SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Lemoxol 1 g Powder for Solution for Injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 1.165g of ceftazidime pentahydrate (equivalent to 1g of ceftazidime) with 0.118 g sodium carbonate.

For full list of excipients see 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection/infusion.

A white to almost white coloured powder for solution for injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ceftazidime is indicated for the treatment of the following infections when known or likely to be due to one or more susceptible microorganisms (see section 5. 1) and when parenteral therapy is required:

- Respiratory tract infections, including lower respiratory tract infections in patients with cystic fibrosis
- Urinary tract infections; ceftazidime may also be used for peri-operative prophylaxis during trans-urethral prostatectomy
- Skin and soft tissue infections
- Biliary tract infections
- Intra-abdominal infections
- Bone and joint infections
- Infections associated peritoneal dialysis and with continuous ambulatory peritoneal dialysis (CAPD)
- Meningitis due to aerobic gram-negative organisms
-

Whenever possible, it is recommended that the results of bacterial cultures and susceptibility tests are known before commencing treatment. This is especially important if ceftazidime is to be used as monotherapy. Ceftazidime should be used in combination with an additional antibacterial agent(s) when treating infections that are likely to be due to a mixture of susceptible and resistant bacterial species.

Consideration should be given to official guidance regarding the appropriate use of antibacterial agents.

4.2 Posology and method of administration

The dosage and mode of administration of ceftazidime should be determined by the severity of the infection, susceptibility of the causative organism and the condition of the patient, such as age, weight and renal function.

Age Group	**Infection**	**Usual Dose**
Adults	Most uses	1 g 8-hourly OR 2 g 12-hourly
	Severe infections and infections in neutropenic patients	2 g 8-hourly OR 3 g 12-hourly
	UTI	500 mg 12-hourly OR 1 g 12-hourly
	Prophylaxis for prostatectomy	1 g at induction ± 1g at catheter removal
	Cystic fibrosis	100-150 mg/kg/day in three divided doses; not to exceed 9 g/day
Elderly	All infections, especially in those> 80 years	Not to exceed 3 g daily total
Infants> 2 months and children	Most uses	30-100 mg/kg/day in two or three divided doses
	Severe infections	up to 150 mg/kg/day (max 6 g total per day) in three divided doses
Neonates and infants < 2 months	Most uses	25 – 60 mg/kg/day in two divided doses

Renal impairment

Ceftazidime is excreted by the kidneys almost exclusively by glomerular filtration. It is therefore recommended that the dosage of ceftazidime should be reduced when the creatinine clearance is less than 50ml/min.

In patients with suspected renal insufficiency, an initial loading dose of 1g of ceftazidime may be given. An estimate of creatinine clearanceshould be made to determine the appropriate maintenance dose.

For patients in renal failure on continuous arteriovenous haemodialysis or high-flux haemofiltration in intensive therapy units, it is recommended that the dosage should be 1 g daily in divided doses. For low-flux haemofiltration it is recommended that the dosage should be that suggested above for those with suspected renal insufficiency.

Recommended maintenance doses in renal insufficiency are shown below:

Creatinine clearance	*Approx. serum creatinine*[*]	*Recommended unit dose of ceftazidime*	*Frequency of dosing*

(ml/min)	*micromol/l (mg/dl)*	*(g)*	*(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

* These values are guidelines and may not accurately predict renal function in all patients especially in the elderly in whom the serum creatinine concentration may overestimate renal function.

In patients with severe infections, especially those patients with neutropenia, who would normally receive 6 g of ceftazidime daily were it not for renal insufficiency, the unit dose given in the table above may be increased by 50% or the dosing frequency increased appropriately. In such patients it is recommended that the serum concentration of ceftazidime should be monitored and that trough concentrations should not exceed 40 mg/l.

When only serum creatinine is available, the following formula (Cockcroft's equation) may be used to estimate creatinine clearance. To convert serum creatinine in mol/l into mg/dl divide by 88.4. The serum creatinine should represent a steady state of renal function:
Males:

$$\text{Creatinine clearance (ml/min)} = \frac{\text{Weight (kg)} \times (140 - \text{age in years})}{72 \times \text{serum creatinine (mg/dl)}}$$

Females:
0.85 x above value.

Haemodialysis

The serum half-life of ceftazidime during haemodialysis ranges from 3 - 5 hours. The appropriate maintenance dose of ceftazidime should be repeated following each haemodialysis period.

Children

The creatinine clearance should be adjusted for body surface area or lean body mass, and the dosing frequency reduced in cases of renal insufficiency as for adults.

Hepatic impairment

No dosage adjustment is required in patients with hepatic impairment.

Dosage in peritoneal dialysis:

Ceftazidime may also be used in patients who are undergoing peritoneal dialysis and continuous ambulatory peritoneal dialysis (CAPD) at a dose adjusted according to renal function. In such patients, a loading dose of lg of ceftazidime

may be given, followed by 500mg every 24 hours. In addition, for intra peritoneal infections, ceftazidime can be incorporated into the dialysis fluid (usually 125 to 250 mg for 2 L of dialysis fluid).

Method of Administration

Intravenous injection or infusion
After reconstitution of the solution according to the directions provided (see Section 6.6), ceftazidime may be administered intravenously.

Intramuscular injection
After reconstitution of the solution according to the directions provided (see Section 6.6), ceftazidime may be administered by deep intramuscular injection into a large muscle mass, such as the upper outer quadrant of the gluteus maximus or lateral part of the thigh.

4.3 Contraindications

Hypersensitivity to ceftazidime or to any of the cephalosporins.

Hypersensitivity to sodium carbonate.

Previous immediate and/or severe hypersensitivity reaction to a penicillin or to any other type of beta-lactam drug.

4.4 Special warnings and precautions for use

Before therapy with ceftazidime is instituted, careful inquiry should be made to determine whether the patient has had any previous hypersensitivity reactions to ceftazidime, cephalosporins, penicillins, or other beta-lactam drugs.

Ceftazidime is contraindicated in patients who have had a previous hypersensitivity reaction to any cephalosporin. It is also contraindicated in patients who have had a previous immediate and/or any severe hypersensitivity reaction to any penicillin or to any other beta-lactam drug. Ceftazidime should be given with caution to patients who have had any other type of hypersensitivity reaction to a penicillin or any other beta-lactam drug.

Antibiotic-associated diarrhoea, colitis and pseudomembranous colitis have all been reported with the use of ceftazidime. These diagnoses should be considered in any patient who develops diarrhoea during or shortly after treatment. Ceftazidime should be discontinued if severe and/or bloody diarrhoea occurs during treatment and appropriate therapy instituted.

Ceftazidime should be used with caution in individuals with a previous history of gastro-intestinal disease, particularly colitis.

Ceftazidime has not been shown to be nephrotoxic. However, the total daily dosage should be reduced when ceftazidime is administered to patients with acute

or chronic renal insufficiency in order to avoid potential clinical consequences, such as seizures (see section 4.2).

Cephalosporin antibiotics should be given with caution to patients receiving concurrent treatment with nephrotoxic drugs such as aminoglycoside antibiotics or potent diuretics (such as furosemide) as these combinations may have an adverse effect on renal function and have been associated with ototoxicity (see section 4.5).

As with other cephalosporins, prolonged use of Ceftazidime may result in the overgrowth of non-susceptible organisms, such as enterococciand Candida *spp*.

This vial contains 4.52mmol of sodium in total. The sodium content should be taken into consideration when prescribing to patients requiring sodium restriction.

4.5 Interaction with other medicinal products and other forms of interaction

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.

Laboratory Tests

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.

Ceftazidime does not interfere with enzyme-based tests for glycosuria. Slight interference with copper reduction methods (Benedict's test, Fehling's test, Clinitest) may be observed.

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

Nephrotoxicity has been reported following concomitant administration of cephalosporins and aminoglycoside antibiotics or potent diuretics, such as furosemide (frusemide). Renal function should be carefully monitored, especially if higher dosages of the aminoglycosides are to be administered or if therapy is prolonged, because of the potential nephrotoxicity and ototoxicity of aminoglycoside antibiotics.

4.6 Pregnancy and Lactation

Pregnancy
Reproduction studies have not revealed any evidence of impaired fertility or harm to the foetus due to ceftazidime. However, as animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed

Lactation

Ceftazidime is excreted in human milk in low concentrations, and consequently caution should be exercised when ceftazidime is administered to a nursing mother.

4.7 Effects on ability to drive and use machinery

Dizziness can occur which can affect the ability to drive and to use machines.

4.8 Undesirable effects

The most common adverse reactions during treatment with ceftazidime treatment are local reactions following intravenous injection, allergic reactions, and effects on the gastro-intestinal tract.

A table of the MedDRA System Organ Class and Frequency of Adverse Reactions is provided below.

MedRA System Organ Class	**Frequency of Adverse Drug Reaction**
Blood and lymphatic system disorders	
Transient elevation of blood urea, blood urea nitrogen and/or serum creatinine	Very rare (≤1/10,000)
Leucopenia, neutropenia, agranulocytosis, thrombocytopenia and lymphocytosis	Very rare (≤1/10,000)
Immune system disorders	
Maculopapular or urticarial rash, fever, pruritus.	Rare (≥1/10,000 to ≤1/1,000)
Angioedema and anaphylaxis (including bronchospasm and/or hypotension).	Rare (≥1/10,000 to ≤1/1,000)
Nervous system disorders	
Headache, dizziness, paraesthesia and bad taste.	Uncommon (≥1/1,000 to ≤1/100)
Tremor, myoclonia **myoclonus**, convulsions, and encephalopathy in patients with renal impairment in whom the dose of ceftazidime has not been appropriately reduced.	Very rare (≤1/10,000)
Gastrointestinal disorders	
Diarrhoea, nausea, vomiting, abdominal pain.	Uncommon (≥1/1,000 to ≤1/100)
Oral thrush or colitis. As with other cephalosporins, colitis may be associated with *Clostridium difficile* and may present as pseudomembranous colitis.	Rare (≥1/10,000 to ≤1/1,000)

Hepato-biliary disorders	
Jaundice.	Very rare (≤1/10,000)
Skin and subcutaneous tissue disorders	
Erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis	Rare (≥1/10,000 to ≤1/1,000)
Reproductive system disorders	
Candidiasis, vaginitis.	Rare (≥1/10,000 to ≤1/1,000)
General disorders and administration site conditions	
Phlebitis or thrombophlebitis with intravenous administration, pain and/or inflammation after intramuscular injection.	Uncommon (≥1/1,000 to ≤1/100)
Investigations	
Laboratory test changes noted transiently during ceftazidime therapy include: eosinophilia, positive Coombs' test, haemolytic anaemia, thrombocytosis and elevations in one or more of the hepatic enzymes, ALT (SGPT), AST (SGOT), LDH, GGT and alkaline phosphatase.	Very rare (≤1/10,000)

4.9 Overdose

An overdose of ceftazidime may be associated with pain, inflammation and phlebitis at the injection site.

Overdose or the administration of inappropriately large doses in the presence of renal insufficiency can lead to neurological sequelae including dizziness, paraesthesiae, headache, encephalopathy, convulsion and coma.

Laboratory abnormalities that may occur after an overdose include elevations in creatinine, BUN, liver enzymes and bilirubin, a positive Coombs' test, thrombocytosis, thrombocytopenia, eosinophilia, leucopenia and prolongation of the prothrombin time.

General symptomatic and supportive measures should be instituted, together with specific measures to control any seizures. In cases of severe overdose, especially in a patient with renal failure, combined haemodialysis and haemoperfusion may be considered if response to more conservative therapy fails.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

General properties

Pharmacotherapeutic group:

Third generation cephalosporins (ATC code: J01DD02)

Mode of Action
Ceftazidime is a semi-synthetic bactericidal antibacterial agent of the cephalosporin class. Like other beta-lactam drugs, Ceftazidime exerts antibacterial activity by binding to and inhibiting the action of certain bacterial cell wall synthetic enzymes (transpeptidases). Inhibition of one or more of these essential penicillin-binding proteins results in the interruption of cell wall biosynthesis at the final stage of peptidoglycan production, resulting in bacterial cell lysis and death.

Mechanisms 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 certain of the extended-spectrum beta-lactamases (ESBLs) and by the chromosomally-encoded (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
- drug efflux pumps

More than one of these mechanisms of resistance may co-exist in a single bacterial cell. Depending on the mechanism(s) present, bacteria may express cross-resistance to several or all other beta-lactams and/or antibacterial drugs of other classes.

Breakpoints
Clinical MIC breakpoints to separate susceptible (S) pathogens from resistant (R) pathogens according to EUCAST are:

- Enterobacteriaceae: S≤1.0 mg/l; R>8 mg/l.

- Pseudomonas spp.: S≤8 mg/l; R>8 mg/l.

- Non-species related breakpoints: S≤4 mg/l; R>8 mg/l.

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 the agent in at least some types of infections is questionable.

Commonly susceptible species
Gram-positive micro-organisms:
Streptococcus pyogenes
Streptococcus agalactiae
Gram-negative micro-organisms:
Haemophilus influenzae
Morganella morganii
Neisseria gonorrhoeae
Neisseria meningitidis
Proteus mirabilis
Proteus vulgaris
Providencia species

Species for which acquired resistance may be a problem
Gram-negative micro-organisms:
Acinetobacter spp.
Escherichia coli
Klebsiella species
Pseudomonas aeruginosa
Stenotrophomonas maltophilia

Inherently resistant organisms
Gram-positive micro-organisms:
Enterococcus species
Staphylococcus species, Coagulase negative*
*Staphylococcus aureus**
Streptococcus milleri
Streptococcus pneumoniae#
Viridans Streptococci

Anaerobes
Bacteroides species
Clostridium species
Fusobacterium species
Peptostreptococcus species

Others
Chlamydia species
Campylobacter species
Legionella species
Mycobacterium species
Mycoplasma species

+ Based on published data from several different sources

* Shows some in-vitro activity against methicillin-susceptible strains but should not be relied upon to treat staphylococcal infections.
# Shows some in-vitro activity against penicillin-susceptible strains but should not be relied upon to treat pneumococcal infections.

5.2 Pharmacokinetic properties

Absorption
Ceftazidime administered by the parenteral route reaches high and prolonged serum concentrations in man. After intramuscular administration of 500 mg and 1 g serum mean peak concentrations of 18 and 37 mg/l respectively are rapidly achieved. Five minutes after an intravenous bolus injection of 500 mg, 1 g or 2 g, serum mean concentrations are respectively 46, 87 and 170 mg/l.

Therapeutically effective concentrations are still found in the serum 8 to 12 hours after both intravenous and intramuscular administration. The serum half-life is about 1.8 hours in normal volunteers, and about 2.2 hours in patients with apparently normal renal function. The serum protein binding of ceftazidime is low at about 10%.

Metabolism
Ceftazidime is not metabolised in the body and is excreted unchanged in the active form into the urine by glomerular filtration.

Distribution
Concentrations of ceftazidime in excess of the minimum inhibitory concentrations for common pathogens can be achieved in tissues such as bone, heart, bile, sputum, aqueous humour, synovial and pleural and peritoneal fluids.

Transplacental transfer of the antibiotic readily occurs.

Ceftazidime penetrates the intact blood brain barrier poorly, and low concentrations are achieved in the cerebrospinal fluid in the absence of inflammation. Therapeutic concentrations of 4 - 20 mg/l or more are achieved in the cerebrospinal fluid when the meninges are inflamed.

Excretion
Excretion is almost exclusively by the kidney. Approximately 80 - 90% of the dose is recovered in the urine within 24 hours. Less than 1% is excreted via the bile, significantly limiting the amount entering the bowel.

5.3 Preclinical safety data

No additional data of relevance.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium carbonate.

6.2 Incompatibilities

Ceftazidime is less stable in Sodium Bicarbonate Injection than other intravenous fluids. It is not recommended as a diluent.

Ceftazidime and aminoglycosides should not be mixed in the same giving set or syringe.

Precipitation has been reported when vancomycin has been added to ceftazidime in solution. It is recommended that giving sets and intravenous lines are flushed between administration of these two agents.

Solutions containing ceftazidime should not be mixed with or added to solutions containing other agents than listed below (see section 6.6).

6.3 Shelf life

Unopened vial:

Three years.

Reconstituted solution:

Chemical and physical stability has been demonstrated in the following conditions:

- for 24 hours at 25°C and
- for 7 days at 5±3°C

when dissolved in 10 or 3 ml of WFI.

- for 6 hours at 25°C and
- for 36 hours at 5±3°C

when dissolved in 0.5% or 1% Lidocaine HCl injection.

- for 6 hours at 25°C and
- for 24 hours at 5±3°C

when dissolved in all the solutions studied (see table in Section 6.6).

From a microbiological point of view, unless the method of opening/reconstitution precludes the risk of microbial contamination, the product should be used immediately

If not used immediately, the 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 - 8 °C, unless opening, reconstitution, and dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Unopened vial:
Store below 30°C. Keep the vial in the outer carton.

Reconstituted solution:
Store below 2 - 8°C. See section 6.3 for further information on shelf life of reconstituted solutions.

6.5 Nature and contents of container

Type III glass vials with rubber (Type I) closures sealed with aluminium caps. The vials are placed in cartons.

Boxes of one, ten, or fifty vials.

6.6 Instructions for use and handling

The use of freshly prepared solutions is recommended (see section 6.3).

The reconstituted solution should be clear. Do not use if particles are present.

Ceftazidime solutions range from a light yellow to amber solution depending on the concentration, diluent and storage conditions used. Within the stated recommendations, variations in the intensity of the colour will not affect the potency of the drug.

Each 1 g vial contains 52 mg (2.26 mmol) of sodium.

As the product dissolves, carbon dioxide is released and a positive pressure develops. For ease of use, it is recommended that the following techniques of reconstitution are adopted.

1g Intramuscular/Intravenous 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.

Intramuscular injection:
Lemoxol 1 g Powder for Solution for Injection should be dissolved in 3 ml of 0.5% or 1.06% Lidocaine Hydrochloride BP. The resulting solution contains approximately 260 mg/ml ceftazidime.

Solutions in Lidocaine should <u>not</u> be administered intravenously.

Intravenous injection:

Lemoxol 1 g Powder for Solution for Injection should be dissolved in 10 ml of Water for Injections Ph. Eur. The resulting solution contains approximately 90 mg/ml ceftazidime.

Satisfactory potency is retained for
- 24 hours at 25°C and
- for 7 days at 5±3°C

when dissolved in 10 or 3 ml of Water for Injections.

- for 6 hours at 25°C and
- for 36 hours at 5±3°C

when dissolved in 0.5% or 1% Lidocaine HCl injection.

- for 6 hours at 25°C and
- for 24 hours at 5±3°C

when dissolved in the solutions in the following table:

Reconstitution Diluent
At Ceftazidime concentration 1 mg/ml - 40 mg/ml: 0.9% Sodium Chloride Injection BP 0.225% Sodium Chloride and 5% Dextrose Injection BP 0.45% Sodium Chloride and 5% Dextrose Injection BP 0.9% Sodium Chloride and 5% Dextrose Injection BP 0.18% Sodium Chloride and 4% Dextrose Injection BP M/6 Sodium Lactate Injection BP Compound Sodium Lactate Injection BP (Hartmann's Solution) 5% Dextrose Injection BP 10% Dextrose Injection BP Dextran 40 Injection BP 10% in 0.9% Sodium Chloride Injection BP Dextran 40 Injection BP 10% in 5% Dextrose Injection BP Dextran 70 Injection BP 6% in 0.9% Sodium Chloride Injection BP Dextran 70 Injection BP 6% in 5% Dextrose Injection BP
At Ceftazidime concentration 0.05 mg/ml - 0.25 mg/ml: Intraperitoneal Dialysis Fluid (Lactate) BPC 1973
When admixed at 4 mg/m, either components will retain satisfactory potency: Cefuroxime (cefuroxime sodium) 3mg/ml in 0.9% Sodium Chloride Injection BP Cloxacillin (cloxacillin sodium) 4mg/ml in 0.9% Sodium Chloride Injection BP Heparin 10 IU/ml in 0.9% Sodium Chloride Injection BP Heparin 50 IU/ml in 0.9% Sodium Chloride Injection BP Hydrocortisone (hydrocortisone sodium succinate) 1mg/ml in 0.9% Sodium Chloride Injection BP Hydrocortisone (hydrocortisone sodium succinate) 1mg/ml in 5% Dextrose Injection BP Potassium Chloride 10 mEq/L in 0.9% Sodium Chloride Injection BP Potassium Chloride 40 mEq/L in 0.9% Sodium Chloride Injection BP

7 MARKETING AUTHORISATION HOLDER

DEMO S.A. Pharmaceutical Industry,
21st km National Road Athens-Lamia,
145 68 Krioneri, Attiki, Greece

8 MARKETING AUTHORISATION NUMBER

9 DATE OF FIRST AUTHORISATION/ RENEWAL OF AUTHORISATION

10 DATE OF REVISION OF TEXT

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