SUMMARY OF PRODUCT CHARACTERISTICS
Fortum 1 gram
Fortum 2 gram

1. NAME OF THE MEDICINAL PRODUCT

Fortum 1 gram

Fortum 2 gram

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Fortum 1 gram: Vials contain 1g ceftazidime (as pentahydrate) with sodium carbonate (118mg per gram of ceftazidime).

Fortum 2 gram: Vials contain 2g ceftazidime (as pentahydrate) with sodium carbonate (118mg per gram of ceftazidime).

Excipient known effect
Fortum 1 gram: Each vial contains 52 mg (2.26 mmol) of sodium per vial.
Fortum 2 gram: Each vial contains 104 mg (4.52 mmol) of sodium per vial.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Fortum 1 gram - Powder for solution for injection or infusion
Fortum 2 gram - Powder for solution for injection or infusion
Vials containing white to cream sterile powder.

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 patient 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 transurethral 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 causive 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

Intermittent Administration	
Infection	Dose to be administered
Broncho-pulmonary infections in cystic fibrosis	100 to 150 mg/kg/day every 8 h, maximum 9 g per day[1]
Febrile neutropenia	2 g every 8 h
Nosocomial pneumonia	
Bacterial meningitis	
Bacteraemia*	
Bone and joint infections	1-2 g every 8 h
Complicated skin and soft tissue infections	
Complicated intra-abdominal infections	
Peritonitis associated with dialysis in patients on CAPD	
Complicated urinary tract infections	1-2 g every 8 h or 12 h
Per-operative prophylaxis for transurethral resection of prostate (TURP)	1 g at induction of anaesthesia, and a second dose at catheter removal
Chronic suppurative otitis media	1 g to 2 g every 8 h
Malignant otitis externa	
Continuous infusion	
Infection	Dose to be administered
Febrile neutropenia	Loading dose of 2 g followed by a continuous infusion of 4 to 6 g every 24 h[1]
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	

[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 4.1.

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 with 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 suspects 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 tables 5 & 6 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 5 & 6 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 (litre/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

The dose depends on the severity, susceptibility, site and type of infection and on the age and renal function of the patient.

Fortum 1 g 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. Fortum 2 g should be administered by intravenous injection or infusion. 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.

4.3. Contraindications

Hypersensitivity to ceftazidime, to any other cephalosporin or to any of the excipients listed in section 6.1.

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

Hypersensitivity
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.

Spectrum of activity
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.

Pseudomembranous colitis
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.

Renal function
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 section 4.2 and 4.8).

Overgrowth of non-susceptible organisms
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.

Test and assay interactions
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.

Sodium content
Important information about one of the ingredients of Fortum:

Fortum 1 g contains 52 mg (2.26 mmol) of sodium per vial, equivalent to 2.6% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Fortum 2 g contains 104 mg (4.52 mmol) of sodium per vial, equivalent to 5.2% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

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

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 eosinphilia, thrombocytosis, phlebitis or thrombophlebitis with intravenous administration, diarrhoea, transient increases in hepatic enzymes, maculopapular or uticarcial rash, pain and/or inflammation following intramuscular injection and positive Coomb's test.

Data from sponsored and unsponsored 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 and <1/10
Uncommon ≥1/1,000 and <1/100
Rare ≥1/10,000 and <1/1000
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
Heptobiliary 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 Drug Reaction with Eosinophilia

				and Systemic Symptoms (DRESS)[4]
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[5]			

[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]There have been rare reports where DRESS has been associated with ceftazidime.
[5]A positive Coombs test develops in about 5% of patients and may interfere with blood cross matching.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/.
Additionally, you should also report to GSK Israel (il.safety@gsk.com).

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.

PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-bacterials 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* *Haemophilus influenzae* *Moraxella catarrhalis* *Neisseria menigitidis* *Pasteurella multocida* *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* *Escherichia coli* *Klebsiella pneumoniae* *Klebsiella spp (other)* *Pseudomonas aeruginosa* *Serratia spp* *Morganella morganii*
Gram-positive aerobes: *Staphylococcus aureus*[£] *Staphylococcus pneumoniae*[ff] *Viridans group streptococcus*
Gram-positive anaerobes: *Clostridium perfringens* *Peptostreptococcus spp.*
Gram-negative anaerobes *Fusobacterium spp.*

Inherently resistant organisms
Gram-positive aerobes: Enterococcus spp 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-resistance *S. Aureus* are resistant to ceftazidime. [££]S.pneumoniae that demonstrate intermediate susceptibility 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.

PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium carbonate (anhydrous sterile)

6.2. Incompatibilities

Fortum is less stable in Sodium Bicarbonate Injection than in other intravenous 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 ceftazidime in solution. Therefore, it would be prudent to flush giving sets and intravenous lines between administration of these two agents.

6.3. Shelf life

The expiry date of the product is indicated on the label and packaging.

<u>After reconstitution:</u>
Chemical and physical in-use stability has been demonstrated for 6 days at 4°C and 9 hours at 25°C.

From a microbiological point of view, the reconstituted solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless reconstitution has taken place in controlled and validated aseptic conditions.

<u>After dilution:</u>
Chemical and physical in-use stability has been demonstrated for 6 days at 4°C and 9 hours at 25°C.

From a microbiological point of view, the reconstituted and diluted solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless reconstitution has taken place in controlled and validated aseptic conditions.

6.4. Special precautions for storage

Store below 25°C.

Keep vials in the outer carton to protect from light.

For storage conditions after reconstitution see section 6.3
.

6.5. Nature and contents of container

Fortum 1 g powder for solution for injection or infusion is packaged in clear Ph.Eur.Type III glass 17 ml, 26 ml, 60 ml or 77 ml vial with a bromobutyl rubber plug and a flip-off type aluminium overseal.
Packs of 1 or 5 vials

Fortum 2 g powder for solution for injection or infusion is packaged in clear Ph.Eur.Type III glass 60 ml or 77 ml vial with a bromobutyl rubber plug and a flip-off type aluminium overseal.
Pack of 1 vial.
Not all pack sizes may be marketed.

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 7 and table 8 for addition volumes and solution concentrations, which may be useful when fractional doses are required.

Table 7: Powder for Solution for Injection

Presentation		Amount of diluent to be added (ml)	Approximate concentration (mg/ml)
1 g			
	Intramuscular Intravenous bolus	3 ml 10 ml	260 90
2 g			
	Intravenous bolus	10 ml	170

Note:
- The resulting volume of the solution of ceftazidime in reconstitution medium is increased due to the displacement factor of the drug product resulting in the listed concentrations in mg/ml presented in the above table.

Table 8: Powder for Solution for Infusion

Presentation		Amount of diluent to be added (ml)	Approximate concentration (mg/ml)
1 g			
	Intravenous infusion	50 ml*	20
2 g			
	Intravenous infusion	50 ml*	40

* Addition should be in two stages.

Note:

- The resulting volume of the solution of ceftazidime in reconstitution medium is increased due to the displacement factor of the drug product resulting in the listed concentrations in mg/ml presented in the above table.

Solutions range in colour from light yellow to amber depending on concentration, diluents 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).

Fortum 1 g: Ceftazidime at concentrations detailed in Table 7 may be constituted for intramuscular use with 0.5% or 1% Lidocaine Hydrochloride Injection.
Preparation of solution 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 intravenous fluids listed above.

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 of compatible diluents (listed above), added in TWO stages as below.

Introduce the syringe needle through the vial closure and inject 10 ml of diluent. Withdraw the needle and shake the vial to give a clear solution.

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.

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, 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.

Any residual antibiotic solution should be discarded.

For single use only.

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

7. Manufacturer

GlaxoSmithKline Manufacturing S.p.A., Verona, Italy.

8. License Holder and Importer

GlaxoSmithKline (Israel) Ltd., 25 Basel St., Petach Tikva.

9. License Number

Fortum 1 gram 046-44-23497
Fortum 2 gram 046-40-23499

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For DR v4