**Scheduling status:** S4

**Proprietary names and dosage forms:**

**Ceftazidime 1g Oethmaan Powder for solution for injection**

**Composition:**

**Ceftazidime 1g Oethmaan**: 1 vial with 1,29 g of powder contains ceftazidime pentahydrate corresponding to 1,0 g of ceftazidime.

**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* (formally *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 g IM 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., Citobacter 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 to 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:**

CEFTAZIDIME 1g OETHMAAN 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 CEFTAZIDIME 1,0 g OETHMAAN 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 CEFTAZIDIME 1g OETHMAAN.

There is also some evidence for enhanced nephrotoxicity with a loop diuretic like furosemide. The renal excretion of CEFTAZIDIME 1g OETHMAAN is inhibited by probenecid.

There may be antagonism between CEFTAZIDIME 1g OETHMAAN and bacteriostatic antibacterials.

**Pregnancy and lactation:**

The safety in pregnancy and lactation has not been established.

**Dosage and directions for use:**

CEFTAZIDIME 1g OETHMAAN 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 to 6 g daily in divided doses every 8 to 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 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 CEFTAZIDIME 1g OETHMAAN 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 to 50 | 1 g every 12 hours |
| 16 to 30 | 1 g every 24 hours |
| 6 to 15 | 0,5 g every 24 hours |
| < 5 | 0,5 g every 48 hours |

In severe infection 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 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:***

CEFTAZIDIME 1g OETHMAAN 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 CEFTAZIDIME 1g OETHMAAN**. See table below for addition volumes and solution concentrations:

| Vial size | Amount of diluent to be added (ml) | Approximate concentration (mg/ml) |
|---|---|---|
| 0,5 g | 1,5 | 238 |

| | | |
|---|---|---|
| intramuscular | | |
| 0,5 g intravenous | 5,0 | 91 |
| 1 g intramuscular | 3,0 | 263 |
| 1 g intravenous | 10 | 91 |
| 2 g intravenous bolus | 10 | 174 |

When ceftazidime is dissolved, carbon dioxide is released and a positive pressure develops. For ease of use, follow the recommended techniques of reconstitution described below.

*Intramuscular administration:*

Ceftazidime should be reconstituted with Water for Injection or 0,5 % or 1 % Lidocaine hydrochloride injection, as indicated in the table above. The package insert for Lidocaine should be consulted before reconstitution of ceftazidime with lidocaine.

*Intravenous administration:*

For direct intermittent intravenous administration, reconstitute ceftazidime with Water for Injection (see table above). Slowly inject the solution directly into the vein over a period of up to 5 minutes or give through the tubing of a giving set.

Instructions for reconstitution:

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 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 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), CEFTAZIDIME 1g OETHMAAN 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 to 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:***

CEFTAZIDIME 1g OETHMAAN should not be mixed with solutions with a pH above 7,5, for example sodium bicarbonate solution for injection. CEFTAZIDIME 1g OETHMAAN and aminoglycosides should not be mixed in the solution for injection because of the risk for precipitation.

At ceftazidime concentrations between 20 mg/ml and 333 mg/ml the CEFTAZIDIME 1g OETHMAAN powders for injection/infusion may be mixed in commonly used solutions for infusion:

- 0,9 % sodium chloride solution (physiological saline solution)
- 5 % glucose solution
- 0,9 % sodium chloride + 5 % glucose solution
- Ringer's Lactate Solution

When reconstituted for intramuscular use, CEFTAZIDIME 1g OETHMAAN powder for injection/infusion can also be diluted with 1 % lidocaine solutions.

**Side effects and special precautions:**

***Side effects*:**

*Haematological disorders:*

The following side-effects have been reported and the frequencies are unknown: neutropenia and thrombocytopaenia. Bleeding complications related to hypothrombinaemia and/or platelet dysfunction have occurred. Haemolytic anaemia may also occur.

*Gastrointestinal disorders:*

The following side-effects have been reported and the frequencies are unknown: gastrointestinal adverse effects such as nausea, vomiting, and diarrhoea. Prolonged use may result in overgrowth of non-susceptible organisms and pseudomembranous colitis may develop.

*Hepato-biliary disorders:*

The following side-effects have been reported and the frequencies are unknown: transient increases in liver enzyme values. Hepatitis and cholestatic jaundice.

*Immune system disorders (including skin reactions):*

The following side-effects have been reported and the frequencies are unknown: the most common adverse effects are hypersensitivity reactions, including skin reactions, urticaria, eosinophilia, fever, reactions resembling serum sickness, and anaphylaxis.

*Nervous system disorders:*

The following side-effects have been reported and the frequencies are unknown: convulsions and other signs of CNS toxicity have been associated with high doses, especially in patients with severe renal impairment.

*Renal and urinary disorders:*

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

*General disorders and administration site conditions:*

The following side-effects have been reported but the frequencies are unknown: there may be pain at the injection site following intra-muscular administration, and thrombophlebitis has occurred following intravenous infusion. There may be a positive response to the Coombs' test.

***Special precautions*:**

CEFTAZIDIME 1g OETHMAAN 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.

CEFTAZIDIME 1g OETHMAAN 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 CEFTAZIDIME 1g OETHMAAN and these can interfere with blood cross-matching.

The urine of patients being treated with CEFTAZIDIME 1g OETHMAAN 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 CEFTAZIDIME 1g OETHMAAN are reduced by dialysis.

Treatment is supportive and symptomatic.

**Identification:**

**Ceftazidime 1g Oethmaan**: a white to cream coloured powder.

**Presentation:**

**Ceftazidime 1,0 g Oethmaan** powder for solution for injection is packed in cartons containing 1 or 10 single dose, clear, colourless glass vial/s with a grey rubber stopper and aluminium cap with a transparent flip-off seal.

**Storage instructions:**

Store in the original packaging (in the carton) below 25 °C.

The reconstituted solution is intended for immediate use, but the solution may be stored in the original vials in the refrigerator at 2 to 8 °C for 24 hours. After use, discard any remaining solution.

KEEP OUT OF THE REACH OF CHILDREN.

**Registration numbers:**

Ceftazidime 1g Oethmaan: 41/20.1.1/0922

**Name and business address of the holder of the certificates of registration:**

**Oethmaan Biosims (Pty) Ltd.**

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