# SUMMARY OF PRODUCT CHARACTERISTICS

**SUMMARY OF PRODUCT CHARACHTERISTICS**

## 1. NAME OF THE MEDICINAL PRODUCT

DELTAZIME 250 mg/ 1 ml powder and solvent for injection solution for intramuscular use
DELTAZIME 500 mg/ 1.5 ml powder and solvent for injection solution for intramuscular use
DELTAZIME 1 g/ 3 ml powder and solvent for injection solution for intramuscular use
DELTAZIME 1 g/ 10 ml powder and solvent for injection solution for intravenous use
DELTAZIME 2 g powder for solution for infusion

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

*DELTAZIME 250 mg/ 1 ml powder and solvent for injection solution for intramuscular use*
A vial of powder contains:
Active substance: ceftazidime pentahydrate 291 mg (equal to ceftazidime 250 mg);

*DELTAZIME 500 mg/ 1.5 ml powder and solvent for injection solution for intramuscular use*
A vial of powder contains:
Active substance: ceftazidime pentahydrate 582 mg (equal to ceftazidime 500 mg);

*DELTAZIME 1 g/ 3 ml powder and solvent for injection solution for intramuscular use*
A vial of powder contains:
Active substance: ceftazidime pentahydrate 1.164 g (equal to ceftazidime 1 g);

*DELTAZIME 1 g/ 10 ml powder and solvent for injection solution for intravenous use*
A vial of powder contains:
Active substance: ceftazidime pentahydrate 1.164 g (equal to ceftazidime 1 g);

*DELTAZIME 2 g powder for solution for infusion*
A vial of powder contains:
Active substance: ceftazidime pentahydrate 2.328 g (equal to ceftazidime 2 g);

For a full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

250 mg, 500 mg powder for solution for injection
Powder for solution for injection

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

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Deltazime is indicated for the treatment of infections stated below in adults and children, including infants (from birth).

- Nosocomial pneumonia

- Bronchopulmonary infections in patients with cystic fibrosis
- Bacterial meningitis
- Chronic suppurative otitis media
- Malignant external otitis
- Complicated urinary tract infections
- Complicated skin and soft tissue infections
- Complicated intra-abdominal infections
- Bone and joint infections
- Dialysis-associated peritonitis in patients undergoing 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 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 |
| Bronchopulmonary infections in patients with cystic fibrosis | 100 to 150 mg/kg/day every 8 hours, up to a maximum of 9 g per day[1]. |
| Febrile neutropenia | 2 g every 8 hours |
| Nosocomial pneumonia | |
| Bacterial meningitis | |
| Bacteraemia* | |
| Bone and joint infections | 1-2 g every 8 hours |
| 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 or 12 hours |
| 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 hours |
| Malignant otitis media | |
| *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 hours[1] |
| Nosocomial pneumonia | |
| Bronchopulmonary infections in patients with 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 have been used without adverse effects.<br>* When associated with, or suspected to be associated with, any of the infections listed in section 4.1. | |

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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, up to a maximum of 6 g/day | |
| Chronic suppurative otitis media | | |
| Malignant external otitis | | |
| Neutropenic children | 150 mg/kg/day in three divided doses, up to a maximum of 6 g/day | |
| Bronchopulmonary infections in patients with cystic fibrosis | | |
| Bacterial meningitis | | |
| Bacteraemia* | | |

| | |
|---|---|
| Bone and joint infections | 100-150 mg/kg/day in three divided doses, up to a maximum of 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 of 100-200 mg/kg/day, up to a maximum of 6 g/day. |
| Nosocomial pneumonia | |
| Bronchopulmonary infections in patients with 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 doses[1]. | |

[1] In neonates and infants ≤ 2 months, serum half-life can be three to four times higher than that in adults.

* When associated with, or suspected to be associated with, any of the infections listed in section 4.1.

Paediatric population

Safety and effectiveness of Deltazime administered as continuous infusion in neonates and children ≤ 2 months of age 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 failure

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 failure (see also section 5.2). Close clinical monitoring for safety and efficacy is advised.

Renal failure

Ceftazidime is excreted unmodified through the kidneys. In patients with impaired renal function the dosage must therefore 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: Maintenance doses of Deltazime recommended in renal failure - intermittent infusion

*Adults and children ≥ 40 kg*

| Creatinine Clearance (ml/min.) | Serum creatinine µmol/l (mg/dl) about | Recommended unit dose of Deltazime (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 should either the unit dose be increased by 50% or the frequency of dosing prolonged.

In children, the creatinine clearance should be adjusted according to body surface area or lean body mass.

Children < 40 kg

| Creatinine Clearance (ml/min) ** | Serum creatinine µmol/l (mg/dl) about | 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.<br>** Estimated based on body surface area, or measured. | | | |

Close clinical monitoring for safety and efficacy is advised.

Table 4: Maintenance doses of Deltazime recommended in renal failure – continuous infusion

*Adults and children ≥40 kg*

| Creatinine Clearance (ml/min.) | Serum creatinine µmol/l (mg/dl) about | 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 h |
| 30-16 | 200-350 (2,3-4,0) | Loading dose of 2 g followed by 1 g/24 h |
| ≤15 | >350 (>4,0) | Not evaluated |

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

*Children < 40 kg*

Safety and effectiveness of Deltazime administered as continuous infusion in children weighing < 40 kg has not been established. Close clinical monitoring for safety and efficacy is advised.

If continuous infusion is used in children with renal failure, the creatinine clearance should be adjusted according to body surface area or lean body mass.

Haemodialysis
The drug serum half-life during haemodialysis ranges from 3 to 5 hours.

Following each haemodialysis session, the maintenance dose of ceftazidime recommended in the table below should be repeated.

Peritoneal dialysis

Ceftazidime can be used both in peritoneal dialysis and in 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 liters of dialysis solution)

For renally impaired patients 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.
In case of low flux haemofiltration apply the recommended dosage for subjects with reduced renal function.

In patients undergoing veno-venous haemofiltration and veno-venous hemodialysis follow the dosage recommendations reported in the following tables:

Table 5: Continuous veno-venous haemofiltration dose guidelines

| **Residual renal function (creatinine clearance ml/min)** | **Maintenance dose (mg) for 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]The maintenance dose should be administered every 12 hours.

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 litres/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] The maintenance dose should be administered every 12 hours.

Method of administration

Ceftazidime should be administered by intravenous injection/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.

## 4.3 Contraindications

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

## 4.4 Special warnings and opportune precautions for use

As with all beta-lactam antibacterial agents, serious and occasionally fatal hypersensitivity reactions have been reported. In case of severe hypersensitivity reactions, treatment with ceftazidime must be discontinued immediately and adequate emergency measures must be initiated.

Before beginning treatment, it should be established whether the patient has a history of severe hypersensitivity reactions to ceftazidime, to other cephalosporins or to any other type of beta-lactam agent. Caution should be used if ceftazidime is given to patients with a history of non-severe hypersensitivity to other beta-lactam agents.

Ceftazidime has a limited spectrum of antibacterial activity. It is not suitable for use as a single agent for the treatment of some types of infections unless the pathogen is already documented and known to be susceptible or there is a very high suspicion that the most likely pathogen 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.

A concurrent treatment with high dosages of cephalosporins and nephrotoxic drugs, such as aminoglycosides or strong diuretics (e.g. furosemide) can negatively affect the 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 a slight interference (false-positive) may occur with copper reduction methods (Benedict's, Fehling's, Clinitest).

Ceftazidime does not interfere with creatinine test in the assay with alkaline picrate.

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 Deltazime:
250 mg powder for solution for injection
Deltazime 250 mg contains 13 mg sodium per vial.

500 mg powder for solution for injection
Deltazime 500 mg contains 26 mg sodium per vial.

1 g powder for solution for injection
Deltazime 1 g contains 52 mg sodium per vial.

2 g powder for solution for infusion.
Deltazime 2 g contains 104 mg sodium per vial.

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

## 4.5 Interactions with other medicinal products and other forms of interaction

Interaction studies have only been conducted with probenecid and furosemide.

The concurrent use of high dosages of nephrotoxic drugs can have a negative impact on renal function (see section 4.4).

Chloramphenicol is an *in vitro* antagonist of ceftazidime and other cephalosporins. The clinical relevance of this observation is unknown, but if ceftazidime and chloramphenicol are administered concurrently, the possible occurrence of antagonism between these two antibiotics should be considered.

## 4.6 Fertility, pregnancy and breastfeeding

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).

Deltazime should be prescribed to pregnant women 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 breastfeeding.

Fertility

No data is available.

## 4.7 Effects on ability to drive vehicles and to 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 following intravenous administration, diarrhoea, transient increases in hepatic enzymes, maculopapular or urticarial rash, pain and/or inflammation following intramuscular injection and positive Coombs' 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 the remaining undesirable effects were mainly established on pharmacovigilance data following the drug marketing and refer to patients' reports rather than to the actual 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 - <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 candidiasis) | | |
| Blood and lymphatic system disorders | Eosinophilia<br>Thrombocytosis | Neutropenia<br>Leucopenia<br>Thrombocytopenia | | Agranulocitosis<br>Haemolytic anaemia<br>Lymphocytosis |
| Immune system disorders | | | | Anaphylaxis (including bronchospasm and/or hypotension) (see section 4.4) |
| Nervous system disorders | | Headache<br>Dizziness | | Neurological sequelae [1]<br>Paraesthesia |
| Vascular disorders | Phlebitis or thrombophlebitis after intravenous administration | | | |
| Gastrointestinal disorders | Diarrhoea | Antibacterial agent-associated diarrhoea and colitis[2] (see section 4.4)<br>Abdominal pain<br>Nausea<br>Vomiting | | Unpleasant taste |
| Hepatobiliary disorders | Transient elevations in one or more hepatic enzymes3 | | | Jaundice |
| Skin and subcutaneous tissue disorders | Maculopapular or urticarial rash | Itching | | Toxic epidermal necrolysis<br>Stevens-Johnson-Syndrome<br>Erythema multiforme<br>Angioedema<br>DRESS[5] |
| Renal and urinary disorders | | Transient elevations of blood urea, blood urea | Interstitial nephritis<br>Acute renal failure | |

| | | | | |
|---|---|---|---|---|
| | | nitrogen and/or serum creatinine | | |
| General disorders and administration site conditions | Pain and/or inflammation after intramuscular injection | Fever | | |
| Investigations | Positive results with Coombs test 4 | | | |

[1] There have been reports of neurological sequelae including tremor, myoclonia, convulsions, encephalopathy, and coma in patients with renal failure in whom the dose of Deltazime was not 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.

[5] There have been rare reports where DRESS has been associated with ceftazidime.

### 4.9 Overdose

Overdosage can lead to neurological sequelae, e.g. encephalopathy, seizures and coma.

Symptoms of overdose can occur if the dose is not reduced appropriately in patients with renal failure (see sections 4.2 and 4.4).

Ceftazidime serum levels are 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 breakpoints2* | ≤ 4 | 8 | > 8 |

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

1Breakpoints related 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. If necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of ceftazidime in some types of infections is questionable.

| Commonly Susceptible Species |
|---|
| Gram-positive aerobes:<br>*Streptococcus pyogenes*<br>*Streptococcus agalactiae* |
| Gram-negative aerobes:<br>*Citrobacter koseri*<br>*Escherichia coli*<br>*Haemophilus influenzae*<br>*Moraxella catarrhalis*<br>*Neisseria meningitidis*<br>*Proteus mirabilis*<br>*Proteus spp. (other)*<br>*Providencia spp.* |
| Species for which acquired resistance may be a problem |

| |
|---|
| Gram-negative aerobes:<br>*Acinetobacter baumannii*£+<br>*Burkholderia cepacia*<br>*Citrobacter freundii*<br>*Enterobacter aerogenes*<br>*Enterobacter cloacae*<br>*Klebsiella pneumoniae*<br>*Klebsiella spp. (other)*<br>*Pseudomonas aeruginosa*<br>*Serratia spp.*<br>*Morganella morganii* |
| Gram-positive aerobes:<br>*Staphylococcus aureus*£<br>*Streptococcus pneumoniae* ££ |
| Gram-positive anaerobes:<br>*Clostridium Perfringens*<br>*Peptococcus spp.*<br>*Peptostreptococcus spp.* |
| Gram-negative anaerobes:<br>*Fusobacterium spp.* |
| Inherently resistant organisms |
| Gram-positive aerobes:<br>Enterococci including *Enterococcus faecalis and Enterococcus faecium*<br>*Listeria spp.* |
| Gram-positive anaerobes:<br>*Clostridium difficile* |
| Gram-negative anaerobes:<br>*Bacteroides spp.* (many strains of *Bacteroides fragilis* are resistant). |
| Others:<br>*Chlamydia spp.*<br>*Mycoplasma spp.*<br>*Legionella spp.* |
| £ *S. aureus* that is methicillin-susceptible is considered to have inherent low susceptibility to ceftazidime. All methicillin-resistant S. aureus are resistant to ceftazidime.<br>†† *S. pneumoniae* that demonstrate intermediate susceptibility or are resistant to penicillin can be expected to demonstrate at least reduced susceptibility to ceftazidime.<br><br>+ High rates of resistance have been observed in one or more areas/countries/regions within the EU. |

## 5.2 Pharmakokinetic 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, which results 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 metabolized.

Elimination

After parenteral administration plasma levels decrease with a half-life of about 2 hours. 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.

Specific groups of patients

*Renal failure*

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

*Hepatic failure*

The presence of mild to moderate hepatic dysfunction had no effect on the pharmacokinetics of ceftazidime following individual administrations of 2 g by intravenous route every 8 hours for 5 days, provided that 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 repeated BID dosing of 2 g IV bolus injections in elderly patients 80 years old 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, repeated dose toxicity, genotoxicity, toxicity to reproduction. Carcinogenicity studies have not been performed with ceftazidime.

# 6. PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

Vials with powder: Sodium carbonate anhydrous.
Vial with solvent: water for injectable preparations.

## 6.2 Incompatibilities

Ceftazidime can be diluted in the usual infusion fluids, except sodium bicarbonate solutions in which it is less stable. Moreover, ceftazidime should not be administered in the same infusion set or in the same syringe with aminoglycosides.
Formations of precipitates were reported when adding vancomycin to ceftazidime solutions. Should it be required to administer these two antibiotics sequentially, it is recommended to let a proper amount of infusion fluid run in order to wash the infusion set properly between the two administrations.

## 6.3 Shelf life

21 months

## 6.4 Special precautions for storage

Before reconstitution store the vials protected from light at a temperature not higher than 25°C.
Reconstituted solutions with water for injectable preparations or compatible infusion fluids (e.g. glucose or sodium lactate saline) should be normally used within 6 hours if stored at room temperature or within 1 day if stored at 4 °C.
Solutions can range from light yellow to amber depending on the concentration, the diluent used and the storage conditions.
The vials of DELTAZIME can develop, after reconstitution, a positive pressure in their interior, due to the release of carbon dioxide.

## 6.5 Nature and contents of container

Colourless glass vials of type III with elastomeric caps and aluminium caps; colourless glass vials type I.
DELTAZIME 250 mg/1 ml powder and solvent for injection solution for intramuscular use – 1 vial with powder + 1 vial with solvent 1 ml
DELTAZIME 500 mg/1,5 ml powder and solvent for injection solution for intramuscular use – 1 vial with powder + 1 vial with solvent 1,5 ml
DELTAZIME 1 g/3 ml powder and solvent for injection solution for intramuscular use – 1 vial with powder + 1 vial with solvent 3 ml
DELTAZIME 1 g/10 ml powder and solvent for injection solution for intravenous use – 1 vial with powder + 1 vial with solvent 10 ml
DELTAZIME 2 g powder for solution for infusion – 1 vial with powder

## 6.6 Special precautions for disposal and handling

All sizes of vials of Deltazime 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 reconstituted solution may be ignored.

Instructions for reconstitution

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

| Vial sizes | Amount of diluent to be added (ml) | Approximate concentration (mg/ml) |
|---|---|---|
| 250 mg powder for solution for injection | | |

| | | | |
|---|---|---|---|
| 250 mg | Intramuscular<br>Intravenous bolus | 1.0 ml<br>2.5 ml | 210<br>90 |
| 500 mg powder for solution for injection | | | |
| 500 mg | Intramuscular<br>Intravenous bolus | 1.5 ml<br>5 ml | 260<br>90 |
| 1 g powder for solution for injection or for infusion | | | |
| 1 g | Intramuscular<br>Intravenous bolus.<br>Intravenous infusion | 3 ml<br>10 ml<br>50 ml* | 260<br>90<br>20 |
| 2 g powder for solution for injection or for infusion | | | |
| 2 g | Intravenous bolus<br>Intravenous infusion | 10 ml<br>50 ml* | 170<br>40 |

*Note: Addition should be in two stages.

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

Ceftazidime, at concentrations ranging from 1 mg/ml to 40 mg/ml, is compatible with:

- sodium chloride 9 mg/ml (0.9%) for injectable preparations
- M/6 sodium lactate for injectable preparations
- compound sodium lactate for injectable preparations (Hartmann's solution)
- 5% dextrose for injectable preparations
- 0.225% sodium chloride and 5% dextrose for injectable preparations
- 0.45% sodium chloride and 5% dextrose for injectable preparations
- 0.9% sodium chloride and 5% dextrose for injectable preparations
- 0.18% sodium chloride and 4% dextrose for injectable preparations
- 10% dextrose for injectable preparations
- 10% Dextran 40 for injectable preparations in 0.9 sodium chloride for injectable preparations
- 10% Dextran 40 for injectable preparations in 5% dextrose for injectable preparations
- 6% Dextran 70 for injectable preparations in 0.9 sodium chloride for injectable preparations
- 6% Dextran 70 for injectable preparations in 5% dextrose for injectable preparations

Ceftazidime, at concentrations ranging from 0.05 mg/ml to 0.25 mg/ml, is compatible with lactate solution for intraperitoneal dialysis.

Ceftazidime may be reconstituted for intramuscular use with 0.5% or 1% Lidocaine Hydrochloride for injectable preparations.

The contents of a 500 mg vial of ceftazidime for injection, reconstituted with 1.5 ml water for injections, may be added to metronidazole solutions (500 mg in 100 ml) and both retain their activity.

250 mg, 500 mg powder for solution for injection, 1 g, 2 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. 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 most commonly used intravenous fluids.

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

Preparation of solutions for intravenous infusion of ceftazidime injection in standard vial presentation (minibag or burette-type set)
Prepare the solution by using a total of 50 ml (for 1 g and 2 g vials) of compatible diluent and add it in TWO stages as described below.

1. Introduce the syringe needle through the vial closure and inject 10 ml of diluent for the 1 g and 2 g vials.
2. Withdraw the needle and shake the vial to give a clear solution.
3. Do not insert a gas relief needle until the product has dissolved. Insert a gas relief needle through the vial closure to relieve the internal pressure.
4. Transfer the reconstituted solution to final delivery vehicle (e.g. mini-bag or burette-type set) making up a total volume of at least 50 ml and administer by intravenous infusion over 15 to 30 minutes.

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.

1 g, 2 g powder for solution for infusion (Monovial presentation)

Preparation of solutions for intravenous infusion
The contents of the Monovial is reconstitued by using small volume infusion bags containing 0.9% Sodium Chloride solution or 5% Dextrose or another compatible infusion fluid.

The 2 g Monovial must be reconstituted by using 100 ml infusion bags.

1. Peel off the removable top part of the label and remove the protection cap.
2. Insert the needle of the Monovial into the additive port of the infusion bag.
3. To activate, push the plastic needle holder of the Monovial down onto the vial shoulder until a “click” is heard.
4. Holding it upright, fill the vial to approximately two-thirds capacity by squeezing the bag several times.
5. Shake the vial to reconstitute the ceftazidime.
6. On reconstitution, the ceftazidime will effervesce slightly.
7. With the vial uppermost, transfer the reconstituted ceftazidime into the infusion bag by squeezing and releasing the bag.
8. Repeat steps 4 to 7 to rinse the inside of the vial. Dispose of the empty Monovial safely. Check that the powder has dissolved, and that the bag has no leaks.

The unused product and the waste deriving from this drug must be disposed of in accordance with local legal requirements.

## 7. MARKETING AUTHORIZATION HOLDER

Laboratorio Farmaceutico C.T. S.r.l. - Strada Solaro, 75/77 - 18038 Sanremo (IM)

**8. MARKETING AUTHORISATION NUMBER**

DELTAZIME 250 mg/1 ml powder and solvent for injection solution for intramuscular use – 1 vial with powder + vial with solvent 1 ml: MA no 036590014

DELTAZIME 500 mg/1.5 ml powder and solvent for injection solution for intramuscular use – 1 vial with powder + vial with solvent 1.5 ml: MA no 036590026

DELTAZIME 1 g/3 ml powder and solvent for injection solution for intramuscular use – 1 vial with powder + vial with solvent 3 ml: MA no 036590038

DELTAZIME 1 g/10 ml powder and solvent for injection solution for intravenous use – 1 vial with powder + vial with solvent 10 ml: MA no 036590040

DELTAZIME 2 g powder for solution for infusion – 1 vial with powder: MA no 036590053

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

07/2005

**10. DATE OF REVISION OF THE TEXT**

09/2016

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