Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ceftazidime hameln 1 g powder for solution for injection/infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Ceftazidime hameln 1 g
Each vial contains ceftazidime pentahydrate equivalent to 1 g ceftazidime.

Excipient with known effect: Each vial contains 50 mg of sodium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Ceftazidime hameln 1 g
Powder for solution for injection/infusion

White or pale-yellow powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Ceftazidime hameln 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 continuous ambulatory peritoneal dialysis (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 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 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 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	*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 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	
	Complicated skin and soft tissue infections	
	Complicated intra-abdominal infections	100-150 mg/kg/day in three divided doses, maximum 6 g/day
	Peritonitis associated with dialysis in patients on CAPD	
Continuous Infusion		
	Febrile neutropenia	
	Nosocomial pneumonia	
	Broncho-pulmonary infections in cystic fibrosis	
	Bacterial meningitis	
	Bacteraemia*	
	Bone and joint infections	Loading dose of 60-100 mg/kg followed by a continuous infusion 100-200 mg/kg/day, maximum 6 g/day
	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 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 hameln 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 the Ceftazidime hameln 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 [Invented name] [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 hameln in renal impairment – continuous infusion

Adults and children ≥ 40 kg

Creatinine clearance	Approx. serum creatinine	Frequency of dosing

[ml/min]	[µmol/l] (mg/dl)	[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 hameln 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 hours.

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 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 hours.				

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 / hour			2.0 litres / hour		
	Ultrafiltration rate [litres / hour]			Ultrafiltration rate [litres / hour]		
	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 hours.						

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 hameln 1 g should be administered by intravenous injection, intravenous continuous 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 hameln 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 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 (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 pathogens would be suitable for treatment with ceftazidime. This particularly applies when considering the treatment of patients with bactearemia 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 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 4.8). Discontinuation of therapy with ceftazidime and the administration of specific treatment for *Clostridioides difficile* should be considered. Medicinal products that inhibit peristalsis should not be given.

Renal function
Concominant 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 sequale have occasionally been reported when the dose has not been reduced in patients with renal impairment (see sections 4.2 and 4.8).

Skin reactions

Severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (AGEP), which can be life-threatening or fatal, have been reported with unknown frequency in association with ceftazidime treatment. Patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of these reactions appear, ceftazidime should be withdrawn immediately, and an alternative treatment considered. If the patient has developed a serious reaction such as SJS, TEN, DRESS or AGEP with the use of ceftazidime, treatment with ceftazidime must not be restarted in this patient at any time.

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 50 mg sodium per vial, equivalent to 2.5% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

This medicinal product is administered only after reconstitution - see section 6.6.
The sodium content of the diluent should be taken into account when calculating the total sodium content of the prepared dilution of the product. For detailed information on the sodium content of the solution used to dilute the product, please refer to the product characteristics of the diluent used.

This should be particularly taken into account for those on a low salt 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 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 hameln may be prescribed to pregnant women only if the benefit outweighs the potential 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 associated 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 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-Johnson syndrome Erythema multiforme Angioedema Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)4 Acute generalized exanthematous pustulosis (AGEP)
Renal and		Transient	Interstitial nephritis	

urinary disorders		elevations of blood urea, blood urea nitrogen and/or serum creatinine	Acute renal failure	
General disorders and administration site conditions	Pain and/or inflammation after intramuscular injection	Fever		
Investigations	Positive Coombs' test[5]			

[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 *Clostridioides 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, 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.

Pharmacokinetic/pharmacodynamic (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 the affinity of penicillin-binding proteins for ceftazidime;

- outer membrane impermeability, which restricts access of ceftazidime to penicillin binding proteins in Gram-negative organism;
- bacterial efflux pumps.

Susceptibility testing breakpoints

MIC (minimum inhibitory concentration) interpretive criteria for susceptibility testing have been established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for ceftazidime and are listed here:
https://www.ema.europa.eu/documents/other/minimum-inhibitory-concentration-mic-breakpoints_en.xlsx

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 cloacae* *Escherichia coli* *Klebsiella aerogenes* *Klebsiella pneumoniae* *Klebsiella spp*. (other) *Pseudomonas aeruginosa* *Serratia* spp. *Morganella morganii*
Gram-positive aerobes *Staphylococcus aureus*[£] *Streptococcus pneumoniae*[£££] *Streptococcus viridans*
Gram-positive anaerobes *Clostridium perfringens* *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 *Clostridioides 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* strains are resistant to ceftazidime. [£££] *S. pneumoniae* that demonstrate intermediate susceptibility or 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 kinetic of ceftazidime is linear within the single dose range of 0.5 to 2.0 g following intravenous or intramuscular dosing.

Distribution

Less than 10% of ceftazidime is bound to plasma proteins. Concentrations in excess of the MIC for common pathogens can be achieved in tissues, fluids and secretions 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 cerebrospinal fluid (CSF) in the absence of inflammation. However, concentrations of 4 to 20 mg/L or more are achieved in the cerebrospinal fluid 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 hours. 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 conventional studies of safety pharmacology, repeat dose toxicity, genotoxicity, and toxicity to reproduction. Carcinogenicity studies have not been performed with ceftazidime.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium carbonate

6.2 Incompatibilities

Ceftazidime is less stable in sodium bicarbonate solution than in 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 with vancomycin added to ceftazidime in solution. Therefore, the application kit and intravenous access should be flushed between the administration of these two drugs.

6.3 Shelf life

Unopened vials: 2 years

After reconstitution and dilution:
Chemical and physical in-use stability has been demonstrated for 3 hours at 25°C and 24 hours at 2 to 8°C. The reconstituted and diluted products do not require protection from light.

From a microbiological point of view, unless the method of reconstitution and dilution precludes the risk of contamination, the product should be used immediately.
If not used immediately, in use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

The medicinal product does not require any special temperature storage conditions. Keep the vial in the outer carton in order to protect from light.

For storage conditions after reconstitution/dilution/first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Glass vial with bromobutyl rubber stopper and aluminium seal or aluminium seal with blue plastic flip-off cap. Each pack contains 10 vials.

6.6 Special precautions for disposal and other handling

Vials of Ceftazidime hameln are supplied under reduced pressure. As the product dissolves, carbon dioxide is released and a positive pressure develops. Small bubbles of carbon dioxide in the constituted solution may be ignored.

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

Presentation	Route of administration	Amount of diluent to be added [ml]	Approx. ceftazidime concentration [mg/ml]
1 g	intramuscular injection	3	260
	intravenous bolus	10	90
	intravenous infusion	50*	20
2 g	intravenous bolus	10	170
	intravenous infusion	50*	40

* Addition should be in two stages

Note:
The resulting volume of the solution of ceftazidime in reconstitution medium is increased due to the displacement factor of the drug product resulting in the listed concentrations in mg/ml presented in the above table.

Solutions may range in colour from colorless to pale-yellow depending on concentration and storage conditions used. Within the stated recommendations, product potency is not adversely affected by such colour variations.

Recommended dilution media are:

- 0.9% sodium chloride;
- 5% glucose solution for infusion;
- 5% glucose and 0.9% sodium chloride, 1:1;
- 5% glucose and 0.9% sodium chloride, 2:1;
- Ringer solution;

- lactated Ringer's solution;
- water for injection.

Ceftazidime at concentrations between 1 mg/ml and 40 mg/ml is compatible with the listed above diluents.
Ceftazidime may be constituted for intramuscular use with 1% lidocaine hydrochloride for injections.

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 the intravenous fluids listed above.

Preparation of solutions for intravenous infusion
Prepare using a total of 50 ml (for 1 g and 2 g vials) of compatible diluent (listed above), added in TWO stages as described below.

1. Puncture the stopper with a needle and inject 10 ml of the diluent into a 1 g and 2 g vial.
2. Withdraw the needle and shake the vial to obtain a clear solution. The clear solution will be 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 final delivery vehicle 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 the gas relief needle is not inserted through the vial closure before the product has dissolved.

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

7 MARKETING AUTHORISATION HOLDER

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10 DATE OF REVISION OF THE TEXT