MODULE 1- ADMINISTRATIVE PARTICULARS OF THE PRODUCT

1.3 Product Information

1.3.1 Summary of Product Characteristics (SmPC)

1.3.1.1. Name of the medicinal product:

1.3.1.1.1 (Invented) name of the medicinal product:

Generic Name/INN Name:

Combipack of Ceftazidime for Injection USP 1 gm & Sterilised Water for Injections BP

Brand Name:

BIOSZIME

1.3.1.1.2 Strength:

Each vial contains:

Ceftazidime Pentahydrate USP eq. to.

Anhydrous Ceftazidime 1 gm

1.3.1.1.3 Pharmaceutical form:

Powder for Injection

1.3.1.2. Qualitative and Quantitative Composition:

Sr. No.	Ingredients	Specification	Label Claim	Std. Qty (mg/ Vial)	Function
1.	Sterile Ceftazidime Pentahydrate USP eq. to Anhydrous Ceftazidime*	USP	1000 mg	1000 mg	Active

Note: *The quantity of Ceftazidime USP has to be calculated based on Assay and Loss on Drying.

1.3.1.3. Pharmaceutical form:

Dosage Form:

Powder for Injection

MODULE 1- ADMINISTRATIVE PARTICULARS OF THE PRODUCT

Visual & Physical characteristics of the product:

A white crystalline powder filled in an Intactly sealed clear glass vials.

1.3.1.4. Clinical particulars:

1.3.1.4.1 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.

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.

MODULE 1- ADMINISTRATIVE PARTICULARS OF THE PRODUCT

1.3.4.2 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	

Table 2: Children < 40 kg

Infants and toddlers >2 months and children <	Infection	Usual dose

MODULE 1- ADMINISTRATIVE PARTICULARS OF THE PRODUCT

40 kg		
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	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

Paediatric population

MODULE 1- ADMINISTRATIVE PARTICULARS OF THE PRODUCT

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.

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.			

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

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.

1.3.4.3 Contraindications:

Hypersensitivity to the active substance, to any other cephalosporin or to any of the excipients being used in this formulation.

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

1.3.4.4 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.

MODULE 1- ADMINISTRATIVE PARTICULARS OF THE PRODUCT

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. 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.

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

Important information about one of the ingredients of Ceftazidime:

1 g powder for solution for injection or infusion, 1 g powder for solution for infusion Ceftazidime 1 g contains 2.26mmol of sodium per vial.

This should be considered for patients who are on a controlled sodium diet.

1.3.4.5 Interaction with other medicinal products and other forms of interaction

Chloramphenicol is antagonistic in vitro with Ceftazidime and other cephalosporins. The clinical relevance of this finding is unknown, but if concurrent administration of ceftazidime is proposed, the possibility of antagonism should be considered.

1.3.4.6 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.

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

Breastfeeding

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.

1.3.4.7 Effects on ability to drive and use machines:

No Specific Data Available.

1.3.4.8 Undesirable effects:

Like all medicines, Ceftazidime can cause side effects, although not everybody gets them.

Conditions you need to look out for

The following serious side effects have occurred in a small number of people but their exact frequency is unknown:

- Severe allergic reaction. Signs include raised and itchy rash, swelling, sometimes of the face or mouth causing difficulty in breathing.
- Skin rash, which may blister, and looks like small targets (central dark spot surrounded by a paler area, with a dark ring around the edge).
- A widespread rash with blisters and peeling skin. (These may be signs of 'Stevens-Johnson syndrome' or 'toxic epidermal necrolysis').

- Nervous system disorders: tremors, fits and, in some cases coma. These have occurred in people when the dose they are given is too high, particularly in people with kidney disease.

Contact a doctor or nurse immediately if you get any of these symptoms.

Common side effects

These may affect up to 1 in 10 people:

- Diarrhoea
- Swelling and redness along a vein
- Red raised skin rash which may be itchy
- Pain, burning, swelling or inflammation at the injection site.

Tell your doctor if any of these are troubling you.

Common side effects that may show up in blood tests:

- An increase in a type of white blood cell (eosinophilia)
- An increase in the number of cells that help the blood to clot
- An increase in liver enzymes.

Uncommon side effects

These may affect up to 1 in 100 people:

- Inflammation of the gut which can cause pain or diarrhoea which may contain blood
- thrush - fungal infections in the mouth or vagina
- Headache
- Dizziness
- Stomach ache
- Feeling sick or being sick
- Fever and chills.

Uncommon side effects that may show up in blood tests:

- A decrease in the number of white blood cells
- A decrease in the number of blood platelets (cells that help the blood to clot)
- An increase in the level of urea, urea nitrogen or serum creatinine in the blood.

Other side effects

Other side effects have occurred in a small number of people but their exact frequency is unknown:

- Inflammation or failure of the kidneys
- Pins and needles
- Unpleasant taste in the mouth
- Yellowing of the whites of the eyes or skin.

Other side effects that may show up in blood tests:

- Red blood cells destroyed too quickly
- An increase in a certain type of white blood cells
- Severe decrease in the number of white blood cells.

1.3.4.9 Overdose:

Overdose can lead to neurological sequelae including encephalopathy, convulsion and coma. Serum levels of ceftazidime can be reduced by haemodialysis or peritoneal dialysis.

1.3.5. Pharmacological properties:

1.3.5.1 Pharmacodynamic properties:

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

Mode 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.

1.3.5.2 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.

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.

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.

1.3.6. Pharmaceutical particulars:

1.3.6.1 List of Excipients:

Not Applicable for powder for injection

1.3.6.2 Incompatibilities:

Not applicable

1.3.6.3 Shelf life:

24 months

1.3.6.4 Special precautions for storage:

Store at temperature not exceeding 30 ºC. Protect from light.

1.3.6.5 Nature and contents of container:

Combipack of one 20ml clear glass Vial USP Type III & One 20 ml Plastic ampoule of Sterilised water for injections along with package insert in monocarton.

MODULE 1- ADMINISTRATIVE PARTICULARS OF THE PRODUCT

1.3.6.6 Special precautions for disposal:

No special requirements.

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

1.3.7. Registrant:

CHEZ RESOURCES PHARMACEUTICAL NIGERIA LIMITED,

No. 7, Calabar Street,

Fegge, Onitsha, Anambra State,

NIGERIA.

1.3.8. Manufacturer:

Name	**:**	**Bharat Parenterals Ltd.**
Address	**:**	144 & 146, Jarod Samlaya Road, Vill. Haripura, Ta. Savli, Dist. Vadodara – 391520, Gujarat INDIA.
Telephone Number	**:**	+91-2667-251669, 251670, 251679, 251680
Fax Number	**:**	+91-2667-251679, 251680
E-mail	**:**	bplbrd@yahoo.com, info@bplindia.in, bplbrd@bplindia.in.

1.3.9. Date of revision of the text:

1.3.10. Instructions for Preparation of Radiopharmaceuticals (If Applicable):

Not Applicable