APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

PROPRIETARY NAMES (and dosage forms)

AURO CEFTAZIDIME 250 mg (Powder for injection)

AURO CEFTAZIDIME 500 mg (Powder for injection)

AURO CEFTAZIDIME 1.0 g (Powder for injection)

AURO CEFTAZIDIME 2.0 g (Powder for injection)

COMPOSITION

AURO CEFTAZIDIME 250 mg: Each vial contains ceftazidime pentahydrate equivalent to ceftazidime 250 mg.

AURO CEFTAZIDIME 500 mg: Each vial contains ceftazidime pentahydrate equivalent to ceftazidime 500 mg.

AURO CEFTAZIDIME 1.0 g: Each vial contains ceftazidime pentahydrate equivalent to ceftazidime 1.0 g.

AURO CEFTAZIDIME 2.0 g: Each vial contains ceftazidime pentahydrate equivalent to ceftazidime 2.0 g.

The vials contain a blend of ceftazidime pentahydrate (90,8% m/m) and anhydrous sodium carbonate (9,2% m/m).

PHARMACOLOGICAL CLASSIFICATION

A 20.1.1. Broad and medium spectrum antibiotics.

PHARMACOLOGICAL ACTION

Ceftazidime is a bactericidal cephalosporin antibiotic.

Bacteriology:

Ceftazidime is bactericidal in action, exerting its effect on target cell wall proteins and causing inhibition of cell wall synthesis. A wide range of pathogenic strains and isolates associated with hospital acquired infections are susceptible to ceftazidime *in vitro*, including resistant strains and multi-resistant strains. It is stable to most clinically important beta-lactamases produced by both Gram-negative and Gram-positive organisms including multi-resistant strains. Ceftazidime has high intrinsic activity *in vitro* and acts with few changes in minimum inhibitory concentration (MIC) at varied inoculum levels. Ceftazidime has been shown to have *in vitro* activity against the following organisms:

Gram-negative:

Pseudomonas aeruginosa, Pseudomonas spp. (other), *Klebsiella pneumoniae, Klebsiella* spp. (other), *Proteus mirabilis, Proteus vulgaris, Morganella morganii* (formerly *Proteus morganii*), *Proteus rettgeri*, *Providencia* spp*., Escherichia coli*, *Enterobacter* spp., *Citrobacter* spp., *Serratia* spp., *Salmonella* spp., *Shigella* spp., *Yersinia enterocolitica*, *Pasteurella multocida*, *Acinetobacter* spp., *Neisseria gonorrhoeae, Neisseria meningitides, Haemophilus influenzae* (including ampicillin-resistant strains), *Haemophilus parainfluenzae* (including ampicillin-resistant strains).

Gram-positive:

Micrococcus spp., *Streptococcus pyogenes,* Streptococcus Group B, *Streptococcus pneumoniae*, *Streptococcus mitis, Streptococcus* spp., excluding *Enterococcus (Streptococcus) faecalis*. *Bacteriodes* spp., are mostly resistant. Ceftazidime is not active *in vitro* against methicillin-resistant Staphylococci, *Streptococcus faecalis* and many other Enterococci, *Listeria monocytogenes, Campylobacter* spp., or *Clostridium difficile*.

After 1 gram I.M. injection, ceftazidime serum levels exceed MIC90 for more than 12 hours for Streptococcus Group A and B (except *Strep. faecalis), E. coli, Klebsiella* spp*., Proteus mirabilis*, *Proteus* spp. (indole positive), *Serratia* spp., *Citrobacter* spp., *Salmonella* spp., and *Haemophilus influenzae.*

Ceftazidime is not active against the following bacteria:

Methicillin-resistant staphylococci, *Enterococcus (Streptococcus) faecalis, Clostridium difficile, Listeria monocytogenes, Campylobacter* spp.

Pharmacokinetics:

In healthy subjects, the serum half-life of ceftazidime is 1,8 hours (1,5 - 2 hours) and only slightly altered by dosage or route of administration. The half-life is prolonged in patients with impaired renal function. Ceftazidime has a low serum protein binding (10%).

INDICATIONS

AURO CEFTAZIDIME is indicated for the treatment of the following infections when caused by susceptible organisms:

- **Severe infections including: septicaemia, bacteraemia, peritonitis, and in immunocompromised patients,** caused by *Streptococcus pyogenes,* Streptococcus Group B, *Streptococcus pneumoniae, Streptococcus mitis, Streptococcus* spp., *Escherichia coli, Haemophilus influenzae, Klebsiella pneumoniae, Salmonella* spp., *Acinetobacter* spp., *Yersinia enterocolitica*, or *Pasteurella multocida*.
- **Respiratory tract infections such as pneumonia, bronchopneumonia, and bronchitis including lung infections in patients with cystic fibrosis,** caused by *Streptococcus pneumoniae, Haemophilus influenzae, Klebsiella pneumoniae, Haemophilus parainfluenzae, Escherichia coli, Streptococcus pyogenes, Proteus mirabilis, Serratia* spp., or *Enterobacter* spp.
- **Ear, nose and throat infections,** caused by *Streptococcus pneumoniae, Haemophilus influenzae, Klebsiella pneumoniae, Haemophilus parainfluenzae, Escherichia coli, Streptococcus pyogenes, Proteus mirabilis, Serratia* spp., or *Enterobacter* spp.
- **Urinary tract infections,** caused by *Neisseria gonorrhoeae, Escherichia coli, Proteus mirabilis, Klebsiella pneumoniae, Proteus vulgaris, Morganella morganii, Enterobacter* spp., or *Citrobacter* spp.
- **Skin and soft tissue infections,** caused by *Streptococcus pyogenes, Streptococcus*

spp., *Escherichia coli, Enterobacter* spp., *Klebsiella pneumoniae, Proteus mirabilis*, or *Morganella morganii*.

- **Gastrointestinal, biliary and abdominal infections,** caused by *Escherichia coli, Klebsiella pneumoniae, Streptococcus* spp., *Salmonella* spp., *Shigella* spp., or *Yersinia enterocolitica.*

CONTRA-INDICATIONS

Hypersensitivity to cephalosporin antibiotics.

WARNINGS

Great care should be taken if **AURO CEFTAZIDIME** is to be given to patients who are penicillin-sensitive. Care is also necessary in patients with known histories of allergy.

INTERACTIONS

The concomitant use of a nephrotoxic medicine such as the aminoglycoside gentamicin may increase the risk of kidney damage with **AURIZEF**. There is also some evidence for enhanced nephrotoxicity with a loop diuretic like furosemide. The renal excretion of **AURO CEFTAZIDIME** is inhibited by probenecid.

There may be antagonism between **AURO CEFTAZIDIME** and bacteriostatic antibacterials.

PREGNANCY AND LACTATION

The safety in pregnancy and lactation has not been established.

DOSAGE AND DIRECTIONS FOR USE

AURO CEFTAZIDIME is given by deep intramuscular injection, slow intravenous injection over 3 to 5 minutes, or intravenous infusion over up to 30 minutes.

Adults:

The usual dose for adults ranges from 1 g to 6 g daily in divided doses every 8 or 12 hours. The higher doses are used in severe infections especially in immunocompromised

patients. In adults with cystic fibrosis who have pseudomonal lung infection, high doses of 90 to 150 mg per kg body-weight daily in 3 divided doses are used; up to 9 g daily has been given to adults with normal renal function. Single doses of more than 1 g should be given intravenously.

Children:

Children are usually given 30 to 100 mg per kg daily in 2 or 3 divided doses, but in severely ill children up to 150 mg per kg daily to a maximum of 6 g daily may be given in 3 divided doses.

Neonates and infants up to 2 months old:

A dose of 25 to 60 mg per kg daily in 2 divided doses is effective.

Elderly:

In the elderly, the dose should generally not exceed 3 g daily.

Renal impairment:

In patients with renal impairment the dosage of **AURO CEFTAZIDIME** may need to be reduced. Following a loading dose of 1 g, maintenance doses are based on the creatinine clearance.

Maintenance doses are:

Creatinine Clearance (ml/min)	*Recommended dosage*
31 — 50	1 g every 12 hours
16 — 30	1 g every 24 hours
6 —15	0,5 g every 24 hours
< 5	0,5 g every 48 hours

In severe infections these doses may need to be increased by 50%. In these patients ceftazidime trough serum concentrations should not exceed 40 µg/ml. In patients undergoing peritoneal dialysis a loading dose of 1 g may be given followed by 500 mg every 24 hours; ceftazidime sodium may also be added to the dialysis fluid, usually 125 mg to 250 mg of ceftazidime for 2 litres of dialysis fluid. In patients undergoing haemodialysis a loading dose of 1 g is given and should be repeated after each

dialysis period.

Administration:

AURO CEFTAZIDIME may be given intravenously or 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.

Instructions for reconstitution:

It is preferable to use freshly constituted solutions of **AURO CEFTAZIDIME**

See table below for addition volumes and solution concentrations:

Vial size	**Amount of diluent to be added (ml)**	**Approximate concentration (mg/ml)**
0.25 g intramuscular& 0.25 g intravenous&	1.0 2.5	200 90
0.5 g intramuscular 0.5 g intravenous	1.5 5.0	260 90
1 g intramuscular 1 g intravenous 1 g intravenous infusion	3.0 10 50*	260 90 20
2 g intravenous bolus 2 g intravenous infusion	10 50*	170 40

*Note: Addition should be in two stages (see text). All sizes of vials as supplied are under reduced pressure. 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.

1. Insert the 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 obtained in about 1-2 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 headspace. The withdrawn solution may contain small bubbles of carbon dioxide, they may be disregarded.

For short intravenous infusion (e.g. up to 30 minutes), 1 g or 2 g

AURO CEFTAZIDIME may be dissolved in 50 ml Water for Injections as follows:

1. Insert the syringe needle through the vial closure and inject 10 ml 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 obtained in about 1 - 2 minutes.
3. Insert a gas relief needle through the vial closure to relieve the internal pressure. With the gas relief in position, add the remaining 40 ml of diluent.
   Remove the gas relief needle and syringe needle; shake the vial and set up for infusion use in the normal way.

Note: To preserve product sterility, it is important that a gas relief needle is not inserted through the vial closure before the product has dissolved. 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.

Compatibility with fluids:

AURO CEFTAZIDIME is compatible with the most commonly used intravenous fluids (see **STORAGE INSTRUCTIONS**). ****AURO CEFTAZIDIME** is incompatible with vancomycin and is less stable in Sodium Bicarbonate Injection than in other intravenous fluids.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS

Side-effects:

Haematological disorders:

Less frequent:

Neutropaenia[1a], thrombocytopaenia[1b], bleeding complications related to hypothrombinaemia[1c] and/or platelet dysfunction, haemolytic anaemia[1d].

Gastrointestinal disorders:

Frequent:

Nausea[1e], vomiting[1e], diarrhoea[1e], *oral candidiasis[1x].

Less frequent:

Pseudomembranous colitis[1g].

The following side-effects have been reported and frequencies are unknown:

Prolonged use may result in overgrowth of non-susceptible organisms[1f].

Hepato-biliary disorders:

The following side-effects have been reported and frequencies are unknown:

Hepatitis and cholestatic jaundice have occurred[1h].

Immune system disorders (including skin reactions):

Frequent:

Hypersensitivity reactions, including eosinophilia[1i].

Less frequent:

Hypersensitivity reactions, including skin reactions[1j], urticaria[1j], fever[1j], reactions resembling serum sickness[1l], and anaphylaxis[1m].

Nervous system disorders:

Less frequent:

Convulsions and other signs of CNS toxicity have been associated with high doses, especially in patients with severe renal impairment[1n].

Renal and urinary disorders:

The following side-effects have been reported and frequencies are unknown:

Nephrotoxicity has been reported. Acute renal tubular necrosis has followed excessive dosage and has also been associated with its use in older patients or those with pre-existing renal impairment or those with the concomitant administration of nephrotoxic medicines such as aminoglycosides. Acute interstitial nephritis is also a possibility as a manifestation of hypersensitivity.

Reproductive system and breast disorders:

Frequent:

*Vaginal candidiasis[1z].

General disorders and administration site conditions:

Less frequent:

Thrombophlebitis[1o] has occurred following intravenous infusion.

The following side effects have been reported and frequencies are unknown:

Positive response to the Coombs' test, pain at the injection site following intra-muscular administration.

Investigations:

The following side-effects have been reported and frequencies are unknown:

Transient increases in liver enzyme values have been reported.

SPECIAL PRECAUTIONS:

AURO CEFTAZIDIME should be given with caution to patients with renal impairment; a dosage reduction is necessary. Renal and haematological status should be monitored especially during prolonged and high-dose therapy.

AURO CEFTAZIDIME may interfere with the Jaffé method of measuring creatinine concentrations and may produce falsely high values; this should be borne in mind when measuring renal function.

Positive results to the direct Coombs' test have been found during treatment with **AURO CEFTAZIDIME** and these can interfere with blood cross matching.

The urine of patients being treated with **AURO CEFTAZIDIME** may give false-positive reactions for glucose using copper-reduction reactions.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

See side-effects and special precautions.

Serum levels of **AURO CEFTAZIDIME** are reduced by dialysis.

Treatment is supportive and symptomatic.

IDENTIFICATION

A white to cream coloured powder. When reconstituted, a light yellow to amber coloured, clear liquid is formed.

PRESENTATION

AURO CEFTAZIDIME 250 mg:

15 ml clear glass vials fitted with grey bromo butyl rubber stoppers sealed with deep blue colour aluminium flip off seals.

Pack size: Single vial packed in printed carton with a package insert.

AURO CEFTAZIDIME 500 mg:

15 ml clear glass vials fitted with grey bromo butyl rubber stoppers sealed with orange colour aluminium flip off seals.

Pack size: Single vial packed in printed carton with a package insert.

AURO CEFTAZIDIME 1.0 g:

20 ml clear glass vials fitted with grey bromo butyl rubber stoppers sealed with orange colour aluminium flip off seals.

Pack size: Single vial packed in printed carton with a package insert.

AURO CEFTAZIDIME 2.0 g:

50 ml clear glass vials fitted with grey bromo butyl rubber stoppers sealed with german blue colour aluminium flip off seals.

Pack size: Single vial packed in printed carton with a package insert.

STORAGE INSTRUCTIONS

Vials of **AURO CEFTAZIDIME** should be stored at a temperature below 25°C.

In keeping with good pharmaceutical practice it is preferable to use freshly constituted solutions of **AURIZEF**. If this is not practicable, satisfactory potency is retained for 24 hours at room temperature (below 25 °C) when prepared in Water for Injection BP or any of the injections listed below. At ceftazidime concentrations between 1 mg/ml and 40 mg/ml in:

0.9 % Sodium Chloride Injection BP

Compound Sodium Lactate Injection BP (Hartmann's Solution)

M/6 Sodium Lactate Injection BP

5 % Dextrose 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

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

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

When reconstituted for intramuscular use with:

0.5 % or 1 % Lignocaine Hydrochloride Injection BP

**Ceftazidime and aminoglycosides should not be mixed in the same infusion set or syringe. *Precipitation has been reported when vancomycin has been added to ceftazidime in solution. Therefore, it would be prudent to flush giving sets and intravenous lines between administration of these two agents.

Solutions range from light yellow to amber depending on concentration, diluent and storage conditions used. Within the stated recommendations, product potency is not adversely affected by such colour variations.

Keep out of reach of children.

Protect from light.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

AURO CEFTAZIDIME 250 mg - 43/20.1.1/1026

AURO CEFTAZIDIME 500 mg - 43/20.1.1/1027

AURO CEFTAZIDIME 1,0 g - 43/20.1.1/1028

AURO CEFTAZIDIME 2,0 g - 43/20.1.1/1029

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

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