Scheduling status:

S4

Proprietary names and dosage forms:

CEFAZOLIN 500 mg OETHMAAN Powder for injection

CEFAZOLIN 1 g OETHMAAN Powder for injection

Composition:

Each CEFAZOLIN 500 mg OETHMAAN vial contains cefazolin sodium equivalent to 500 mg cefazolin.

Each CEFAZOLIN 1 g OETHMAAN vial contains cefazolin sodium equivalent to 1,0 g cefazolin.

CEFAZOLIN OETHMAAN (cefazolin sodium) is a semi-synthetic cephalosporin for parenteral administration. It is the sodium salt of 3- (5-methyl-1,3,4-thiadiazol-2-yl) thio] methyl]-7-[2-(1H-tetrazol-1-yl) acetamido]-3-cephem-4-carboxylic acid. The sodium content is 48,3 mg/g of cefazolin sodium. The molecular formula is $C_{14}H_{14}N_8O_4S_3$ (sodium salt). The molecular mass is 476,5.

The pH of the reconstituted solution is between 4,0 and 6,0.

Pharmacological classification:

A 20.1.1 Broad and Medium Spectrum Antibiotics

Pharmacological action:

Human pharmacology: Table 1 demonstrates the mean serum levels and duration of cefazolin following intramuscular administration.

Table 1: Serum concentrations after intramuscular administration:

	Serum Concentrations (μg/ml)					
Dose	***½ hr***	***1 hr***	***2 hr***	***4 hr***	***6 hr***	***8 hr***
250 mg	15,5	17	13	5,1	2,5	
500 mg	36,2	36,8	37,9	15,5	6,3	3
1 g*	60,1	63,8	54,3	29,3	13,2	7,1

* Average of two studies

In normal volunteers, constant intravenous infusion of cefazolin in doses of 3,5 mg/kg for one hour (approximately 250 mg), followed by 1,5 mg/kg for the next two hours (approximately 100 mg), produced a steady serum level of approximately 28 μg/ml during the third hour.

Table 2 shows the average serum concentrations following a single 1 g bolus intravenous injection. The average half-life was 1,4 hours.

Table 2: Serum concentrations after a 1 g intravenous dose:

Time lapse after administration	***Serum concentrations (μg/ml)***
5 minutes	188,4
15 minutes	135,8
30 minutes	106,8
1 hour	73,7
2 hours	45,6
4 hours	16,5

Cefazolin is excreted unchanged in the urine primarily by glomerular filtration and, to a lesser degree, by tubular secretion. Following an intramuscular injection of 500 mg, 56 % to 89 % of the administered dose is recovered within six hours and 80 % to nearly 100 % in 24 hours. Following the intramuscular administration of 500 mg and 1 g of cefazolin, peak urine concentrations greater than 1 000 μg/ml and 4 000 μg/ml respectively are attained.

In patients undergoing peritoneal dialysis (2 litres/hr), mean serum levels of cefazolin were approximately 10 and 30 μg/ml after 24 hours' instillation of a dialyzing solution containing 50 mg/litre and 150 mg/litre respectively. Mean peak levels were 29 μg/ml (range 13 to 44 μg/ml) with 50 mg/litre (3 patients) and 72 μg/ml (range 26 to 142 μg/ml) with 150 mg/litre (6 patients). At the end of dialysis, 1 g of cefazolin was inserted and left in the peritoneal cavity. The final 1 g resulted in a mean peak level of 63 μg/ml within 2 hours.

When cefazolin is administered to patients with unobstructed biliary tracts, high concentrations, well above serum levels, occur in the gall-bladder tissue and bile. In the presence of obstruction, however, concentration of the antibiotic is considerably lower in bile than in serum.

Cefazolin readily crosses an inflamed synovial membrane and the concentration of the antibiotic achieved in the joint space is comparable to levels measured in serum.

Cefazolin readily crosses the placental barrier into the umbilical cord blood and amniotic fluid. Cefazolin is excreted in breast milk.

Microbiology: *In vitro* tests demonstrate that the bactericidal action of cephalosporins results from inhibition of cell-wall synthesis. Cefazolin is active against the following organisms *in vitro*:

- *Staphylococcus aureus* (including penicillinase-producing strains).
- *Staphylococcus epidermidis.*
- Methicillin-resistant staphylococci are uniformly resistant to cefazolin.
- Group A β-haemolytic streptococci and other strains of streptococci (many strains of enterococci are resistant).
- *Streptococcus pneumoniae.*
- *Escherichia coli.*
- *Proteus mirabilis.*
- Klebsiella species.
- *Enterobacter aerogenes.*
- *Haemophilus influenzae.*

Most strains of indole-positive Proteus (*Proteus vulgaris*), *Enterobacter cloacae*, *Morganella morganii* and *Providencia rettgeri* are resistant. Serratia, Pseudomonas and *Acinetobacter calcoaceticus* are almost uniformly resistant to cefazolin.

Indications:

CEFAZOLIN OETHMAAN is indicated in the treatment of the following infections due to susceptible micro-organisms:

Respiratory tract infections due to *S. pneumoniae*, Klebsiella species, *H. influenzae*, *S. aureus* (including penicillinase-producing strains) and group A β-haemolytic streptococci.

The agent of choice for streptococcal infection and prevention of rheumatic fever is penicillin.

Genito-urinary tract infections due to *E. coli*, *P. mirabilis*, Klebsiella species and some strains of Enterobacter and enterococci.

Skin and skin structure infections due to *S. aureus* (including penicillinase-producing strains) and group A β-haemolytic streptococci and other strains of streptococci.

Bone and joint infections due to *S. aureus.*

Septicaemia due to *S. pneumoniae*, *S. aureus* (penicillin-sensitive and penicillin-resistant), *P. mirabilis*, *E. coli* and Klebsiella species.

Endocarditis due to *S. aureus* (penicillin-sensitive and penicillin-resistant) and group A β-haemolytic streptococci. Not first line therapy for *S. aureus* endocarditis or septicaemia.

Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to CEFAZOLIN OETHMAAN.

Peri-operative prophylaxis: The prophylactic administration of CEFAZOLIN OETHMAAN pre-operatively, intra-operatively, and post-operatively may reduce the incidence of post-operative wound infections in patients undergoing abdominal hysterectomy.

The prophylactic administration of CEFAZOLIN OETHMAAN should usually be discontinued within a 24-hour period after the surgical procedure.

Contraindications:

CEFAZOLIN OETHMAAN is contra-indicated in patients with a known allergy to the cephalosporin group of antibiotics and other beta-lactam group of antibiotics, e.g. Penicillins. (See “Warnings”).

Warnings and Special precautions:

BEFORE CEFAZOLIN OETHMAAN THERAPY IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS AND PENICILLIN. CEFAZOLIN OETHMAAN SHOULD BE ADMINISTERED WITH CAUTION TO PENICILLIN-SENSITIVE PATIENTS.

SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY OCCUR. CEFAZOLIN OETHMAAN SHOULD BE DISCONTINUED AND THE PATIENT TREATED WITH ADRENALINE, CORTICOSTEROIDS AND ANTIHISTAMINES.

There is some clinical and laboratory evidence of partial cross-allergenicity between the penicillins and the cephalosporins. Patients have been reported to have had severe reactions, including anaphylaxis, to both agents.

Pseudomembranous colitis has been reported with many broad spectrum antibiotics, therefore it is important to consider its diagnosis in patients who develop diarrhoea in association with their use. Such colitis may be life-threatening and appropriate measures should be taken, including discontinuation of the antibiotic.

Concomitant use of alcohol may result in disulfiram-like effects such as stomach cramps, facial flushing, headache, hypotension, nausea, palpitations, shortness of breath, sweating, tachycardia, or vomiting.

If an allergic reaction to CEFAZOLIN OETHMAAN occurs, the medication should be discontinued and the patient treated with the appropriate agents, eg adrenaline, corticosteroids, aminophylline and antihistamines.

Prolonged use of CEFAZOLIN OETHMAAN may result in the overgrowth of non-susceptible organisms. Careful clinical observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

When CEFAZOLIN OETHMAAN is administered to patients with low urinary output because of impaired renal function, lower daily dosage is required (see “Dosage and directions for use”).

The intrathecal administration of CEFAZOLIN OETHMAAN is not an approved route of administration for this antibiotic; in fact, there have been reports of severe central nervous system (CNS) toxicity including seizures when CEFAZOLIN OETHMAAN was administered in this manner.
Broad spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Usage in infants: Safety for use in prematures and infants under 1 month of age has not been established.

Interactions:

Used concurrently, probenecid may decrease renal tubular secretion of CEFAZOLIN OETHMAAN, resulting in increased and more prolonged cephalosporin blood levels.
CEFAZOLIN OETHMAAN may possibly enhance the effects of warfarin.
Medicine/laboratory test interactions:
A false-positive reaction for glucose in the urine may occur with Benedict's or Fehling's solution or with Clinitest tablets, but not with glucose oxidase urine sugar analysis test, e.g. Tes-Tape.
Positive direct and indirect antiglobulin (Coombs') tests have occurred; these may also occur in neonates whose mothers received cephalosporins before delivery.

Human Reproduction:

Safety of this product for use during pregnancy has not been established. CEFAZOLIN OETHMAAN is present in very low concentrations in the milk of nursing mothers.

Dosage and directions for use:

CEFAZOLIN OETHMAAN may be administered intramuscularly or intravenously after reconstitution.
The total daily dosages are the same for either route of administration.
The intrathecal administration of CEFAZOLIN OETHMAAN is not an approved route of administration for this antibiotic; in fact, there have been reports of severe CNS toxicity, including seizures, when CEFAZOLIN OETHMAAN was administered in this manner.

Intramuscular or intravenous administration:

For intramuscular administration : reconstitute with 0,5 % lidocaine according to Table 3. Shake well until dissolved.

CEFAZOLIN OETHMAAN should be injected into a large muscle mass.

For intravenous administration: reconstitute with water for injection or 0,9 % sodium chloride according to Table 3.

For preparing solutions for intravenous infusion fill up the infusion bottle with 50 – 100 ml 0,9 % sodium chloride solution, allow dry substance to dissolve and infuse slowly.

Prior to administration, the reconstituted solution should be inspected visually for particulate matter and discolouration. The reconstituted solution is clear.

Table 3: Dilution table:

Vial size	***Diluent to be added***
500 mg 1 g	2 ml 4 ml

Dosage:

Usual adult dosage: The usual adult dosages are given in Table 4.

Table 4: Usual adult dosage

Type of infection	***Dose***	***Frequency***
Pneumococcal pneumonia	500 mg to 1 g	Every 6 to 12 hours
Mild infections caused by susceptible Gram-positive cocci	250 mg to 500 mg	Every 8 hours
Acute uncomplicated urinary tract infections	1 g	Every 12 hours
Moderate to severe infections	500 mg to 1 g	Every 6 to 8 hours
Severe, life-threatening infections (e.g. endocarditis, septicaemia)	1 g to 1,5 g	Every 6 hours

Dosage adjustment for patients with reduced renal function:

CEFAZOLIN OETHMAAN may be used in patients with reduced renal function with the following dosage adjustments: Patients with a creatinine clearance of ≥ 55 ml/min or a serum creatinine of ≤ 130 μmol/l can be given full doses. Patients with creatinine clearance rates of 35 to 54 ml/min or serum creatinine of 139 μmol/l to 260 μmol/l can also be given full doses, but dosage should be restricted to at least 8-hour intervals. Patients with creatinine clearance rates of 11 to 34 ml/min or serum creatinine of 269 μmol/l to 390 μmol/l should be given one-half the usual dose every 12 hours. Patients with creatinine clearance rates of ≤ 10 ml/min or serum creatinine of ≥ 399 μmol/l should be given one-half the usual dose every 18 to 24 hours. All reduced dosage recommendations apply after an initial loading dose appropriate to the severity of the infection. For information about peritoneal dialysis, see "Human pharmacology'".

Peri-operative prophylactic use:

To prevent post-operative infection in contaminated or potentially contaminated abdominal hysterectomy, the recommended doses are as follows:

a. 1 g IV or IM administered one-half to 1 hour prior to the start of surgery.
b. For lengthy operative procedures (e.g. 2 hours or longer), 1 g IV or IM during surgery (administration modified according to the duration of the operative procedure).
c. 1 g IV or IM every 6 to 8 hours for a maximum of 24 hours post-operatively has been used.

It is important that:

1. The pre-operative dose be given just prior (½ to 1 hour) to the start of surgery so that adequate antibiotic levels are present in the serum and tissues at the time of the initial surgical incision.
2. If exposure to infectious organisms is likely, CEFAZOLIN OETHMAAN should be administered at appropriate intervals during surgery in order that sufficient levels of the antibiotic be present when needed.

Paediatric dosage:

In children a total daily dosage of 25 mg/kg to 50 mg/kg of body mass, divided into three or four equal doses, is effective for most mild to moderately severe infections (Table 5). Total daily dosage may be increased to 100 mg/kg of body mass for severe infections.

In children with mild to moderate renal impairment (creatinine clearance of 70 to 40 ml/min), 60 % of the normal daily dosage given in divided doses every 12 hours should be sufficient. In children with moderate renal impairment (creatinine clearance of 40 to 20 ml/min), 25 % of the normal daily dosage given in divided doses every
12 hours should be sufficient. In children with severe renal impairment (creatinine clearance of 20 to 5 ml/min), 10 % of the normal daily dose given every 24 hours should be sufficient. All dosage recommendations apply after an initial loading dose is administered.

Table 5: Paediatric dosage guide (500 mg vial with 2 ml diluent or 1 g vial with 4 ml diluent)

Mass	***25 mg/kg per day divided into 3 doses***		***25 mg/kg per day divided into 4 doses***	
kg	***Approximate single dose (every 8 hours)***	***Volume needed with dilution of 225 mg/ml***	***Approximate single dose (every 6 hours)***	***Volume needed with dilution of 225 mg/ml***
4,5	40 mg	0,17 ml	30 mg	0,12 ml
9,0	75 mg	0,33 ml	55 mg	0,25 ml
13,5	115 mg	0,50 ml	85 mg	0,37 ml
18,0	150 mg	0,66 ml	115 mg	0,50 ml
22,5	190 mg	0,83 ml	140 mg	0,61 ml

Mass	***50 mg/kg per day divided into 3 doses***		***50 mg/kg per day divided into 4 doses***	
kg	***Approximate single dose (every 8 hours)***	***Volume needed with dilution of 225 mg/ml***	***Approximate single dose (every 6 hours)***	***Volume needed with dilution of 225 mg/ml***

4,5	75 mg	0,35 ml	55 mg	0,25 ml
9,0	150 mg	0,7 ml	110 mg	0,5 ml
13,5	225 mg	1 ml	170 mg	0,75 ml
18,0	300 mg	1,35 ml	225 mg	1 ml
22,5	375 mg	1,7 ml	285 mg	1,25 ml

In the treatment of beta-haemolytic streptococcal infections, a therapeutic dose must be administered for at least 10 days.

Side-effects:

The following side effects have been reported:

Infections and infestations:

Prolonged use may result in overgrowth of non-susceptible organisms.

Blood and lymphatic system disorders:

Less frequent: Hypoprothrombinaemia, leucopenia, neutropenia, thrombocytosis, thrombocytopenia and agranulocytosis

Positive direct and indirect Coombs' tests have occurred.

Nervous system disorders:

Frequent: Headache

Less frequent: Convulsion (especially with high doses and in patients with renal function impairment), dizziness, confusion and stupor.

Gastrointestinal disorders:

Frequent: Abdominal cramps, diarrhoea, nausea or vomiting, anorexia and oral candidiasis (oral thrush).

Less frequent: Flatulence, dyspepsia. Symptoms of pseudomembranous colitis (diarrhoea) may appear either during or after antibiotic treatment.

Hepato-biliary disorders:

Less frequent: Rise in transaminase liver enzymes and alkaline phosphatase levels have been observed. Hepatitis and cholestatic jaundice have been reported.

Skin and subcutaneous tissue disorders:

Less frequent: Urticaria, pruritus and skin rash, toxic epidermal necrolysis, erythema multiforme or Stevens-Johnson syndrome .

Renal and urinary disorders:

Less frequent: Renal dysfunction and interstitial nephritis.

Increased levels of urea may occur, and are not always associated with clinical evidence of renal impairment. The combined use of potassium and loop diuretics or aminoglycosides has been associated with an increased incidence of renal function impairment.

Reproductive system and breast disorders:

Frequent: Vaginal candidiasis

Less frequent: Genital and anal pruritus, genital moniliasis and vaginitis.

General disorders and administration site conditions:

Frequent: A common side-effect of CEFAZOLIN OETHMAAN is hypersensitivity reactions including skin rashes, urticaria, eosinophilia, fever, reactions resembling serum sickness and anaphylaxis.

Less frequent: Thrombophlebitis at the site of injection, pain on intramuscular injection, sometimes with in duration.

Known symptoms of overdosage and particulars of its treatment:

The administration of inappropriately large doses of parenteral CEFAZOLIN OETHMAAN may cause dizziness, paraesthesias, headaches, confusion and stupor. Seizures may occur following

overdosage with some cephalosporins, particularly in patients with renal impairment in whom accumulation is likely to occur.

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

Treatment: Treatment is symptomatic and supportive.

In cases of severe overdosage, especially in a patient with renal failure, combined haemodialysis and haemoperfusion may be considered if response to more conservative therapy fails. However, no data supporting such therapy is available.

Identification:

CEFAZOLIN 500 MG OETHMAAN Powder for injection vial is sealed with a rubber stopper and an aluminium cap. It contains sterile powder for injection.

CEFAZOLIN 1 G OETHMAAN Powder for injection vial is sealed with a rubber stopper and an aluminium cap. It contains sterile powder for injection.

Presentation:

CEFAZOLIN 500 MG OETHMAAN and CEFAZOLIN 1 g OETHMAAN Powder for injection vials are supplied in cartons containing 10 vials.

Storage instructions:

Store dried powder at or below 25 °C.

Reconstituted (ready for use) solution: Stable for 24 hours when stored at 2 to 8 °C. Any unused solution should be discarded.

Keep in the outer carton.

KEEP OUT OF THE REACH OF CHILDREN.

Registration numbers:

CEFAZOLIN 500 MG OETHMAAN Powder for Injection : 31/20.1.1/0675

CEFAZOLIN 1 G OETHMAAN Powder for Injection : 31/20.1.1/0676

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