Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ceftazidime 1g Powder for solution for injection or infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains ceftazidime 1g (as pentahydrate).

Excipient with known effect
Each gram of ceftazidime contains approximately 52mg (2.26mmol) of sodium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for injection or infusion (Powder for injection or infusion).
White to cream coloured, crystalline powder

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 guidelines on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

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 day1
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 8h
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 h1
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	Infection	Usual dose
Intermittent Administration		
	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	150 mg/kg/day in three divided doses, maximum 6 g/day

	children	
	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		
	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	Infection	Usual dose
Intermittent Administration		
	Most infections	25-60 mg/kg/day in two divided doses1
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 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 (1.7-2.3)	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 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)	Frequency of dosing (hourly)
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: 1 g 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 5 & 6below.

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 in ml/min)	Maintenance dose (mg) for a dialysate in flow rate of 1:					
	1.0 litre/h			2.0 litre/h		
	Ultrafiltration rate (litre/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
[1] Maintenance dose to be administered every 12 h.						

Method of administration

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

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.

4.3 Contraindications

Hypersensitivity to the active substance, to any other cephalosporins 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 (penicillins, monobactams and carbapenems).

4.4 Special warnings and precautions for use

Hypersensitivity
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.

Spectrum of activity
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.

Pseudomembranous colitis
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.

Renal function
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).

Overgrowth of non-susceptible organisms
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.

Test and assay interactions
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.

Sodium content
This medicinal product contains 52mg sodium per 1g vial, equivalent to 2.6% of the WHO recommended maximum daily intake of 2g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interactions

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 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 woman 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)

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 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 colitis2 (see section 4.4) Abdominal pain Nausea Vomiting		Bad taste
Hepatobiliary disorders	Transient elevations in one or more hepatic enzymes3			Jaundice
Skin and subcutaneous tissue disorders	Maculopapular or urticarial rash	Pruritus		Toxic epidermal necrolysis Stevens-johnson syndrome Erythema multiforme Angioedema Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) [4]
Renal and urinary disorders		Transient elevations of blood urea, blood	Interstitial nephritis Acute renal failure	

		urea nitrogen and/or serum creatinine		
General disorders and administration site conditions	Pain and/or inflammation after intramuscular injection	Fever		
Investigations	Positive Coombs' test[5]			

1There 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 There have been rare reports where DRESS has been associated with ceftazidime.
5 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 medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Website: www.hpra.ie.

4.9 Overdose

Overdose can lead to neurological sequelae including encephalopathy, convulsion 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	≤ 81	-	> 8
Non-species related breakpoints2	≤4	8	> 8

S=susceptible, I=intermediate, R=resistant.
1The breakpoints relate to high dose therapy (2 g x 3).
2Non-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* *Haemophilus influenzae* *Moraxella catarrhalis* *Neisseria meningitidis* *Pasteurella multocida* *Proteus mirabilis* *Proteus spp. (other)* *Providencia spp.*
Species for which acquired resistance may be a problem
Gram-negative aerobes: *Acinetobacter baumannii+* *Burkholderia cepacia* *Citrobacter freundii* *Enterobacter aerogenes* *Enterobacter cloacae* *Escherichia coli* *Klebsiella pneumoniae* *Klebsiella spp. (other)* *Pseudomonas aeruginosa* *Serratia spp.* *Morganella morganii*
Gram-positive aerobes: *Staphylococcus aureus*£ *Streptococcus pneumoniae*££ *Viridans group streptococcus*
Gram-positive anaerobes: *Clostridium perfringens*

Peptostreptococcus spp.
Gram-negative anaerobes: *Fusobacterium spp.*
Inherently resistant organisms
Gram-positive aerobes: Enterococcus spp 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. pneumoniae*that demonstrate intermediate suseptibility or are resistant to penicillin 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 sterile)

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

Ceftazidime is less stable in Sodium Bicarbonate Injection than other intravenous 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.
Ceftazidime is incompatible with aminophylline. There is a possible incompatibility with pentamide.

6.3 Shelf life

Unopened - 3 years.

For reconstituted solution, chemical and physical in-use stability has been demonstrated for eight hours at 25^{o}C and 24 hours at 4°C. From a microbiological point of view, once opened, 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 2-8°C, unless reconstitution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Unopened: Do not store above 25°C. Keep the vials in the outer carton.
After reconstitution: Store at 2-8°C. (See 6.3 shelf life)

6.5 Nature and contents of container

Packs of one, five or ten Type II colourless glass 10ml vials stoppered with coated rubber stopper, capped with flip-off cap.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

For single use. Discard any unused contents.

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

PREPARATION OF SOLUTION

INTRAMUSCULAR INJECTION					
Strength	Diluent	Amount of diluent to be added (ml)	Approximate concentration (mg/ml)	Approximate available volume (ml)	Approximate displacement volume (ml)
1 g	0.5% lidocaine	3 ml	278	3.6 ml	0.6 ml
1 g	1% lidocaine	3 ml	270	3.7 ml	0.7 ml

INTRAVENOUS BOLUS					
Strength	Diluent	Amount of diluent to be added (ml)	Approximate concentration (mg/ml)	Approximate available volume (ml)	Approximate displacement volume (ml)
1 g	Water for Injection	10 ml	92	10.9 ml	0.9 ml

INTRAVENOUS INFUSION			
Strength	Diluent	Amount of diluent to be added (ml)[#]	Approximate concentration (mg/ml)
1 g	See list of compatible diluents below	50 ml	20

[#]Note: addition should be in two stages. See preparation for intravenous infusion instructions below.

Compatible diluents for intravenous infusion

Ceftazidime at concentrations between 1 mg/ml and 40 mg/ml is compatible with the following diluent solutions for intravenous infusion preparation:

Sodium Chloride 0.9%
Ringer Solution
Ringer Lactate Solution
Glucose 5%
Glucose 10%
Glucose 5% and Sodium Chloride 0.9%
Glucose 5% and Sodium Chloride 0.45%
Glucose 5% and Sodium Chloride 0.2%

Dextran 40%/10% and Sodium Chloride 0.9%
Dextran 70%/6% and Sodium Chloride 0.9%

Solutions range from light yellow to amber depending on concentration, diluent and storage conditions used.

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.

Preparation of solution for bolus injection:

1. Insert the syringe needle through the vial closure and inject
10 ml of Water for Injection. 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.

Preparation of solution for intravenous infusion:

Prepare using a total of 50 ml of compatible diluent, added in TWO stages as follows:

1. Insert the syringe needle through the vial closure and inject 10ml of Water for Injection or one of the listed compatible diluent solutions for intravenous infusion preparation to reconstitute. The vacuum may assist entry of the diluent. Remove the syringe needle.
2. Shake to dissolve: carbon dioxide is released and a clear solution obtained in about 1 to 2 minutes.
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 the final delivery vehicle (e.g. mini-bag or burette-type set) and add 40ml of compatible diluent* to make up a total volume of approximately 50ml and administer by slow intravenous infusion over 20 to 30 minutes.

* For the second stage of preparation use Sodium Chloride 0.9%, Glucose 5% or one of the listed compatible diluent solutions for intravenous infusion preparation, as Water for Injection produces hypotonic solutions when used at higher concentrations.

Ceftazidime at concentrations between 1 mg/ml and 40 mg/ml is compatible with the diluent solutions for intravenous infusion preparation listed above.

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.

7 MARKETING AUTHORISATION HOLDER

Pinewood Laboratories Ltd,
Ballymacarbry
Clonmel
Co. Tipperary
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0281/224/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17 December 2004
Date of last renewal: 02 November 2005

10 DATE OF REVISION OF THE TEXT

August 2021