SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the Medicinal Product

FORTUM ™, Ceftazidime

2. 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).

Cetftazidime pentahydrate is formulated in a mixture with sodium carbonate. When constituted, this mixture provides a solution of ceftazidime sodium.

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 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 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.

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 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.

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.

- **Neonates (0 to 2 months)**

25 to 60 mg/kg/day in two divided doses.

In neonates, the serum half-life of ceftazidime can be three to four times that in adults.

- **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 unit dose of *FORTUM* (g)**	**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 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.

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.

4.5 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.

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 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.

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 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

Pharmacotherapeutic group

ATC Code: J01DD02

Antibacterials for systemic use. Third-generation cephalosporins.

5.1 Pharmacodynamics

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 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 Pharmacokinetics

Absorption

After i.m. administration of 500 mg and 1 g, peak levels of 18 and 37 mg/1, 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 Pre-clinical 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

6.4 Special Precautions for Storage

Store below 25°C; Protect from light.

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.

6.5 Nature and Contents of Container

As registered locally.

6.6 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. Small bubbles of carbon dioxide in the constituted solution may be ignored.

Table 4: Instructions for reconstitution

Vial Size		**Amount of Diluent to be added (ml)**	**Approximate Concentration (mg/ml)**
250 mg	Intramuscular	1.0 ml	210
	Intravenous	2.5 ml	90

500 mg	Intramuscular	1.5 ml	260
	Intravenous	5 ml	90
1 g	Intramuscular	3 ml	260
	Intravenous bolus	10 ml	90
	Intravenous infusion	50 ml #	20
2 g	Intravenous bolus	10 ml	170
	Intravenous infusion	50 ml #	40
3 g	Intravenous bolus	15 ml	170
	Intravenous infusion	75 ml #	40

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.

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% Lidocaine Hydrochloride Injection.

Both components retain satisfactory potency when ceftazidime at 4 mg/ml is mixed 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 metronidazole 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 i.v. 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 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.

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

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.

FORTUM is a trademark of the GlaxoSmithKline group of companies

7. **Manufacturer** (name, address, company)

GlaxoSmithKline Manufacturing S.p.A., Via A. Fleming 2, 37135, Verona, Italy

8. Marketing Authorisation Holder

GlaxoSmithKline Manufacturing S.p.A., Via A. Fleming 2, 37135, Verona, Italy

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