ceftazidime and aminoglycosides should not be mixed in the solution for injection because of the risk for precipitation.
Cannulae and catheters for intravenous use should be flushed with physiological salt-solution between administrations of ceftazidime and vancomycin to avoid precipitation.

Posology and method of administration

Dosage depends on the severity, sensitivity, site and type of infection and upon the age and renal function of the patient.
Use ceftazidime by intravenous (i.v.) or by deep intramuscular (i.m.) 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.

Adults
1 to 6 g/day in two or three divided doses by i.v. or 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 eight or 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.

When used as a prophylactic agent in prostatic surgery, 1 g should be given at the induction of anaesthesia. A second dose should be considered at the time of catheter removal.

Infants and children (greater than 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 to 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
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 µmol/l (mg/dl)	Recom-mended unit dose of Ceftazidime (g)	Frequency of dosing (hourly)
>50	<150 (<1.7)	Normal dosage	
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

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 h.
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 arterio-venous haemodialysis or high-flux haemofiltration in intensive therapy untis: 1 g daily either as a single dose or in divided doses. For low-flux haemofiltration, follow the dose recommended under renal impairment.

Method of Administration:
Ceftazidime should be administered by intravenous injection or infusion, or by deep intramuscular injection. Recommended intramuscular 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.

The standard recommended route of administration is by intravenous intermittent injection or intravenous continuous infusion. Intramuscular administration should only be considered when the intravenous route is not possible or less appropriate for the patient.

The dose depends on the severity, susceptibility, site and type of infection and on the age and renal function of the patient.

Overdose

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

Symptoms of overdose can occur if the dose is not reduced appropriately in patients with renal impairment (see sections Posology and method of administration and Special Warnings and Precautions for Use).

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

PHARMACOLOGICAL PROPERTIES
Pharmacodynamics
Mechanism of Action
Ceftazidime is bactericidal in action. It acts by inhibiting bacterial cell wall synthesis.

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 Ceftazidime

Commonly Susceptible Species
Where clinical efficacy of ceftazidime has been demonstrated in clinical trials this is indicated with an asterisk (*).

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.** *Salmonella spp.* *Shigella spp.*
Species for which acquired resistance may be a problem
Gram-negative aerobes: *Acinetobacter spp.* *Burkholderia cepacia* *Citrobacter spp.**
*Enterobacter spp.** *Escherichia coli** *Klebsiella spp. including K. Pneumonia* *Pseudomonas spp. including P. Aeruginosa** *Serratia spp.** *Morganella moganii* *Yersinia enterocolitica*
Gram-positive aerobes: *Streptococcus pneumonia**
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. incluing E. Faecalis and E. Faecium* *Listeria spp.*
Gram-negative aerobes: *Campylobacter spp.*
Gram-positive: *Clostridium difficile*
Gram-negative anaerobes: *Bacteroides spp. including B. Fragilis*
Others: *Chlamydia spp.* *Mycoplasma spp.* *Legionella spp.*

Pharmacokinetics

Absorption
After i.m. administration of 500 mg and 1 g, peak levels of 18 and 37 mg/1, respectively, are achieved rapidly. Five 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.

Metabolism
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. Less than 1% is excreted via the bile, which limits the amount entering the bowel.

Special Patient Populations
Elimination of ceftazidime is decreased in patients with impaired renal function and the dose should be reduced (*see Dosage and Administration - Renal Impairment, Warnings and Precautions).*

Undesirable Effects

The most common adverse reactions are eosinophilia, thrombocytosis, phlebitis or thrombophlebitis with intravenous administration, diarrhoea, transient increases in hepatic enzymes, maculopapular or urticarcial rash, pain and/or inflammation following intramuscular injection and positive Coomb's test.

Data from sponsored and un-sponsored clinical trials have been used to determine the frequency of common and 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. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. 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 from the available data)

System Organ Class	Common	Uncommon	Very rare	Unknown
Infections and infestations		Candidiasis (including vaginitis and oral thrush)		
Blood and lymphatic system disorders	Eosinophilia Thrombocytosis	Neutropenia Leucopenia Thrombocytopenia		Agranulocytosis Haemolytic anaemia Lymphocytosis
Immune system disorders				Anaphylaxis (including bronchospasm and/or hypotension) (see section Special Warnings and Precautions for Use)
Nervous system disorders		Headache Dizziness		Neurological sequelae[1] Paraesthesia
Vascular disorders	Phlebitis or thrombophlebitis with intravenous administration			
Gastrointestinal disorders	Diarrhoea	Antibacterial agent-associated diarrhoea and colitis[2] (see section Special Warnings and Precautions for Use) Abdominal pain Nausea Vomiting		Bad taste
Hepatobiliary disorders	Transient elevations in one or more hepatic enzymes[3]			Jaundice
Skin and subcutaneous tissue disorders	Maculopapular or urticarial rash	Pruritus		Toxic epidermal necrolysis Stevens-johnson syndrome Erythema multiforme Angioedema
Renal and urinary disorders		Transient elevations of blood urea, blood urea nitrogen and/or serum creatinine	Interstitial nephritis Acute renal failure	
General disorders and administration site conditions	Pain and/or inflammation after intramuscular injection	Fever		
Investigations	Positive Coombs' test[4]			

[1]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.
[2]Diarrhoea and colitis may be associated with Clostridium difficile and may present as pseudomembranous colitis.
[3]ALT (SGPT), AST (SOGT), LHD, GGT, alkaline phosphatase.
[4]A positive Coombs test develops in about 5% of patients and may interfere with blood cross matching.

Pharmaceutical precautions

This medicinal product is for single use only. Discard any unused contents. Reconstitute immediately before use

Intravenous use - injection
For direct intermittent intravenous administration, ceftazidime should be reconstituted with Water for Injections (see table below). The solution has to be injected slowly directly into the vein over a period of to 5 minutes or given through the tubing of a giving set.

Intramuscular use:
Ceftazidime should be reconstituted with Water for Injections or Lidocaine Hydrochloride 10 mg/ml (1%) solution for injection as indicated in the table below. Information for Lidocaine should be consulted before reconstitution of ceftazidime with lidocaine.

Intravenous use – infusion (see section Posology and Method of Administration):
For intravenous infusion, the content of the 2 g infusion vial should be reconstituted with 10 ml of water for injections (for bolus) and 50 ml of water for injections (intravenous infusion) or one of the compatible intravenous fluids. Alternatively, the content of the 500 mg 1 g vial should be reconstituted and an appropriate quantity of the resulting solution should be added to an IV container with one of the compatible intravenous fluids.– Administer by intravenous infusion over 15-30 minutes. Intermittent intravenous infusion with a Y-type giving set can be accomplished with compatible solutions. However, during infusion of a solution containing ceftazidime, it is desirable to discontinue the other solution.

All sizes of vials of Ceftazidime 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 constitution

See table for addition volumes and solution concentrations, which may be useful when fractional doses are required.

Vial size		Amount of diluent to be added (ml)	Approximate concentration (mg/ml)
500 mg powder for solution for injection			
500 mg	Intramuscular Intravenous bolus	1.5 ml 5 ml	260 90
1 g powder for solution for injection			
1 g	Intramuscular Intravenous bolus	3 ml 10 ml	260 90
2 g powder for solution for injection or infusion			
2 g	Intravenous bolus Intravenous infusion	10 ml 50 ml*	170 40

* Addition should be in 2 stages

Compatible intravenous fluids:
At ceftazidime concentrations between 40 mg/ml and 260 mg/ml the Ceftazidime Kabi powders for injection may be mixed in commonly used solutions for infusion:
- sodium chloride 9 mg/ml (0.9%) solution (physiological saline solution),
- Ringer Lactate Solution
- Glucose 100 mg/ml (10%) solution

When reconstituted for intramuscular use, the Ceftazidime Kabi powder for injection can also be diluted with lidocaine 10 mg/ml (1%) solutions.

When ceftazidime is dissolved, carbon dioxide is released and a positive pressure develops. For ease of use, the recommended techniques of reconstitution described below should be followed.

Instructions for reconstitution:

For 500mg IM/IV and 1g IM/IV:
Preparation of solutions for bolus injection
1. Insert the syringe needle through the vial closure and inject the recommended volume of diluent. The vacuum may assist entry of the diluent. Remove the syringe needle.
2. Shake to dissolve: carbon dioxide is released and a clear solution will be obtained in about 1 to 2 minutes.
3. Invert the vial. With the syringe plunger fully depressed, insert the needle through the vial closure and withdraw the total volume of solution into the syringe (the pressure in the vial may aid withdrawal). Ensure that the needle remains within the solution and does not enter the head space. The withdrawn solution may contain small bubbles of carbon dioxide; they may be disregarded.

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. Ceftazidime is compatible with above mentioned intravenous fluids.

For 2g infusion vials
Preparation of solutions for iv infusion from ceftazidime injection in standard vial presentation (minibag or burette-type set):

1. Introduce the syringe needle through the vial closure and inject 10 ml of diluent.
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 to 30 min.

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.

The dilution is to be made under aseptic conditions.
Single use only.
Any unused product or waste material should be disposed of in accordance with local requirements.
Only clear solutions practically free from particles should be used.
Free from bacterial endotoxins.

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 color variations.

Special precautions for storage

Keep the vial in the outer carton in order to protect from light.
Do not store above 30°C.

Poroposed shelf-life: 3 years.
Reconstituted solution: Chemical and physical in use stability has been demonstrated up to 6 h at 25°C and 12 h at 5°C after reconstitution of the product with water for injection, 1 % lidocain solution, 0.9 % sodium chloride solution, ringer lactate and 10 % glucose solution. From a microbiological point of view, the product should be used immediately.

Presentation

Ceftazidime Kabi 500 mg powder for solution for injection
Nature: Colourless type II glass vials closed with type I rubber stoppers covered with aluminium caps and plastic flip off caps.
Contents: Each pack contains:
1 x 10 ml vial
10 x 10 ml vials

Ceftazidime Kabi 1000 mg powder for solution for injection
Nature: Colourless type II glass vials closed with type I rubber stoppers covered with aluminium caps and plastic flip off caps.
Contents: Each pack contains:
1 x 10 ml vial
10 x 10 ml vials

Ceftazidime Kabi 2000 mg powder for solution for injection or infusion
Nature: Colourless type II glass bottles closed with type I rubber stoppers covered with aluminium caps and plastic flip off caps.
Contents: Each pack contains:
1 x 50 ml bottle
10 x 50 ml bottles

Not all pack sizes may be marketed.

Revision date

May 2016

FRESENIUS KABI

XXXXXX/XX