ANNEX III

SUMMARY OF PRODUCT CHARACTERISTICS,
LABELLING AND PACKAGE LEAFLET

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Fortum and associated names (see Annex I) 250 mg powder for solution for injection
Fortum and associated names (see Annex I) 500 mg powder for solution for injection
Fortum and associated names (see Annex I) 1 g powder for solution for injection or infusion
Fortum and associated names (see Annex I) 2 g powder for solution for injection or infusion
Fortum and associated names (see Annex I) 3 g powder for solution for injection or infusion
Fortum and associated names (see Annex I) 1 g powder for solution for infusion
Fortum and associated names (see Annex I) 2 g powder for solution for infusion
[See Annex 1 – to be completed nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

[To be completed nationally]

3. PHARMACEUTICAL FORM

250 mg, 500 mg powder for solution for injection
Powder for solution for injection
[To be completed nationally]

1 g, 2 g, 3 g powder for solution for injection or infusion
Powder for solution for injection or infusion
[To be completed nationally]

1 g, 2 g powder for solution for infusion (Monovial presentation)
Powder for solution for infusion
[To be completed nationally]

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Fortum is indicated for the treatment of the infections listed below in adults and children including neonates (from birth).

- Nosocomial pneumonia
- Broncho-pulmonary infections in cystic fibrosis
- Bacterial meningitis
- Chronic suppurative otitis media
- Malignant otitis externa
- Complicated urinary tract infections
- Complicated skin and soft tissue infections
- Complicated intra-abdominal infections
- Bone and joint infections
- Peritonitis associated with dialysis in patients on 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 that is 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

<table>
<tr><td colspan="2">Intermittent Administration</td></tr>
<tr><td>Infection</td><td>Dose to be administered</td></tr>
<tr><td>Broncho-pulmonary infections in cystic fibrosis</td><td>100 to 150 mg/kg/day every 8 h, maximum 9 g per day[1]</td></tr>
<tr><td>Febrile neutropenia</td><td rowspan="4">2 g every 8 h</td></tr>
<tr><td>Nosocomial pneumonia</td></tr>
<tr><td>Bacterial meningitis</td></tr>
<tr><td>Bacteraemia*</td></tr>
<tr><td>Bone and joint infections</td><td rowspan="4">1-2 g every 8 h</td></tr>
<tr><td>Complicated skin and soft tissue infections</td></tr>
<tr><td>Complicated intra-abdominal infections</td></tr>
<tr><td>Peritonitis associated with dialysis in patients on CAPD</td></tr>
<tr><td>Complicated urinary tract infections</td><td>1-2 g every 8 h or 12 h</td></tr>
<tr><td>Peri-operative prophylaxis for transuretheral resection of prostate (TURP)</td><td>1 g at induction of anaesthesia,
and a second dose at catheter removal</td></tr>
<tr><td>Chronic suppurative otitis media</td><td rowspan="2">1 g to 2 g every 8h</td></tr>
<tr><td>Malignant otitis externa</td></tr>
<tr><td colspan="2">Continuous Infusion</td></tr>
<tr><td>Infection</td><td>Dose to be administered</td></tr>
<tr><td>Febrile neutropenia</td><td rowspan="10">Loading dose of 2 g followed by a continuous infusion of 4 to 6 g every 24 h[1]</td></tr>
<tr><td>Nosocomial pneumonia</td></tr>
<tr><td>Broncho-pulmonary infections in cystic fibrosis</td></tr>
<tr><td>Bacterial meningitis</td></tr>
<tr><td>Bacteraemia*</td></tr>
<tr><td>Bone and joint infections</td></tr>
<tr><td>Complicated skin and soft tissue infections</td></tr>
<tr><td>Complicated intra-abdominal infections</td></tr>
<tr><td>Peritonitis associated with dialysis in patients on CAPD</td></tr>
<tr><td colspan="2">[1] In adults with normal renal function 9 g/day has been used without adverse effects.
* When associated with, or suspected to be associated with, any of the infections listed in section 4.1.</td></tr>
</table>

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, maximum 6 g/day
	Chronic suppurative otitis media	
	Malignant otitis externa	
	Neutropenic children	150 mg/kg/day in three divided doses, maximum 6 g/day
	Broncho-pulmonary infections in cystic fibrosis	
	Bacterial meningitis	
	Bacteraemia*	
	Bone and joint infections	100-150 mg/kg/day in three divided doses, maximum 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 100-200 mg/kg/day, maximum 6 g/day
	Nosocomial pneumonia	
	Broncho-pulmonary infections in 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, the serum half life of ceftazidime can be three to four times that in adults.
* Where associated with or suspected to be associated with any of the infections listed in section 4.1.

Paediatric population
The safety and efficacy of Fortum administered as continuous infusion to neonates and infants ≤ 2 months 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 impairment

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

Renal impairment

Ceftazidime is excreted unchanged by the kidneys. Therefore, in patients with impaired renal function, the dosage should 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: Recommended maintenance doses of Fortum in renal impairment – intermittent infusion

Adults and children ≥ 40 kg

Creatinine clearance (ml/min)	Approx. serum creatinine µmol/l (mg/dl)	Recommended unit dose of Fortum (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 the unit dose should be increased by 50% or the dosing frequency increased.
In children the creatinine clearance should be adjusted for body surface area or lean body mass.

Children < 40 kg

Creatinine clearance (ml/min)**	Approx. serum creatinine* µmol/l (mg/dl)	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. ** Estimated based on body surface area, or measured.			

Close clinical monitoring for safety and efficacy is advised.

Table 4: Recommended maintenance doses of Fortum in renal impairment – continuous infusion

Adults and children ≥ 40 kg

Creatinine clearance (ml/min)	Approx. serum creatinine µmol/l (mg/dl)	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 hours
30-16	200-350 (2.3-4.0)	Loading dose of 2 g followed by 1 g/24 hours
≤15	>350 (>4.0)	Not evaluated

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

Children < 40 kg

The safety and effectiveness of Fortum administered as continuous infusion in renally impaired children < 40 kg has not been established. Close clinical monitoring for safety and efficacy is advised.

If continuous infusion is used in children with renal impairment, 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 h.

Following each haemodialysis period, the maintenance dose of ceftazidime recommended in the below 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 250 mg for 2 litres of dialysis solution).

For patients in renal failure 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. For low-flux haemofiltration, follow the dose recommended under renal impairment.

For patients on veno-venous haemofiltration and veno-venous haemodialysis, follow the dosage recommendations in the tables below.

Table 5: Continuous veno-venous haemofiltration dose guidelines

Residual renal function (creatinine clearance ml/min)	Maintenance dose (mg) for an 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] Maintenance dose to be administered every 12 h.				

Table 6: Continuous veno-venous haemodialysis dose guidelines

Residual renal function (creatinine clearance in ml/min)	Maintenance dose (mg) for a dialysate in flow rate of [1]:					
	1.0 litre/h			2.0 litre/h		
	Ultrafiltration rate (litre/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
[1] Maintenance dose to be administered every 12 h.						

Method of administration

Fortum should be administered by intravenous injection or 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. 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.

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 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(s) 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.

Concurrent treatment with high doses of cephalosporins and nephrotoxic medicinal products such as aminoglycosides or potent diuretics (e.g. furosemide) may adversely affect 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 slight interference (false-positive) may occur with copper reduction methods (Benedict's, Fehling's, Clinitest).

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

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 Fortum:

250 mg powder for solution for injection
Fortum 250 mg contains 13 mg of sodium per vial.

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

1 g powder for solution for injection or infusion, 1 g powder for solution for infusion
Fortum 1 g contains 52 mg of sodium per vial.

2 g powder for solution for injection or infusion, 2 g powder for solution for infusion
Fortum 2 g contains 104 mg of sodium per vial.

3 g powder for solution for injection or infusion
Fortum 3 g contains 156 mg of sodium per vial.

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

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been conducted with probenecid and furosemide.

Concurrent use of high doses with nephrotoxic medicinal products may adversely affect renal function (see section 4.4).

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

4.6 Fertility, pregnancy and lactation

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).

Fortum should be prescribed to pregnant women only if the benefit outweighs the risk.

Breast-feeding

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 breast-feeding.

Fertility
No data are available.

4.7 Effects on ability to drive and 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 with intravenous administration, diarrhoea, transient increases in hepatic enzymes, maculopapular or urticarcial rash, pain and/or inflammation following intramuscular injection and positive Coomb's 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 all other undesirable effects were mainly determined using post-marketing data and refer to a reporting rate rather than a true 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 to <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 thrush)		
Blood and lymphatic system disorders	Eosinophilia Thrombocytosis	Neutropenia Leucopenia Thrombocytopenia		Agranulocytosis Haemolytic anaemia Lymphocytosis
Immune system disorders				Anaphylaxis (including bronchospasm and/or hypotension) (see section 4.4)
Nervous system disorders		Headache Dizziness		Neurological sequelae[1] Paraesthesia
Vascular disorders	Phlebitis or thrombophlebitis with intravenous administration			
Gastrointestinal disorders	Diarrhoea	Antibacterial agent-associated diarrhoea and colitis[2] (see section 4.4) Abdominal pain Nausea Vomiting		Bad taste
Hepatobiliary disorders	Transient elevations in one or more hepatic enzymes[3]			Jaundice
Skin and subcutaneous tissue disorders	Maculopapular or urticarial rash	Pruritus		Toxic epidermal necrolysis Stevens-johnson syndrome Erythema multiforme Angioedema
Renal and urinary disorders		Transient elevations of blood urea, blood urea nitrogen and/or serum creatinine	Interstitial nephritis Acute renal failure	
General disorders and administration site conditions	Pain and/or inflammation after intramuscular injection	Fever		
Investigations	Positive Coombs' test[4]			

[1]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.
[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.

4.9 Overdose

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

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

Serum levels of ceftazidime can be 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 breakpoints[2]	≤4	8	> 8

S=susceptible, I=intermediate, R=resistant.
[1]The breakpoints relate to high dose therapy (2 g x 3).
[2]Non-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. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of ceftazidime in at least some types of infections is questionable.

Commonly Susceptible Species
Gram-positive aerobes: *Streptococcus pyogenes* *Streptococcus agalactiae*
Gram-negative aerobes: *Citrobacter koseri* *Escherichia coli* *Haemophilus influenzae* *Moraxella catarrhalis* *Neisseria meningitidis* *Proteus mirabilis* *Proteus* spp. (other) *Providencia* spp.
Species for which acquired resistance may be a problem
Gram-negative aerobes: *Acinetobacter baumannii*£+ *Burkholderia cepacia* *Citrobacter freundii* *Enterobacter aerogenes* *Enterobacter cloacae* *Klebsiella pneumoniae* *Klebsiella* spp. (other) *Pseudomonas aeruginosa* *Serratia* spp. *Morganella morganii*
Gram-positive aerobes: *Staphylococcus aureus*£ *Streptococcus pneumoniae*££

Gram-positive anaerobes: *Clostridium perfringens* *Peptococcus* spp. *Peptostreptococcus* spp.
Gram-negative anaerobes: *Fusobacterium* spp.
Inherently resistant organisms
Gram-positive aerobes: Enterococci including *Enterococcus faecalis* and *Enterococcus faecium* *Listeria* spp.
Gram-positive anaerobes: *Clostridium difficile*
Gram-negative anaerobes: *Bacteroides* spp. (many strains of *Bacteroides fragilis* are resistant).
Others: *Chlamydia* spp. *Mycoplasma* spp. *Legionella* spp.
£*S. aureus* that is methicillin-susceptible are considered to have inherent low susceptibility to ceftazidime. All methicillin-resistant *S. aureus* are resistant to ceftazidime. ££*S. pneumoniae* that demonstrate intermediate suseptibility or are resistant to penicillin can be expected to demonstrate at least reduced susceptibility to ceftazidime. + High rates of resistance have been observed in one or more areas/countries/regions within the EU.

5.2 Pharmacokinetic 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, resulting 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 metabolised.

Elimination

After parenteral administration plasma levels decrease with a half-life of about 2 h. Ceftazidime is excreted unchanged into the urine by glomerular filtration; approximately 80 to 90% of the dose is recovered in the urine within 24 h. Less than 1% is excreted via the bile.

Special patient populations

Renal impairment

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

Hepatic impairment

The presence of mild to moderate hepatic dysfunction had no effect on the pharmacokinetics of ceftazidime in individuals administered 2 g intravenously every 8 hours for 5 days, provided 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 repeat BID dosing of 2 g IV bolus injections in elderly patients 80 years 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 studies of safety pharmacology, repeat dose toxicity, genotoxicity, toxicity to reproduction. Carcinogenicity studies have not been performed with ceftazidime.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

[To be completed nationally]

6.2 Incompatibilities

[To be completed nationally]

6.3 Shelf life

[To be completed nationally]

6.4 Special precautions for storage

[To be completed nationally]

6.5 Nature and contents of container

[To be completed nationally]

6.6 Special precautions for disposal and other handling

All sizes of vials of Fortum 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.

Instructions for constitution

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

Vial size		Amount of diluent to be added (ml)	Approximate concentration (mg/ml)
250 mg powder for solution for injection			
250 mg	Intramuscular Intravenous bolus	1.0 ml 2.5 ml	210 90
500 mg powder for solution for injection			
500 mg	Intramuscular Intravenous bolus	1.5 ml 5 ml	260 90
1 g powder for solution for injection or infusion			
1 g	Intramuscular Intravenous bolus Intravenous infusion	3 ml 10 ml 50 ml*	260 90 20
2 g powder for solution for injection or infusion			
2 g	Intravenous bolus Intravenous infusion	10 ml 50 ml*	170 40
3 g powder for solution for injection or infusion			
3 g	Intravenous bolus Intravenous infusion	15 ml 75 ml*	170 40

* Note: Addition should be in two stages

Solutions 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 between 1 mg/ml and 40 mg/ml is compatible with:

- sodium chloride 9 mg/ml (0.9%) solution for 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).

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

The contents of a 500 mg vial of ceftazidime 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.

250 mg, 500 mg powder for solution for injection, 1 g, 2 g, 3 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, 3 g powder for solution for injection or infusion.:
Preparation of solutions for iv infusion from ceftazidime injection in standard vial presentation (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. 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.

1 g, 2 g powder for solution for infusion (Monovial presentation)
Preparation of solution for intravenous infusion
The contents of the Monovial are added to small volume infusion bags containing 0.9% Sodium Chloride solution for Injection, or 5% Dextrose Injection, or another compatible fluid.

The 2 g Monovial must be constituted using 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 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.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

[To be completed nationally]

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Fortum and associated names (see Annex I) 250 mg powder for solution for injection
Fortum and associated names (see Annex I) 500 mg powder for solution for injection
Fortum and associated names (see Annex I) 1 g powder for solution for injection or infusion
Fortum and associated names (see Annex I) 2 g powder for solution for injection or infusion
Fortum and associated names (see Annex I) 3 g powder for solution for injection or infusion
Fortum and associated names (see Annex I) 1 g powder for solution for infusion
Fortum and associated names (see Annex I) 2 g powder for solution for infusion
[See Annex I - To be completed nationally]

Ceftazidime

2. STATEMENT OF ACTIVE SUBSTANCE(S)

[To be completed nationally]

3. LIST OF EXCIPIENTS

[To be completed nationally]

4. PHARMACEUTICAL FORM AND CONTENTS

[To be completed nationally]

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

250 mg, 500 mg,powder for solution for injection; 1 g powder for solution for injection or infusion
Intramuscular or intravenous use.

2 g, 3 g powder for solution for injection or infusion
1 g, 2 g powder for solution for infusion (Monovial presentation)
Intravenous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

[To be completed nationally]

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and Address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

[To be completed nationally]

16. INFORMATION IN BRAILLE

[To be completed nationally]

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT

Fortum and associated names (see Annex I) 3 g powder for solution for injection or infusion

[See Annex I - To be completed nationally]

Ceftazidime

2. STATEMENT OF ACTIVE SUBSTANCE(S)

[To be completed nationally]

3. LIST OF EXCIPIENTS

[To be completed nationally]

4. PHARMACEUTICAL FORM AND CONTENTS

[To be completed nationally]

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

[To be completed nationally]

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and Address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

[To be completed nationally]

16. INFORMATION IN BRAILLE

[To be completed nationally]

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Fortum and associated names (see Annex I) 250 mg powder for solution for injection
Fortum and associated names (see Annex I) 500 mg powder for solution for injection
Fortum and associated names (see Annex I) 1 g powder for solution for injection or infusion
Fortum and associated names (see Annex I) 2 g powder for solution for injection or infusion
Fortum and associated names (see Annex I) 1 g Monovial powder for solution for infusion
Fortum and associated names (see Annex I) 2 g Monovial powder for solution for infusion
[See Annex I - To be completed nationally]

Ceftazidime

250 mg, 500 mg,powder for solution for injection; 1 g powder for solution for injection or infusion
Intramuscular or intravenous use.

2 g powder for solution for injection or infusion
1 g, 2 g powder for solution for infusion (Monovial presentation)
Intravenous use.

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

[To be completed nationally]

6. OTHER

PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Fortum and associated names (see Annex I) 250 mg powder for solution for injection
Fortum and associated names (see Annex I) 500 mg powder for solution for injection
Fortum and associated names (see Annex I) 1 g powder for solution for injection or infusion
Fortum and associated names (see Annex I) 2 g powder for solution for injection or infusion
Fortum and associated names (see Annex I) 3 g powder for solution for injection or infusion
Fortum and associated names (see Annex I) 1 g powder for solution for infusion
Fortum and associated names (see Annex I) 2 g powder for solution for infusion

[See Annex I - To be completed nationally]

Ceftazidime

Read all of this leaflet carefully before you start using this medicine.
Keep this leaflet. You may need to read it again.
If you have any further questions, ask your doctor.
If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

In this leaflet:

1. WHAT FORTUM IS AND WHAT IT IS USED FOR

Fortum is an antibiotic used in adults and children (including newborn babies). It works by killing bacteria that cause infections. It belongs to a group of medicines called *cephalosporins.*

Fortum is used to treat severe bacterial infections of:

- the lungs or chest
- the lungs and bronchi in patients suffering from cystic fibrosis
- the brain (*meningitis*)
- the ear
- the urinary tract
- the skin and soft tissues
- the abdomen and abdominal wall (*peritonitis*)
- the bones and joints.

Fortum can also be used:
- to prevent infections during prostate surgery in men
- to treat patients with low white blood cell counts (*neutropenia*) who have a fever due to a bacterial infection.

2. BEFORE YOU ARE GIVEN FORTUM

You must not be given Fortum:
- **if you are allergic** (*hypersensitive*) to **ceftazidime** or any of the other ingredients of this medicine (*listed in section 6*).
- if you have had a **severe allergic reaction** to any **other antibiotic** (penicillins, monobactams and carbapenems) as you may also be allergic to Fortum.

➔ **Tell your doctor before** you start on Fortum if you think that this applies to you. You must not be given Fortum.

Take special care with Fortum

You must look out for certain symptoms such as allergic reactions, nervous system disorders and gastrointestinal disorders such as diarrhoea while you are being given Fortum. This will reduce the risk of possible problems. See ('*Conditions you need to look out for*') in Section 4. If you have had an allergic reaction to other antibiotics you may also be allergic to Fortum.

If you need a blood or urine test
Fortum can affect the results of urine tests for sugar and a blood test known as the *Coombs test*. If you are having tests:
➔ **Tell the person taking the sample** that you have been given Fortum.

Taking other medicines
Tell your doctor if you are taking any other medicines, if you've started taking any recently or you start taking new ones. This includes medicines you can obtain without a prescription.

You shouldn't be given Fortum without talking to your doctor if you are also taking:
- an antibiotic called *chloramphenicol*
- a type of antibiotic called *aminoglycosides* e.g. *gentamicin, tobramycin*
- water tablets called *furosemide*

➔ **Tell your doctor** if this applies to you.

Pregnancy and breast-feeding
Tell your doctor before you are given Fortum:
- If you are pregnant, think you might be pregnant or are planning to become pregnant
- If you are breastfeeding

Your doctor will consider the benefit of treating you with Fortum against the risk to your baby.

Driving and using machines
Fortum can cause side effects that affect your ability to drive, such as dizziness.
Don't drive or use machines unless you are sure you're not affected.

Important information about some of the ingredients of Fortum
Fortum contains sodium
You need to take this into account if you are on a controlled sodium diet.

Fortum Strength	Amount per vial
Fortum 250 mg	13 mg
Fortum 500 mg	26 mg
Fortum 1 g	52 mg
Fortum 2 g	104 mg
Fortum 3 g	156 mg
Fortum 1 g Monovial	52 mg
Fortum 2 g Monovial	104 mg

3. How Fortum is used

Fortum is usually given by a doctor or nurse. It can be given as a **drip** (intravenous infusion) or as an **injection** directly into a vein or into a muscle.

Fortum is made up by the doctor, pharmacist or nurse using water for injections or a suitable infusion fluid.

The usual dose

The correct dose of Fortum for you will be decided by your doctor and depends on: the severity and type of infection; whether you are on any other antibiotics; your weight and age; how well your kidneys are working.

Newborn babies (0-2 months)
For every 1 kg the baby weighs, they'll be given 25 to 60 mg Fortum per day divided in two doses.

Babies (over 2 months) and children who weigh less than 40 kg
For every 1 kg the baby or child weighs, they'll be given 100 to 150 mg of Fortum per day divided in three doses. Maximum 6 g per day.

Adults and adolescents who weigh 40 kg or more
1 to 2 g of Fortum three times daily. Maximum of 9 g per day.

Patients over 65
The daily dose should not normally exceed 3 g per day, especially if you are over 80 years of age.

Patients with kidney problems
You may be given a different dose to the usual dose. The doctor or nurse will decide how much Fortum you will need, depending on the severity of the kidney disease. Your doctor will check you closely and you may have more regular kidney function tests.

If you are given more Fortum than you should
If you accidentally use more than your prescribed dose, contact your doctor or nearest hospital straight away.

If you forget to use Fortum
If you miss an injection, you should have it as soon as possible. However, if it is almost time for your next injection, skip the missed injection. Don't take a double dose (two injections at the same time) to make up for a missed dose.

If you stop using Fortum
Don't stop taking Fortum unless your doctor tells you to. **If you have any questions ask your doctor or nurse.**

4. POSSIBLE SIDE EFFECTS

Like all medicines, Fortum can cause side effects, although not everybody gets them.

Conditions you need to look out for
The following serious side effects have occurred in a small number of people but their exact frequency is unknown:

- **severe allergic reaction**. Signs include **raised and itchy rash**, **swelling**, sometimes of the face or mouth causing **difficulty in breathing**.
- **Skin rash,** which may **blister**, and looks like **small targets** (central dark spot surrounded by a paler area, with a dark ring around the edge).
- **A widespread rash** with **blisters** and **peeling skin.** (These may be signs of *Stevens-Johnson syndrome* or *toxic epidermal necrolysis*).
- **Nervous system disorders**: tremors, fits and, in some cases coma. These have occurred in people when the dose they are given is too high, particularly in people with kidney disease.

➔ **Contact a doctor or nurse immediately if you get any of these symptoms.**

Common side effects

These may affect **up to 1 in 10** people:

- diarrhoea
- swelling and redness along a vein
- red raised skin rash which may be itchiness
- pain, burning, swelling or inflammation at the injection site.

➔ **Tell your doctor** if any of these are troubling you.

Common side effects that may show up in blood tests:

- an increase in a type of white blood cell (*eosinophilia*)
- an increase in the number of cells that help the blood to clot
- an increase in liver enzymes.

Uncommon side effects

These may affect **up to 1 in 100** people:

- inflammation of the gut which can cause pain or diarrhoea which may contain blood
- thrush -fungal infections in the mouth or vagina
- headache
- dizziness
- stomach ache
- feeling sick or being sick
- fever and chills.

➔ **Tell your doctor** if you get any of these.

Uncommon side effects that may show up in blood tests:

- a decrease in the number of white blood cells
- a decrease in the number of blood platelets (cells that help the blood to clot)
- an increase in the level of urea, urea nitrogen or serum creatinine in the blood.

Other side effects

Other side effects have occurred in a small number of people but their exact frequency is unknown:

- inflammation or failure of the kidneys
- pins and needles
- unpleasant taste in the mouth
- yellowing of the whites of the eyes or skin.

Other side effects that may show up in blood tests:

- red blood cells destroyed too quickly
- an increase in a certain type of white blood cells
- severe decrease in the number of white blood cells.

If you get side effects

➔ **Tell your doctor or pharmacist** if any of the side effects become **severe or troublesome**, or if you notice any side effects not listed in this leaflet.

5. HOW TO STORE FORTUM

Keep out of the reach and sight of children.

[To be completed nationally]

6. FURTHER INFORMATION

What Fortum contains

[To be completed nationally]

What Fortum looks like and contents of the pack

[To be completed nationally]

Marketing Authorisation Holder and Manufacturer

[See Annex I -To be completed nationally]

{Name and Address}
<{tel}>
<{fax}>
<{e-mail}>

This medicinal product is authorised in the Member States of the EEA under the following names:

250 g powder for solution for injection
France – Fortum enfants et nourrisons
Italy – Glazidim, Ceftim
Poland, Sweden, United Kingdom – Fortum

Fortum 500 g powder for solution for injection
Austria, Czech Republic, Denmark, Germany, Hungary, Ireland, Lithuania, Netherlands Norway Poland, Romania, Slovak Republic Sweden, United Kingdom – Fortum
Belgium, Finland, Italy, Luxembourg – Glazidim
France – Fortum enfants et nourrisons
Italy – Ceftim
Portugal – Cefortam
Spain – Fortam IM/IV, Potendal

Fortum 1 g powder for solution for injection or infusion
Austria, Bulgaria, Cyprus, Czech Republic, Denmark, France, Germany, Hungary, Iceland Ireland, Latvia, Lithuania Malta Netherlands, Norway, Poland, Romania, Slovak Republic, Slovenia, Sweden, United Kingdom – Fortum
Belgium, Finland, Italy, Luxembourg – Glazidim
Estonia – Fortum IM/IV
France – Fortumset,
Greece – Solvetan
Italy – Panzid, Ceftim
Portugal – Cefortam
Spain – Fortam IV, Fortam Ig/IV, Fortam IM/IV, Potendal

Fortum 2 g powder for solution for injection or infusion
Austria, Czech Republic Denmark, France, Germany, Hungary, Iceland, Lithuania, Netherlands, Norway, Poland, Romania, Slovak Republic, Sweden, United Kingdom – Fortum
Belgium, Italy, Luxembourg – Glazidim
Finland – Glazidim
France – Fortumset
Greece – Solvetan
Portugal – Cefortam
Spain – Fortam IV, Potendal

Fortum 3 g powder for solution for injection or infusion
Finland – Glazidim
Lithuania, United Kingdom – Fortum

Fortum 1 g Monovial powder for solution for infusion
Ireland – Fortum
Slovenia – Fortum Monovial

Fortum 2 g Monovial powder for solution for infusion
Ireland, United Kingdom – Fortum

This leaflet was last approved in {MM/YYYY}.