Ceftazidime

QUALITATIVE AND QUANTITATIVE COMPOSITION
FORTUM injection contains 250 mg, 500 mg, 1 g, 2 g or 3 g of ceftazidime (as pentahydrate).
FORTUM MONOVIAL™ contains 1 g or 2 g of ceftazidime (as pentahydrate).

PHARMACEUTICAL FORM
Powder for injection/infusion

CLINICAL PARTICULARS
Indications
Treatment of single or multiple infections caused by susceptible organisms.
May be used alone as first choice drug before the results of sensitivity tests are available.
May be used in combination with an aminoglycoside or most other beta-lactam antibiotics.
May be used with an antibiotic against anaerobes when the presence of Bacteroides fragilis is suspected.

Indications include:
- severe infections e.g.
- septicaemia, bacteraemia, peritonitis, meningitis.
- infections in immunosuppressed patients
- infections in patients in intensive care, e.g. infected burns
- respiratory tract infections including lung infections in cystic fibrosis
- ear, nose and throat infections
- urinary tract infections
- skin and soft tissue infections
- gastrointestinal, biliary and abdominal infections
- bone and joint infections
- infections associated with haemo- and peritoneal dialysis and with continuous ambulatory peritoneal dialysis (CAPD)
- prophylaxis: prostatic surgery (transurethral resection).

Dosage and Administration
Dosage depends upon the severity, sensitivity, site and type of infection and upon the age and renal function of the patient.
Use FORTUM injection i.v. or by deep i.m. injection.
Recommended i.m. injection sites are the upper outer quadrant of the gluteus maximus or lateral part of the thigh.
FORTUM solutions may be given directly into the vein or introduced into the tubing of a giving set if the patient is receiving parenteral fluids.
FORTUM MONOVIAL is for i.v. infusion only.

• Adults
1 to 6 g/day in two or three divided doses by i.v. or i.m. injection.
Urinary tract and less severe infections:
– 500 mg or 1 g every 12 h.
Most infections:
– 1 g every 8 h or 2 g every 12 h.
Very severe infections particularly in immunocompromised patients including those with neutropenia:
– 2 g every eight or 12 h, or 3 g every 12 h.
Fibrocystic adults with pseudomonal lung infections:
– 100 to 150 mg/kg/day in three divided doses.
In adults with normal renal function 9 g/day has been used without ill effect.
When used as a prophylactic agent in prostatic surgery, 1 g should be given at the induction of anaesthesia. A second dose should be considered at the time of catheter removal.

• Infants and children (greater than 2 months)
30 to 100 mg/kg/day in two or three divided doses.
Doses up to 150 mg/kg/day (maximum 6 g/day) in three divided doses may be given to infected immunocompromised or fibrocystic children or children with meningitis.
**Peritoneal dialysis**

FORTUM may be used in peritoneal dialysis and continuous ambulatory peritoneal dialysis (CAPD). In addition to i.v. use, FORTUM 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 arteriovenous 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 dosage recommended under impaired renal function.

For patients on venovenous haemofiltration and venovenous haemodialysis, follow the dosage recommendations in the tables below.

### Continuous venovenous haemofiltration dosage guidelines for FORTUM

<table>
<thead>
<tr>
<th>Residual renal function (creatinine clearance in ml/min)</th>
<th>Maintenance dose (mg) for a ultrafiltration rate (ml/min) of</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>16.7</td>
</tr>
<tr>
<td>33.3</td>
<td>50</td>
</tr>
</tbody>
</table>

The serum half-life during haemodialysis ranges from 3 to 5 h. Following each haemodialysis period, the maintenance dose of FORTUM recommended in the above table should be repeated.
Contraindications
- Patients with known hypersensitivity to cephalosporin antibiotics.
- Hypersensitivity to ceftazidime pentahydrate or to any of the excipients of the injection.

Warnings and Precautions
Before beginning treatment establish whether the patient has a history of hypersensitivity reactions to ceftazidime, cephalosporins, penicillins or other drugs.

Special care is indicated in patients who have experienced an allergic reaction to penicillins or other beta-lactams.

If an allergic reaction to FORTUM occurs discontinue the drug. Serious hypersensitivity reactions may require epinephrine (adrenaline), hydrocortisone, antihistamine or other emergency measures.

Concurrent treatment with high doses of cephalosporins and nephrotoxic drugs such as aminoglycosides or potent diuretics (e.g. furosemide) may adversely affect renal function.

Clinical experience has shown that this is not likely to be a problem with FORTUM at the recommended dose levels. There is no evidence that FORTUM adversely affects renal function at normal therapeutic doses.

Ceftazidime is eliminated via the kidneys, therefore the dosage should be reduced according to the degree of renal impairment. Neurological sequelae have occasionally been reported when the dose has not been reduced in patients with renal impairment (see Dosage and Administration – Renal Impairment and Adverse Reactions).

As with other broad spectrum antibiotics, prolonged use may result in the overgrowth of non-susceptible organisms (e.g. Candida, enterococci) which may require interruption of treatment or appropriate measures. Repeated evaluation of the patient’s condition is essential.

As with other extended-spectrum cephalosporins and penicillins, some initially susceptible strains of Enterobacter spp. and Serratia spp. may develop resistance during FORTUM therapy. When clinically appropriate during therapy of such infections, periodic susceptibility testing should be considered.

Interactions
Concurrent use of high doses with nephrotoxic drugs may adversely affect renal function (see Warnings and Precautions).

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

In common with other antibiotics, ceftazidime may affect the gut flora, leading to lower oestrogen reabsorption and reduced efficacy of combined oral contraceptives.

Ceftazidime does not interfere with enzyme-based tests for glycosuria but slight interference may occur with copper reduction methods (Benedict’s, Fehling’s, Clinitest).

Ceftazidime does not interfere in the alkaline picrate assay for creatinine.

Pregnancy and Lactation
There is no experimental evidence of embryopathic or teratogenic effects, but as with all drugs, FORTUM should be administered with caution during the early months of pregnancy and early infancy.

Ceftazidime is excreted in human milk in small quantities and should be used with caution in breast feeding.

Effects on Ability to Drive and Use Machines
None reported.

Adverse Reactions
Data from large clinical trials (internal and published) were used to determine the frequency of very common to 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.
<table>
<thead>
<tr>
<th>The following convention has been used for the classification of frequency:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>very common:</td>
<td>≥1 in 10</td>
</tr>
<tr>
<td>common:</td>
<td>≥1 in 100 and &lt;1 in 10</td>
</tr>
<tr>
<td>uncommon:</td>
<td>≥1 in 1,000 and &lt;1 in 100</td>
</tr>
<tr>
<td>rare:</td>
<td>≥1 in 10,000 and &lt;1 in 1,000</td>
</tr>
<tr>
<td>very rare:</td>
<td>&lt;1/10,000.</td>
</tr>
</tbody>
</table>

**Skin and subcutaneous tissue disorders**

- Common: Maculopapular or urticarial rash.
- Uncommon: Pruritus.
- Very rare: Angioedema, erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis.

**General disorders and administration site conditions**

- Common: Pain and/or inflammation after i.m. injection.
- Uncommon: Fever.

**Investigations**

- Common: Positive Coombs test.
- Uncommon: As with some other cephalosporins, transient elevations of blood urea, blood urea nitrogen and/or serum creatinine have been observed. A positive Coombs test develops in about 5% of patients and may interfere with blood cross-matching.

**Overdose**

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

**Pharmacological Properties**

**Pharmacodynamics**

- **Mechanism of Action**
  - Ceftazidime is bactericidal in action. It acts by inhibiting bacterial cell wall synthesis.

**Pharmacodynamic Effects**

- **Bacteriology**
  - A wide range of pathogenic strains and isolates are susceptible in vitro including strains resistant to gentamicin and other aminoglycosides. Ceftazidime is highly stable to most clinically important beta-lactamases produced by both Gram-positive and Gram-negative organisms, therefore it is active against many ampicillin- and cephalothin-resistant strains.
  - Ceftazidime has high intrinsic activity in vitro and acts within a narrow MIC range for most genera with minimal changes in MIC at varied inoculum levels. In vitro the activities of ceftazidime and aminoglycosides in combination are additive. There is evidence of synergy in some strains.
Ceftazidime is active in vitro against the following organisms:

**Gram-negative:**
- Pseudomonas aeruginosa
- Pseudomonas spp (including Ps. pseudomallei)
- Escherichia coli
- Klebsiella spp. (including Klebsiella pneumoniae)
- Proteus mirabilis
- Proteus vulgaris
- Morganella morganii (formerly Proteus morganii)
- Proteus rettgeri
- Providencia spp.
- Enterobacter spp.
- Citrobacter spp.
- Serratia spp.
- Salmonella spp.
- Shigella spp.
- Yersinia enterocolitica
- Pasteurella multocida
- Acinetobacter spp.
- Neisseria gonorrhoeae
- Neisseria meningitidis
- Haemophilus influenzae (including ampicillin resistant strains)
- Haemophilus parainfluenzae (including ampicillin resistant strains)

**Gram-positive:**
- Staphylococcus aureus (methicillin-sensitive strains)
- Staphylococcus epidermidis (methicillin-sensitive strains)
- Micrococcus spp.
- Streptococcus pyogenes (Group A beta-haemolytic streptococci)
- Streptococcus Group B (S. agalactiae)
- Streptococcus pneumoniae
- Streptococcus mitis
- Streptococcus spp (excluding Enterococcus (Streptococcus faecalis))
- Anaerobic strains:
  - Peptococcus spp.
  - Peptostreptococcus spp.
  - Streptococcus spp.
  - Propionibacterium spp.

Ceftazidime is not active in vitro against the following organisms:

**Fusobacterium spp.**

**Bacteroides spp** (many strains of Bacteroides fragilis resistant).

Ceftazidime is not active in vitro against the following organisms:

**Methicillin-resistant staphylococci.**

**Enterococcus (Streptococcus) faecalis** and many other enterococci.

**Clostridium difficile**

**Listeria monocytogenes**

**Campylobacter spp.**

**Pharmacokinetics**

**Absorption**

After i.m. administration of 500mg and 1g, peak levels of 18 and 37 mg/l, respectively, are achieved rapidly. Five minutes after i.v. bolus injection of 500mg, 1g or 2g, serum levels are, respectively, 46, 87 and 170 mg/l.

**Distribution**

Therapeutically effective concentrations are still present in the serum 8 to 12h after either i.v. or i.m. administration. Serum protein binding is 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, therapeutic levels of 4 to 20 mg/l or more are achieved in the CSF when the meninges are inflamed.

**Metabolism**

Ceftazidime is not metabolised in the body.

**Elimination**

Parenteral administration produces high and prolonged serum levels, which decrease with a half-life of about 2h. Ceftazidime is excreted unchanged, in active form into the urine by glomerular filtration; approximately 80 to 90% of the dose is recovered in the urine within 24h. Less than 1% is excreted via the bile, which limits the amount entering the bowel.
Small bubbles of carbon dioxide in the constituted solution may be ignored.

<table>
<thead>
<tr>
<th>Vial Size</th>
<th>Amount of Diluent to be added (ml)</th>
<th>Approximate Concentration (mg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>250 mg</td>
<td>1.0 ml Intramuscular 2.5 ml Intravenous</td>
<td>210 90</td>
</tr>
<tr>
<td>500 mg</td>
<td>1.5 ml Intramuscular 5 ml Intravenous</td>
<td>260 90</td>
</tr>
<tr>
<td>1 g</td>
<td>3 ml Intramuscular bolus 10 ml Intravenous infusion 50 ml*</td>
<td>260 90 20</td>
</tr>
<tr>
<td>2 g</td>
<td>10 ml Intravenous bolus 50 ml* Intravenous infusion</td>
<td>170 40</td>
</tr>
<tr>
<td>3 g</td>
<td>15 ml Intravenous bolus 75 ml* Intravenous infusion</td>
<td>170 40</td>
</tr>
</tbody>
</table>

*NOTE: Addition should be in two stages (see text)

Solutions range 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 between 1 mg/ml and 40 mg/ml is compatible with:
- 0.9% Sodium Chloride Injection
- M/6 Sodium Lactate Injection
- Compound Sodium Lactate Injection (Hartmann’s Solution)
- 5% Dextrose Injection
- 0.225% Sodium Chloride and 5% Dextrose Injection
- 0.45% Sodium Chloride and 5% Dextrose Injection
- 0.9% Sodium Chloride and 5% Dextrose Injection
- 0.18% Sodium Chloride and 4% Dextrose Injection
- 10% Dextrose Injection
- Dextran 40 Injection 10% in 0.9% Sodium Chloride Injection
- Dextran 40 Injection 10% in 5% Dextrose Injection
- Dextran 70 Injection 6% in 0.9% Sodium Chloride Injection

**Special Patient Populations**
Elimination of ceftazidime is decreased in patients with impaired renal function and the dose should be reduced. (See Dosage and Administration - Renal Impairment, Warnings and Precautions).

**Pre-clinical Safety Data**
No additional data of relevance.

**PHARMACEUTICAL PARTICULARS**

**List of Excipients**
Sodium carbonate (anhydrous).

**Incompatibilities**
FORTUM is less stable in Sodium Bicarbonate Injection than in other i.v. fluids. It is not recommended as a diluent. FORTUM and aminoglycosides should not be mixed in the same giving set or syringe. Precipitation has been reported with vancomycin added to FORTUM in solution. Therefore, it would be prudent to flush giving sets and i.v. lines between administration of these two agents.

**Shelf Life**
The expiry date is indicated on the packaging.

**Special Precautions for Storage**
Vials of FORTUM for Injection should be stored at room temperature (the temperature to be defined by the appropriate pharmacopoeia).
Occasional storage at temperatures not higher than 30°C for up to two months is not detrimental to the product.
Protect unconstituted vials from light.

**Nature and Contents of Container**
As registered locally.

**Instructions for Use/Handling**
FORTUM for injection/infusion is compatible with most commonly used i.v. fluids.
However, Sodium Bicarbonate Injection is not recommended as a diluent (see Incompatibilities).
All sizes of vials of Fortum Injection and Monovial are supplied under reduced pressure.
As the product dissolves, carbon dioxide is released and a positive pressure develops.
DexTRAN 70 Injection 6% in 5% Dextrose Injection. Ceftazidime at concentrations between 0.05 mg/ml and 0.25 mg/ml is compatible with Intra-peritoneal Dialysis Fluid (Lactate).

FORTUM may be constituted for i.m. use with 0.5% or 1% Lignocaine Hydrochloride Injection. Both components retain satisfactory potency when ceftazidime at 4 mg/ml is admixed with: Hydrocortisone (hydrocortisone sodium phosphate) 1 mg/ml in 0.9% Sodium Chloride Injection or 5% Dextrose Injection. Cefuroxime (cefuroxime sodium) 3 mg/ml in 0.9% Sodium Chloride Injection. Cloxacillin (cloxacillin sodium) 4 mg/ml in 0.9% Sodium Chloride Injection. Heparin 10 IU/ml or 50 IU/ml in 0.9% Sodium Chloride Injection. Potassium Chloride 10 mEq/l or 40 mEq/l in 0.9% Sodium Chloride Injection.

The contents of a 500 mg vial of FORTUM for injection, constituted with 1.5 ml Water for Injections, may be added to metronidazol injection (500 mg in 100 ml) and both retain their activity.

**Preparation of solutions for i.m. or i.v. bolus injection**

1. Introduce the syringe needle through the vial closure and inject the recommended volume of diluent.
2. Withdraw the needle and shake the vial to give a clear solution.
3. Invert the vial. With the syringe piston fully depressed insert the needle into the solution. Withdraw the total volume of solution into the syringe ensuring that the needle remains in the solution. Small bubbles of carbon dioxide may be disregarded.

**Preparation of solutions for iv infusion from FORTUM injection (mini-bag or burette-type set)**

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

1 g, 2 g and 3 g vials for i.v. infusion:

1. Introduce the syringe needle through the vial closure and inject 10 ml of diluent for the 1 g and 2 g vials, and 15 ml for the 3 g vial.
2. Withdraw the needle and shake the vial to give a clear solution.
3. Do not insert a gas relief needle until the product has dissolved. Insert a gas relief needle through the vial closure to relieve the internal pressure.
4. 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 (75 ml for the 3 g vial), 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.

**Preparation of solution for i.v. infusion using FORTUM MONOVIAL**

(Mandatory only for those countries where MONOVIAL is registered)

The contents of the Monovial are added to small volume infusion bags containing 0.9% Sodium Chloride Injection, or 5% Dextrose Injection, or another compatible fluid.

The 2 g Monovial must be constituted using a 100 ml infusion bag.

1. Peel off the removable top part of the label and remove the 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 FORTUM.
6. On reconstitution, FORTUM will effervesce slightly.
7. With the vial uppermost, transfer the reconstituted FORTUM 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.
Not all presentations are available in every country.
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the GlaxoSmithKline group of companies