Maximodim 0.5 gm & 1 gm

Powder for IM/IV Injection

1 NAME OF THE MEDICINAL PRODUCT

Maximodim 1 gm for IM/IVInjection
Maximodim 0.5 gm for IM/IVInjection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contain 1260 ceftazidime sodium equ.to Ceftazidime base 1000 mg
Each vial contain 630 ceftazidime sodium equ.to Ceftazidime base 500 mg.
For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Powder for solution for IM/IV injection .

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Maximodim 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 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 .
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

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 day1
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
Peri-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	
[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.	

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	
Neonates and infants ≤ 2 months	Infection	Usual dose
Intermittent Administration		
	Most infections	25-60 mg/kg/day in two divided doses1
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 Maximodim 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 Maximodim in renal impairment – intermittent infusion

Adults and children ≥40 kg

Creatinine clearance (ml/min)	Approx. serum creatinine micromol/l (mg/dl)	Recommended unit dose of Maximodim (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 micromol/l (mg/dl)	Recommended unit dose of Maximodim (g)	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 Maximodim in renal impairment – continuous infusion

Adults and children ≥ 40 kg

Creatinine clearance (ml/min)	Approx. serum creatinine micromol/l (mg/dl)	Frequency of dosing (hourly)
	150-200 (1.7-2.3)	Loading dose of 2 g followed by 1 g to 3 g /24 hours

	200-350 (2.3-4.0)	Loading dose of 2 g followed by 1 g/24 hours
	>300 (>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 Maximodim administered as continuous infusion in renally impaired children < 40 kghas 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 t 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 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:			
0	5	16.7	33.3	50
5	250	250	500	500
10	250	250	500	500
15	250	500	500	750
20	250	500	500	750
Maintenance dose to be administered every 12 h.				

Table 6: Continuous veno-venous haemodialysis dose guidelines

Residual renal function (creatinine clearance ml/min)	Maintenance dose (mg) for a dialysate in flow rate of [1]					
	1.0 litre/h			2.0liter/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

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

Maximodim 1g 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. Maximodim 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.

Maximodim 500 mg should be administered by intravenous injection, or by deep intramuscular injection.

Recommended intramuscular injection sites are the upper outer quadrant of the gluteus maximus or lateral part of the

thigh. Maximodim solutions may be given directly into the vein. The standard recommended route of administration is by intravenous intermittent injection. Intramuscular administration should only be considered when the intravenous route is not possible or less appropriate for the patient.

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).

- **Hypersensitivity to the active substance, to other cephalosporins or to any of the excipients previous immediate and/or severe hypersensitivity reaction to apenicillin or to any other beta-Lactam medicinal products.**

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.

- **Special caution is required to determine any other type of previous hypersensitivity reactions to penicillin or to other beta-Lactam medicinal products because patients hypersensitive to these medicins be hypersensitive to(Generic name) as well(cross-allergy).**

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 asaminoglycosides 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 (seesections 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 maximodim:
Maximodim 1 g contains 52 mg (2.3 mmol) of sodium per vial.
Maximodim 500 mg contains 26 mg (1.15 mmol) 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 interactions
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). maximodim 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 sequelae1 Paraesthesia
Vascular disorders	Phlebitis or thrombophlebitis with intravenous administration			
Gastrointestinal disorders	Diarrhoea	Antibacterial agent-associated diarrhoea and colitis2 (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 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	General disorders and	Fever		

administration site conditions	administration site conditions			
Investigations	Positive Coombs' test5			

1There 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.
4There 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. Healthcare professionals are asked to report any suspected

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

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.

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 section4.2).

*Hepatic impairmen*t

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. owever, by the age of 2 months the half-life is within the range for adults.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Carbonate

6.2 Incompatibilities

Maximodum 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.

shelf life

Three years when stored not exce 30ºC and protected from light and use after reconstitution for 24 hr. at 2-8 ºC

6.3 Nature and contents of container

Carton box containing colorless glass (type (I) vial containing 1260 mg powder with chlorobutyl rubber stopper and aluminum cap + ampouleof 5 ml solvent+insert leaflet

Carton box containing colorless glass (type (I) vial containing 630 mg powder with

chlorobutyl rubber stopper and aluminum cap + ampouleof 2 ml solvent+insert leaflet

6.4Special 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 gm		
Intramuscular Intravenous bolus	3 ml 10 ml	260 90

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.

Preparation of solutions forbolus 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.