

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

1. NAME OF THE MEDICINAL PRODUCT

FORTUM 500MG AND 1G INJECTION

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Fortum 500mg and 1g injection contain 500 mg and 1 g of ceftazidime (as pentahydrate) respectively.

For a full list of excipients, see Section 6.1.

3. PHARMACEUTICAL form

Powder for injection/infusion

4. Clinical particulars

4.1 Therapeutic 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.

Susceptibility to Fortum will vary with geography and time and local susceptibility data should be consulted where available (see Pharmacological properties, Pharmacodynamic effects).

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).

4.2 Posology and method of 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 by intravenous (I.V.) or deep intramuscular (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.

• 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 hours.

Most infections:

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

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

– 2 g every eight or 12 hours, or 3 g every 12 hours.

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.

• Elderly

In view of the reduced clearance of ceftazidime in acutely ill elderly patients, the daily dosage should not normally exceed 3 g, 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 1 g should be given. Maintenance doses should be based on creatinine clearance as shown in Table 1:

Table 1: Recommended maintenance doses of FORTUM in renal insufficiency

Creatinine Clearance (ml / minute)	Approx. Serum creatinine (micromoles / l) (mg / dl)	Recommended dose of FORTUM (g)	unit	Frequency of dosing (hourly)
> 50	< 150 (< 1.7)	Normal dosage		
50 to 31	150 to 200 (1.7 to 2.3)	1.0		12
30 to 16	200 to 350 (2.3 to 4.0)	1.0		24

15 to 6	350 to 500 (4.0 to 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 40 mg/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 FORTUM recommended in the above table should be repeated.

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 table 2 & 3.

Table 2: Continuous venovenous haemofiltration dosage guidelines for Fortum

Residual renal function (creatinine clearance in ml/minute)	Maintenance dose (mg) for an ultrafiltration rate (ml/minute) 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

^a- Maintenance dose to be administered every 12 hours.

Table 3: FORTUM dosage guidelines during continuous venovenous haemodialysis

Residual renal function (creatinine clearance in ml/minute)	Maintenance dose (mg) for a dialysate in flow rate of ^a :					
	1.0 litre/hour			2.0 litres/hour		
	Ultrafiltration rate (litre/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

^a Maintenance dose to be administered every 12 hours

4.3 Contraindications

Patients with known hypersensitivity to cephalosporin antibiotics.

Hypersensitivity to ceftazidime pentahydrate or to any of the excipients of the injection

4.4 Special warnings and precautions for use

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.

Pseudomembranous colitis has been reported with the use of antibiotics and may range in severity from mild to life-threatening. Therefore, it is important to consider its diagnosis in patients who develop diarrhoea during or after antibiotic use. If prolonged or significant diarrhoea occurs or the patient experiences abdominal cramps, treatment should be discontinued immediately, and the patient investigated further.

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.

Each 1 g of ceftazidime contains 52 mg of sodium. The sodium content must be taken into account in patients requiring sodium restriction

4.5 Interaction with other medicinal products and other forms of interaction

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.

4.6 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.

4.7 Effects on ability to drive and use machines

None reported

4.8 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 $\geq 1/100$ to $< 1/10$

uncommon $\geq 1/1,000$ to $< 1/100$,

rare $\geq 1/10,000$ to $< 1/1,000$,

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 Fortum has not been appropriately reduced.

Vascular disorders

Common: Phlebitis or thrombophlebitis with I.V. 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 (See Warnings and Precautions).

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 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.

4.9 Overdose

Symptoms and Signs

Overdosage can lead to neurological sequelae including encephalopathy, convulsions and coma.

Treatment

Serum levels of ceftazidime can be reduced by haemodialysis or peritoneal dialysis

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of Action

Ceftazidime is bactericidal in action. It acts by inhibiting bacterial cell wall synthesis.

Pharmacodynamic Effects

The prevalence of acquired resistance is geographically and time dependent and for select species may be very high. Local information on resistance and prevalence of extended spectrum beta lactamase (ESBLs) producing organisms is desirable, particularly when treating severe infections.

In vitro susceptibility of micro-organisms to Ceftazidime

Where clinical efficacy of ceftazidime has been demonstrated in clinical trials this is indicated with an asterisk (*).

Commonly Susceptible Species

Gram-positive aerobes:

Beta-hemolytic streptococci*

Staphylococcus aureus (methicillin susceptible) *

Coagulase negative staphylococcus (methicillin susceptible)

Gram-negative aerobes:

*Haemophilus influenzae** including ampicillin-resistant strains

Haemophilus parainfluenzae

Neisseria gonorrhoeae

*Neisseria meningitidis**

Pasteurella multocida

*Proteus spp.**

Providencia spp.

Salmonella spp.

Shigella spp.

Species for which acquired resistance may be a problem

Gram-negative aerobes:

Acinetobacter spp.

Burkholderia cepacia

*Citrobacter spp.**

*Enterobacter spp.**

*Escherichia coli**

Klebsiella spp. including *K. pneumoniae**

Pseudomonas spp. including *P. aeruginosa**

*Serratia spp.**

Morganella morganii

Yersinia enterocolitica

Gram-positive aerobes:

*Streptococcus pneumoniae**

Viridans group streptococcus

Gram-positive anaerobes:

Clostridium spp. not including *C. difficile*

Peptostreptococcus spp.

Propionibacterium spp.

Gram-negative anaerobes:

Fusobacterium spp.

Inherently resistant organisms

Gram-positive aerobes:

Enterococcus spp. including *E. faecalis* and *E. faecium*

Listeria spp.

Gram-negative aerobes:

Campylobacter spp.

Gram-positive anaerobes:

Clostridium difficile

Gram-negative anaerobes:

Bacteroides spp. including *B. fragilis*

Others:

Chlamydia spp.

Mycoplasma spp.

Legionella spp.

5.2 Pharmacokinetic properties

Absorption

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

Distribution

Therapeutically effective concentrations are still present in the serum 8 to 12 hours 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 cerebral spinal fluid (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 2 hours. 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 24 hours. Less than 1% is excreted via the bile, which limits the amount entering the bowel.

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).

5.3 Preclinical safety data

No additional data of relevance

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium carbonate (anhydrous).

6.2 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.

6.3 Shelf life

36 months

The shelf life after reconstitution and dilution when Fortum has been stored below:

25°C - 6 days at 4°C or 9 hours at 25°C.

30°C - 3 days at 4°C or 6 hours at 25°C.

In the event that storage of reconstituted solution at or below 25°C cannot be guaranteed, then the product should be used either 'immediately 'or should be stored at 4°C (in a refrigerator) and used within 3 days.

6.4 Special precautions for storage

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.

6.5 Nature and contents of container and special equipment for use, administration or implantation

As registered locally.

6.6 Special precautions for disposal and other 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).

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

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
- Dextran 70 Injection 6% in 5% Dextrose Injection

7. APPLICANT/SUPPLIER

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8. FDA APPLICATION NUMBER

Fortum 500 mg injection; FDA/SD.183-4290

Fortum 1 g injection; FDA/SD.183-4291

9. DATE OF RENEWAL OF REGISTRATION

12/4/2018

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12/2019