Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ceftazidime 1 g powder for solution for injection or infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 1165 mg ceftazidime pentahydrate corresponding to 1 g ceftazidime

Excipient with known effect:
51.2 mg (2.23 mmol) of sodium/vial of powder for solution for injection or infusion

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for injection or infusion.

The powder is white or off-white.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Ceftazidime is indicated for the treatment of the infections listed below in adults and children including neonates (from birth).

- Nosocomial pneumonia
- Broncho-pulmonary infections in cystic fibrosis
- Bacterial meningitis
- Chronic suppurative otitis media
- Malignant otitis externa
- Complicated urinary tract infections
- Complicated skin and soft tissue infections
- Complicated intra-abdominal infections
- Bone and joint infections
- Peritonitis associated with dialysis in patients on CAPD.

Treatment of patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above.

Ceftazidime may be used in the management of neutropenic patients with fever that is suspected to be due to a bacterial infection.

Ceftazidime may be used in the peri-operative prophylaxis of urinary tract infections for patients undergoing trans-urethral resection of the prostate (TURP).

The selection of ceftazidime should take into account its antibacterial spectrum, which is mainly restricted to aerobic Gram negative bacteria (see sections 4.4 and 5.1).

Ceftazidime should be co-administered with other antibacterial agents whenever the possible range of causative bacteria would not fall within its spectrum of activity.

Consideration should be given to official guidances on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Routes of administration:
Only for 500 mg and 1000 mg Powder for solution for injection, 1 g Powder for solution for injection or infusion:
Intravenous use,
Intramuscular use (in exceptional clinical situations)

Only for 2 g and 3 g Powder for solution for injection or infusion:
Intravenous use

Posology

Table 1: Adults and children ≥ 40 kg

Intermittent Administration	
Infection	Dose to be administered
Broncho-pulmonary infections in cystic fibrosis	100 to 150 mg/kg/day every 8 h, maximum 9 g per day[1]
Febrile neutropenia	2 g every 8 h
Nosocomial pneumonia	
Bacterial meningitis	
Bacteraemia*	
Bone and joint infections	1-2 g every 8 h
Complicated skin and soft tissue infections	
Complicated intra-abdominal infections	
Peritonitis associated with dialysis in patients on CAPD	
Complicated urinary tract infections	1-2 g every 8 h or 12 h
Peri-operative prophylaxis for transuretheral resection of prostate (TURP)	1 g at induction of anaesthesia, and a second dose at catheter removal
Chronic suppurative otitis media	1 g to 2 g every 8 h
Malignant otitis externa	
Continuous Infusion	
Infection	Dose to be administered
Febrile neutropenia	Loading dose of 2 g followed by a continuous infusion of 4 to 6 g every 24 h[1]
Nosocomial pneumonia	
Broncho-pulmonary infections in cystic fibrosis	
Bacterial meningitis	
Bacteraemia*	
Bone and joint infections	
Complicated skin and soft tissue infections	
Complicated intra-abdominal infections	
Peritonitis associated with dialysis in patients on CAPD	

[1] In adults with normal renal function 9 g/day has been used without adverse effects.
*When associated with, or suspected to be associated with, any of the infections listed in section 4.1.

Table 2: Children < 40 kg

Infants and toddlers> 2 months and children < 40 kg	
Intermittent Administration	
Infection	Usual dose
Complicated urinary tract infections	100-150 mg/kg/day in three divided doses, maximum 6 g/day
Chronic suppurative otitis media	
Malignant otitis externa	

Neutropenic children	150 mg/kg/day in three divided doses, maximum 6 g/day
Broncho-pulmonary infections in cystic fibrosis	
Bacterial meningitis	
Bacteraemia*	
Bone and joint infections	100-150 mg/kg/day in three divided doses, maximum 6 g/day
Complicated skin and soft tissue infections	
Complicated intra-abdominal infections	
Peritonitis associated with dialysis in patients on CAPD	
Continuous Infusion	
Infection	Usual dose
Febrile neutropenia	Loading dose of 60-100 mg/kg followed by a continuous infusion 100-200 mg/kg/day, maximum 6 g/day
Nosocomial pneumonia	
Broncho-pulmonary infections in cystic fibrosis	
Bacterial meningitis	
Bacteraemia*	
Bone and joint infections	
Complicated skin and soft tissue infections	
Complicated intra-abdominal infections	
Peritonitis associated with dialysis in patients on CAPD	
Neonates and infants ≤ 2 months	
Intermittent Administration	
Infection	Usual dose
Most infections	25-60 mg/kg/day in two divided doses[1]

[1] In neonates and infants ≤ 2 months, the serum half-life of ceftazidime can be three to four times that in adults.
* Where associated with, or suspected to be associated with, any of the infections listed in section 4.1.

Paediatric population
The safety and efficacy of Ceftazidime administered as continuous infusion to neonates and infants ≤ 2 months has not been established.

Elderly
In view of the age related reduced clearance of ceftazidime in elderly patients, the daily dose should not normally exceed 3 g in those over 80 years of age.

Hepatic impairment
Available data do not indicate the need for dose adjustment in mild or moderate liver function impairment. There are no study data in patients with severe hepatic impairment (see also section 5.2). Close clinical monitoring for safety and efficacy is advised.

Renal impairment
Ceftazidime is excreted unchanged by the kidneys. Therefore, in patients with impaired renal function, the dosage should be reduced (see also section 4.4).

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

Table 3: Recommended maintenance doses of Ceftazidime in renal impairment – intermittent infusion

Adults and children ≥40 kg

Creatinine clearance (ml/min)	Approx. serum creatinine µmol/l (mg/dl)	Recommended unit dose of Ceftazidime (g)	Frequency of dosing (hourly)
50-31	150-200	1	12

	(1.7-2.3)		
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 children the creatinine clearance should be adjusted for body surface area or lean body mass.

Children < 40 kg

Creatinine clearance ml/min**	Approx. serum creatinine* µmol/l (mg/dl)	Recommended individual dose mg/kg body weight	Frequency of dosing (hourly)
50 – 31	150 - 200 (1.7 - 2.3)	25	12
30 – 16	200 - 350 (2.3 - 4.0)	25	24
15 – 6	350 - 500 (4.0 - 5.6)	12.5	24
< 5	> 500 (> 5.6)	12.5	48
* The serum creatinine values are guideline values that may not indicate exactly the same degree of reduction for all patients with reduced renal function. ** Estimated based on body surface area, or measured.			

Close clinical monitoring for safety and efficacy is advised.

Table 4: Recommended maintenance doses of Ceftazidime in renal impairment – continuous infusion

Adults and children ≥ 40 kg

Creatinine clearance (ml/min)	Approx. serum creatinine µmol/l (mg/dl)	Usual dose
50-31	150-200 (1.7-2.3)	Loading dose of 2 g followed by 1 g to 3 g /24 hours
30-16	200-350 (2.3-4.0)	Loading dose of 2 g followed by 1 g/24 hours
≤15	>350 (>4.0)	Not evaluated

Caution is advised in dose selection. Close clinical monitoring for safety and efficacy is advised.

Children < 40 kg

The safety and effectiveness of Ceftazidime administered as continuous infusion in renally impaired children < 40 kg has not been established. Close clinical monitoring for safety and efficacy is advised.

If continuous infusion is used in children with renal impairment, 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 below 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 units: 1g daily either as a single dose or in divided doses. For low-flux haemofiltration, follow the dose recommended under renal impairment.

For patients on veno-venous haemofiltration and veno-venous haemodialysis, follow the dosage recommendations in the tables below.

Table 5: Continuous veno-venous haemofiltration dose guidelines

Residual renal function (creatinine clearance ml/min)	Maintenance dose (mg) for an ultrafiltration rate (ml/min) of [1]:			
	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
[1] Maintenance dose to be administered every 12 h				

Table 6: Continuous veno-venous haemodialysis dose guidelines

Residual renal function (creatinine clearance ml/min)	Maintenance dose (mg) for a dialysate in flow rate of [1]:					
	1.0 litre/h			2.0 litres/h		
	Ultra filtration rate (litre/h)			Ultra filtration rate (litre/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
[1] Maintenance dose to be administered every 12 h						

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.

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to ceftazidime, to any other cephalosporin or to any of the excipients listed in section 6.1.

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

4.4 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 agents. 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.

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 life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea during or subsequent to the administration of ceftazidime (see section 4.8). 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 4.2 and 4.8).

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 (false-positive) 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:

Ceftazidime 2 g contains 102.4 mg (4.45 mmol) sodium per vial.

The sodium content has to be taken into consideration by patients on a controlled sodium diet.

4.5 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 sections 4.4).

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.

4.6 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 (see section 5.3).

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

Breast-feeding

Ceftazidime is excreted in human milk in small quantities but at therapeutic doses of ceftazidime no effects on the breast-fed infant are anticipated. Ceftazidime can be used during breast-feeding.

Fertility

No data are available.

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, 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

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 (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000)
Unknown (cannot be estimated from the available data)

Frequency System Organ Class	Very common (≥1/10)	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1,000 to < 1/100)	Rare (≥1/10,000 to <1/1,000)	Very rare (< 10,000)	Unknown (cannot be estimated from the available data)
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 4.4)
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 4.4) 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-Johnsons syndrome Erythema multiforme Angioedema
Renal and urinary disorders			Transient elevations of blood urea, blood urea nitrogen and/or serum creatinine		Interstitial nephritis Acure reneal 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 Ceftazidim Stragen 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.

4.9 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 4.2 and 4.4).

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use. Third generation cephalosporins, ATC code: J01DD02

Mechanism of action

Ceftazidime inhibits bacterial cell wall synthesis following attachment to penicillin binding proteins (PBPs). This results in the interruption of cell wall (peptidoglycan) biosynthesis, which leads to bacterial cell lysis and death.

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 that the unbound concentration remains above the minimum inhibitory concentration (MIC) of ceftazidime for individual target species (i.e. %T>MIC).

Mechanism of Resistance
Bacterial resistance to ceftazidime may be due to one or more of the following mechanisms:
- hydrolysis by beta−lactamases. Ceftazidime may be efficiently hydrolysed by extended−spectrum beta−lactamases (ESBLs), including the SHV family of ESBLs, and AmpC enzymes that may be induced or stably derepressed in certain aerobic Gram-negative bacterial species
- reduced affinity of penicillin−binding proteins for ceftazidime
- outer membrane impermeability, which restricts access of ceftazidime to penicillin binding proteins in Gram-negative organisms
- bacterial efflux pumps.

Breakpoints
Minimum inhibitory concentration (MIC) breakpoints established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) are as follows:

Organism	Breakpoints (mg/L)		
	S	**I**	**R**
Enterobacteriaceae	≤ 1	2-4	> 4
Pseudomonas aeruginosa	≤ 8[1]	-	> 8
Non-species related breakpoints[2]	≤ 4	8	> 8

S=susceptible, I=intermediate, R=resistant.

[1] The breakpoints relate to high dose therapy (2 g x 3).

[2] Non-species related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for species not mentioned in the table or footnotes.

Microbiological Susceptibility

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of ceftazidime in at least some types of infections is questionable.

Commonly susceptible species
Gram-positive aerobes: *Streptococcus pyogenes* *Streptococcus agalactiae*
Gram-negative aerobes: *Citrobacter koseri* *Escherichia coli* *Haemophilus influenzae* *Moraxella catarrhalis* *Neisseria meningitidis* *Proteus mirabilis* *Proteus* spp. (other) *Providencia* spp.
Species for which acquired resistance may be a problem
Gram-positive aerobes: *Staphylococcus aureus* [£] *Streptococcus pneumoniae* [£££]
Gram-negative aerobes: *Acinetobacter baumannii* [£+]. *Burkholderia cepacia* *Citrobacter freundii* *Enterobacter aerogenes* *Enterobacter cloacae* *Klebsiella pneumoniae* *Klebsiella* spp. (other) *Pseudomonas aeruginosa* *Serratia* spp. *Morganella morganii*
Gram-positive anaerobes: *Clostridium perfringens* *Peptococcus* spp. *Peptostreptococcus* spp.
Gram-negative anaerobes: *Fusobacterium* spp.
Inherently resistant organisms
Gram-positive aerobes: Enterococci including *Enterococcus faecalis* and *Enterococcus faecium* *Listeria* spp.
Gram-positive anaerobes: *Clostridium difficile*
Gram-negative anaerobes: *Bacteroides* spp. (many strains of *Bacteroides fragilis* are resistant).
Others: *Chlamydia* spp. *Mycoplasma* spp. *Legionella* spp.

[£] *S .aureus* that is methicillin-susceptible are considered to have inherent low susceptibility to ceftazidime. All methicillin-resistant *S. aureus* are resistant to ceftazidime.

[£££] *S. pneumonia* that demonstrate intermediate susceptibility or are resistant to pencillin can be expected to demonstrate at least reduced susceptibility to ceftazidime.

[+] High rates of resistance have been observed in one or more areas/countries/regions within the EU.

5.2 Pharmacokinetic properties

Absorption

After intramuscular administration of 500 mg and 1 g of ceftazidime, peak plasma levels of 18 and 37 mg/l, respectively, are achieved rapidly. Five minutes after intravenous bolus injection of 500 mg, 1 g or 2 g, plasma levels are 46, 87 and 170 mg/l, respectively. The kinetics of ceftazidime are linear within the single dose range of 0.5 to 2 g following intravenous or intramuscular dosing.

Distribution

The serum protein binding of ceftazidime is low at 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 CSF in the absence of inflammation. However, concentrations of 4 to 20 mg/l or more are achieved in the CSF when the meninges are inflamed.

Biotransformation

Ceftazidime is not metabolised.

Elimination

After parenteral administration plasma levels decrease with a half-life of about 2 h. Ceftazidime is excreted unchanged into the urine by glomerular filtration; approximately 80 to 90% of the dose is recovered in the urine within 24 h. Less than 1% is excreted via the bile.

Special patient populations

Renal impairment

Elimination of ceftazidime is decreased in patients with impaired renal function and the dose should be reduced (see section 4.2).

Hepatic impairment

The presence of mild to moderate hepatic dysfunction had no effect on the pharmacokinetics of ceftazidime in individuals administered 2 g intravenously every 8 hours for 5 days, provided renal function was not impaired (see section 4.2).

Elderly

The reduced clearance observed in elderly patients was primarily due to age-related decrease in renal clearance of ceftazidime. The mean elimination half-life ranged from 3.5 to 4 hours following single or 7 days repeat BID dosing of 2 g IV bolus injections in elderly patients 80 years or older.

Paediatric population

The half-life of ceftazidime is prolonged in preterm and term neonates by 4.5 to 7.5 hours after doses of 25 to 30 mg/kg. However, by the age of 2 months the half-life is within the range for adults.

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 (E500)

6.2 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 infusion 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.

6.3 Shelf life

Vial before opening: 3 years.
Vial after first opening: The product should be used immediately.
After reconstitution: The product should be used immediately.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8 ºC, unless reconstitution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Unopened*:* Store below 25 °C. Keep vial in the outer carton
For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Nature:
Clear colourless type II. Injection vial (50 ml) closed with bromobutyl rubber closure and polypropylene flip-off aluminium cap.

Pack sizes: 10 x 1 vial.

6.6 Special precautions for disposal and other handling

For single use only.

The constitution is to be made under aseptic conditions.

As the product dissolves, carbon dioxide is released and a positive pressure develops. Small bubbles of carbon dioxide in the constitution 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	1.5 ml	260

	Intravenous bolus	5 ml	90
1000 mg Powder for solution for injection			
1000 mg	Intramuscular Intravenous bolus	3 ml 10 ml	260 90
1 g Powder for solution for injection or infusion			
1 g	Intramuscular	3 ml	260
	Intravenous bolus	10 ml	90
	Intravenous infusion	50 ml*	20
2 g Powder for solution for injection or infusion			
2g	Intravenous bolus	10 ml	170
	Intravenous infusion	50 ml*	40
3 g Powder for solution for injection or infusion			
3 g	Intravenous bolus	15 ml	170
	Intravenous infusion	75 ml*	40

**Note: Addition should be in two stages*

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

Ceftazidime is compatible with:

- Water for injection
- Sodium chloride solution 9 mg/ml (0.9 %) solution for injection
- Glucose 50 mg/ml (5 %)
- Glucose 50 mg/ml (5 %) in 0.9% sodium chloride injection

Ceftazidime may be constituted for intramuscular use with 1% lidocaine solution for injection.

500 mg powder for solution for injection, 1000 mg powder for solution for injection, 1 g, 2 g, 3 g powder for solution for injection or infusion.

Preparation of solutions for bolus injection

1. Insert the syringe needle through the vial closure and inject the recommended volume of 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.

1 g, 2 g, 3 g powder for solution for injection or infusion

Preparation of solutions for i.v. infusion:

Prepare using a total of 50 ml (for 1g and 2g vials) and 75 ml (for 3g vials) of compatible diluent, added in TWO stages as below.

1. Introduce the syringe needle through the vial closure and inject 10 ml of the diluent for the 1 g and 2 g vials, and 15 ml for the 3 g vial
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. Add a further 40 ml of diluent for the 1 g and 2 g vials and 60 ml for the 3 g vial. Remove the vent needle.

5. Administer by intravenous infusion over 15 to 30 min. Additional pressure that may develop in the vial especially after storage should be relieved prior to administration to the patient.

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.

The solution should only be used if the solution is clear and free from particles.

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

7 MARKETING AUTHORISATION HOLDER

Clonmel Healthcare Limited
Waterford Road
Clonmel
Co. Tipperary
Ireland

8 MARKETING AUTHORISATION NUMBER

PA126/178/3

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 6th March 2009
Date of last renewal: 19th July 2012

10 DATE OF REVISION OF THE TEXT

February 2013