

DATA SHEET

FORTUM[®] Injection.

FORTUM Injection contains 500mg, 1g, or 2g of ceftazidime (as pentahydrate).

Qualitative and quantitative composition

FORTUM is supplied as a white to faintly yellow powder containing 118mg sodium carbonate per gram of ceftazidime.

On the addition of Water for injection, FORTUM dissolves with effervescence to produce a clear solution for injection or infusion.

Pharmaceutical form

Powder for Injection/Infusion.

Clinical particulars

Therapeutic Indications

Treatment of single or multiple infections caused by susceptible organisms. May be used alone as first choice medicine before the results of sensitivity tests are available.

May be used in combination with an aminoglycoside or most other β -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).

Posology and Method of Administration

Posology

Dosage depends upon the severity, sensitivity, site and type of infection and upon the age and renal function of the patient.

Adults:-

1-6g/day in 2 or 3 divided doses by iv or im injection.

Urinary tract and less severe infections.

- 500mg or 1g every 12 hours.

Most infections.

- 1g every 8 hours or 2g every 12 hours.

Very severe infections particularly in immunocompromised patients including those with neutropenia.

- 2g every 8 or 12 hours, or 3g every 12 hours.

Fibrocystic adults with pseudomonal lung infections.

- 100-150mg/kg/day in 3 divided doses.

In adults with normal renal function 9g/day has been used without ill effect.

Infants and children (> 2 months):-

30 - 100mg/kg/day in 2 or 3 divided doses.

Doses up to 150mg/kg/day (maximum 6g/day) in three divided doses may be given to infected immunocompromised or fibrocystic children or children with meningitis.

Neonates (0 - 2 months):-

25-60mg/kg/day in 2 divided doses.

In neonates the serum half life of ceftazidime can be 3-4 times that in adults.

Use in the Elderly:-

In view of the reduced clearance of ceftazidime in acutely ill elderly patients, the daily dosage should not normally exceed 3g, especially in those over 80 years of age.

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 1g should be given. Maintenance doses should be based on GFR:-

Recommended maintenance doses of ceftazidime in renal insufficiency

Creatinine Clearance (mL/min)	Approx. Serum creatinine (micromol/L) (mg/dL)	Recommended unit dose of ceftazidime (g)	Frequency of dosing (hourly)
> 50	< 150 (< 1.7)	Normal dosage	
50 - 31	150 – 200 (1.7 - 2.3)	1.0	12
30 - 16	200 – 350 (2.3 - 4.0)	1.0	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 such patients the ceftazidime serum levels should be monitored and trough levels should not exceed 40mg/L.

In children 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 above 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 250mg for 2 litres of dialysis solution).

For patients in renal failure on continuous arteriovenous haemodialysis or high-flux haemofiltration in intensive therapy units; 1g 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 ceftazidime

Residual renal function (creatinine clearance in mL/min)	Maintenance dose (mg) for a ultrafiltration rate (mL/min) of ^a :			
	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

^aMaintenance dose to be administered every 12 h.

Ceftazidime dosage guidelines during continuous venovenous haemodialysis

Residual renal function (creatinine clearance in mL/min)	Maintenance dose (mg) for a dialysate inflow rate of ^a :					
	1.0 litres/h			2.0 litres/h		
	Ultrafiltration rate (litres/h)			Ultrafiltration rate (litres/h)		
	0.5	1.0	2.0	0.5	1.0	2.0
0	500	500	500	500	500	750
5	500	500	750	500	500	750
10	500	500	750	500	750	1000
15	500	750	750	750	750	1000
20	750	750	1000	750	750	1000

^aMaintenance dose to be administered every 12 h.

Method of Administration.

Use FORTUM Injection intravenously or by deep intramuscular injection. Recommended im 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.

Contraindications

Patients with known hypersensitivity to cephalosporin antibiotics.

Hypersensitivity to ceftazidime pentahydrate or to any of the excipients.

Special Warnings and Special Precautions for Use

Before beginning treatment establish whether the patient has a history of hypersensitivity reactions to ceftazidime, cephalosporins, penicillins or other medicines. Special care is indicated in patients who have experienced an allergic reaction to penicillins or other beta-lactams. If an allergic reaction to ceftazidime occurs discontinue the medicine. Serious hypersensitivity reactions may require epinephrine (adrenaline), hydrocortisone, antihistamine or other emergency measures.

Concurrent treatment with high doses of cephalosporins and nephrotoxic medicines such as aminoglycosides or potent diuretics (e.g. frusemide) may adversely affect renal function. Clinical experience has shown that this is not likely to be a problem with ceftazidime at the recommended dose levels. There is no evidence that ceftazidime 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 Posology and Method of Administration - Renal Impairment and Undesirable Effects).

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 ceftazidime therapy. When clinically appropriate during therapy of such infections, periodic susceptibility testing should be considered.

Interaction with Other Medicinal Products and Other Forms of Interaction

Concurrent use of high doses with nephrotoxic medicines may adversely affect renal function (see Special Warnings and Special Precautions for Use).

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.

Use During Pregnancy and Lactation

There is no experimental evidence of embryopathic or teratogenic effects, but as with all medicines, ceftazidime 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.

Undesirable Effects

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.

The following convention has been used for the classification of frequency:

very common $\geq 1/10$,
common $\geq 1/100$ and $< 1/10$,
uncommon $\geq 1/1000$ and $< 1/100$,
rare $\geq 1/10,000$ and $< 1/1000$,
very rare $< 1/10,000$.

Infections and infestations

Uncommon: Candidiasis; (including vaginitis and oral thrush).

Blood and lymphatic system disorders

Common: Eosinophilia and thrombocytosis.

Uncommon: Leucopenia, neutropenia, and thrombocytopenia.

Very Rare: Lymphocytosis, haemolytic anaemia, and agranulocytosis.

Immune system disorders

Very Rare: Anaphylaxis (including bronchospasm and/or hypotension).

Nervous system disorders

Uncommon: Headache and dizziness.

Very Rare: Paraesthesia.

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.

Vascular disorders

Common: Phlebitis or thrombophlebitis with IV administration.

Gastrointestinal disorders

Common: Diarrhoea.

Uncommon: Nausea, vomiting, abdominal pain, and colitis.

Very Rare: Bad taste.

As with other cephalosporins, colitis may be associated with *Clostridium difficile* and may present as pseudomembranous colitis.

Hepatobiliary disorders

Common: Transient elevations in one or more of the hepatic enzymes, ALT (SGPT), AST (SOGT), LDH, GGT and alkaline phosphatase.

Very Rare: Jaundice.

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 IM 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

Pharmacodynamic Properties

Bacteriology:-

Ceftazidime is bactericidal in action. It acts by inhibiting bacterial cell wall synthesis. 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 β -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 β -haemolytic streptococci)
Streptococcus Group B (Streptagalactiae).
Streptococcus pneumoniae.
Streptococcus mitis.
Streptococcus spp (excluding Enterococcus (Streptococcus) faecalis).

Anaerobic strains:-

Peptococcus spp.
Peptostreptococcus spp.
Streptococcus spp.
Propionibacterium spp.
Clostridium perfringens.
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.

Pharmacokinetic Properties

Absorption

After im administration of 500mg and 1g, peak levels of 18 and 37mg/L respectively are rapidly achieved and 5 minutes after iv bolus injection of 500mg, 1g or 2g, serum levels are respectively 46, 87 and 170mg/L.

Distribution

Therapeutically effective concentrations are still present in the serum 8-12 hours after either iv or im 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 4-20mg/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 2 hours. Ceftazidime is excreted unchanged, in active form into the urine by glomerular filtration; approximately 80-90% of the dose is recovered in the urine within 24 hours. Elimination of ceftazidime is decreased in patients with impaired renal function and the dose should be reduced. (See section on renal impairment). Less than 1% is excreted via the bile, which limits the amount entering the bowel.

Pharmaceutical particulars

List of Excipients

Sodium carbonate (anhydrous).

Incompatibilities

FORTUM is less stable in Sodium Bicarbonate Injection 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 when vancomycin has been added to ceftazidime in solution. Therefore, it would be prudent to flush giving sets and intravenous lines between administration of these two agents.

Shelf Life

Dry shelf life:-

FORTUM vials for Injection: 3 years below 25°C.

Special Precautions for Storage

Vials of FORTUM for Injection should be stored at room temperature.

Occasional storage at temperatures not higher than 30°C for up to 2 months is not detrimental to the product.

Protect unconstituted vials from light.

Nature and Contents of Container

Individually cartoned vials of FORTUM for Injection containing 500mg or 1g ceftazidime (as pentahydrate) for intramuscular or intravenous use.

Individually cartoned vials of FORTUM for Injection containing 2g ceftazidime (as pentahydrate) for intravenous use.

Instructions for Use/Handling

FORTUM is compatible with most commonly used intravenous fluids.

All sizes of vials of FORTUM for Injection 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.

Vial Size		Amount of Diluent to be added (mL)	Approximate Concentration (mg/mL)
500mg	Intramuscular	1.5mL	260
	Intravenous	5mL	90
1g	Intramuscular	3mL	260
	Intravenous bolus	10mL	90
	Intravenous infusion	50mL #	20
2g	Intravenous bolus	10mL	170
	Intravenous infusion	50mL #	40

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

FORTUM is compatible with most commonly used intravenous fluids.

However, Sodium Bicarbonate Injection is not recommended as a diluent (see incompatibilities).

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 1mg/mL and 40mg/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.
- Dextran 70 Injection 6% in 5% Dextrose Injection.

Ceftazidime at concentrations between 0.05mg/mL and 0.25mg/mL is compatible with Intra-peritoneal Dialysis Fluid (Lactate).

Ceftazidime may be constituted for intramuscular use with 0.5% or 1% Lignocaine Hydrochloride Injection.

Both components retain satisfactory potency when ceftazidime at 4mg/mL is admixed with:

- Hydrocortisone (hydrocortisone sodium phosphate) 1mg/mL in 0.9% Sodium Chloride Injection or 5% Dextrose Injection.

- Cefuroxime (cefuroxime sodium) 3mg/mL in 0.9% Sodium Chloride Injection.

- Cloxacillin (cloxacillin sodium) 4mg/mL in 0.9% Sodium Chloride Injection.

- Heparin 10IU/mL or 50IU/mL in 0.9% Sodium Chloride Injection.

- Potassium Chloride 10mEq/L or 40mEq/L in 0.9% Sodium Chloride Injection.

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

Preparation of solutions for im or iv 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 50ml of compatible diluent, added in TWO stages as below:-

1g and 2g vials for iv infusion:-

1. Introduce the syringe needle through the vial closure and inject 10mL of diluent for the 1g and 2g 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 (75 ml for the 3 g vial), and administer by intravenous infusion over 15-30 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.

Medicines classification

Prescription Only Medicine

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