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. Chemically, it is called Sodium(6R,7R)-3-[[5-methyl-1,3,4-thiadiazol-2-yl)sulphanyl]methyl]-8-oxo-7-[(1H-tetrazol-1-ylacetyl)amino]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate. The sodium content is 48,3 mg/g of cefazolin sodium. The molecular formula is $C_{14}H_{13}N_8NaO_4S_3$. 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	2 ml
1 g	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 with a pink flip off seal. It contains sterile powder for injection.

CEFAZOLIN 1 g OETHMAAN Powder for injection vial is sealed with a rubber stopper and an aluminium cap with a brown flip off seal. 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 1 or 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

Name and business address of the holder of the certificates of registration:
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Eiendomsname en doseervorms:

CEFAZOLIN 500 mg OETHMAAN poeier vir inspuiting

CEFAZOLIN 1 g OETHMAAN poeier vir inspuiting

Samestelling:
Elke flessie **CEFAZOLIN 500 mg OETHMAAN** bevat natriumkefasolien gelykstaande aan 500 mg kefasolien.
Elke flessie **CEFAZOLIN 1 g OETHMAAN** bevat natriumkefasolien gelykstaande aan 1 g kefasolien.
CEFAZOLIN OETHMAAN (natriumkefasolien) is 'n semisintetiese kefalosporien vir parenterale toediening. Chemies is dit genaamd natrium(6R,7R)-3-[[5-metiel-1,3,4-tiadiasol-2-iel)sulfoniel]metiel]-8-oxo-7-[(1H-tetrasool-1-ylasetiel)amino]-5-tia-1-asabisiklo[4.2.0]okt-2-ien-2-karboksilaat. Die natriuminhoud van natriumkefasolien is 48,3 mg/g. Die molekulêre formule is $C_{14}H_{13}N_8NaO_4S_3$. Die molekulêre massa is 476,5 (natriumsout).
Die pH van die aangemaakte oplossing is tussen 4,0 en 6,0.

Farmakologiese klassifikasie
A 20.1.1 Breë- en mediumspektrumantibiotika

Farmakologiese werking
Menslike farmakologie: Tabel 1 toon die gemiddelde serumvlakke en duur van kefasolien na intramuskulêre toediening.

Tabel 1: Serumkonsentrasies na intramuskulêre toediening:

	Serumkonsentrasie (µg/ml)					
Dosis	***½ h***	***1 h***	***2 h***	***4 h***	***6 h***	***8 h***
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

* Gemiddeld van twee studies

In normale vrywilligers het konstante intraveneuse infusie van kefasolien teen dosisse van 3,5 mg/kg vir een uur (ongeveer 250 mg) gevolg deur 1,5 mg/kg vir die volgende twee uur (ongeveer 100 mg) in die derde uur 'n vaste serumvlak van ongeveer 28 µg/ml gelewer.

Tabel 2 toon die gemiddelde serumkonsentrasies na 'n enkele intraveneuse bolusinspuiting van 1 g. Die gemiddelde halfleeftyd was 1,4 uur.

Tabel 2: Serumkonsentrasies na intraveneuse dosis van 1 g:

Tyd na toediening	***Serumkonsentrasie (µg/ml)***
5 minute	188,4
15 minute	135,8
30 minute	106,8
1 uur	73,7
2 uur	45,6
4 uur	16,5

Kefasolien word hoofsaaklik deur glomerulêre filtrasie en tot 'n kleiner mate deur tubulêre sekresie onveranderd in die urien uitgeskei. Na 'n intramuskulêre inspuiting van 500 mg word 56 tot 89 % van die toegediende dosis binne ses uur en 80 tot ongeveer 100 % in 24 uur herwin. Na die intramuskulêre toediening van 500 mg en 1 g kefasolien word piek konsentrasies in die urien van hoër as 1 000 µg/ml en 4 000 µg/ml onderskeidelik verkry.

In pasiënte wat peritoneale dialise (2 liter/h) ondergaan, was die gemiddelde serumvlakke van kefasolien ongeveer 10 en 30 µg/ml na instillasie van 'n dialise-oplossing met 50 mg/liter en 150 mg/liter onderskeidelik vir 24 uur. Gemiddelde piekvlakke was 29 µg/ml (gebied 13 tot 44 µg/ml) met 50 µg/liter (3 pasiënte) en 72 µg/ml (gebied 26 tot 142 µg/ml) met 150 µg/liter (6 pasiënte). Aan die einde van die dialise is 1 g kefasolien in die peritoneale holte geplaas en gelaat. Die laaste 1 g het binne 2 uur 'n piekvlak van 63 µg/ml veroorsaak.

As kefasolien toegedien word aan pasiënte met 'n oop galweg word hoë konsentrasies, heelwat bokant vlakke in die serum, in weefsel van die galblaas en in gal verkry. As daar egter 'n obstruksie is, is die konsentrasie van die antibiotikum in die gal beduidend laer as in die serum.

Kefasolien kruis 'n ontsteekte sinoviale membraan geredelik en die konsentrasie van die antibiotikum in die gesamentlike ruimte is vergelykbaar met vlakke wat in die serum gemeet word.

Kefasolien kruis die plasentale skans tot in die bloed van die naelstring en amniotiese vloeistof geredelik. Kefasolien word in borsmelk uitgeskei.

Mikrobiologie: In *vitro*-toetse toon dat die bakterisidiese werking van kefalosporiene die gevolg van remming van selwandsintese is. Kefasolien is in *vitro* aktief teen die volgende organismes:

- *Staphylococcus aureus* (waaronder stamme wat penisillinase produseer)
- *Staphylococcus epidermidis*
- Metisillienweerstandige stafilokokke is oor die algemeen weerstandig teen kefasolien
- Groep A β-hemolitiese streptokokke en ander stamme streptokokke (baie stamme enterokokke is weerstandig)
- *Streptococcus pneumoniae*
- *Escherichia coli*
- *Proteus mirabilis*
- *Klebsiella-spesies*
- *Enterobacter aerogenes*
- *Haemophilus influenzae*

Die meeste indoolpositiewe stamme van *Proteus (Proteus vulgaris), Enterobacter cloacae, Morganella morganii* en Providencia rettgeri is weerstandig. *Serratia, Pseudomonas* en *Acinetobacter calcoaceticus* is bykans deurgaans weerstandig teen kefasolien.

Indikasies:
CEFAZOLIN OETHMAAN is aangedui vir die behandeling van die volgende infeksies vanweë vatbare mikro-organismes:

Lugweginfeksies vanweë *S. pneumoniae, Klebsiella-spesies, H. influenzae, S. aureus* (waaronder stamme wat penisillinase produseer) en Groep A β-hemolitiese streptokokke.

Penisillien is die voorkeurmiddel vir infeksie deur streptokokke en die voorkoming van rumatiekkoors.

Genito-urienweginfeksies vanweë *E. coli, P. mirabilis, Klebsiella*-spesies en sekere stamme van *Enterobacter* en enterokokke.

Vel- en velstruktuurinfeksies veroorsaak deur *S. aureus* (waaronder stamme wat penisillinase produseer) en Groep A β-hemolitiese streptokokke en ander stamme van streptokokke.

Infeksies van die skeletbene en gewrigte veroorsaak deur *S. aureus.*

Septisemie vanweë *S. pneumoniae, S. aureus* (penisilliensensitief en penisillienweerstandig), *P. mirabilis, E. coli en Klebsiella-spesies.*

Endokarditis vanweë S. *aureus* (penisilliensensitief en penisillienweerstandig) en Groep A β-hemolitiese streptokokke. Nie die eerste lyn vir behandeling van endokarditis of septisemie vanweë S. aureus nie.

Geskikte kweking en sensitiwiteitstoetse behoort gedoen te word om die vatbaarheid van die veroorsakende organisme vir CEFAZOLIN OETHMAAN te bepaal.

Peri-operatiewe profilakse van infeksie: Die profilaktiese toediening van CEFAZOLIN OETHMAAN voor, tydens en na die operasie kan die voorkoms van infeksies van die wond na operasie van pasiënte met abdominale histerektomie verlaag.

Die profilaktiese toediening van CEFAZOLIN OETHMAAN moet gewoonlik binne 24 uur na die chirurgiese prosedure gestaak word.

Kontra-indikasies:
CEFAZOLIN OETHMAAN is teenaangedui vir pasiënte met bekende allergie teenoor kefalosporiene en ander beta-laktaamantibiotika, bv. penisilliene (kyk "Waarskuwings").

Waarskuwings en *Spesiale voorsorgmaatreëls:*
VOORDAT BEHANDELING MET CEFAZOLIN OETHMAAN BEGIN, MOET NOUKEURIG NAVRAAG GEDOEN WORD NA VORIGE HIPERSENSITIWITEITSREAKSIES TEENOOR KEFALOSPORIENE EN PENISILLIENE. CEFAZOLIN OETHMAAN MOET VERSIGTIG GEGEE WORD AAN PASIËNTE WAT SENSITIEF VIR PENISILLIEN IS.
ERNSTIGE AKUTE HIPERSENSITIWITEITSREAKSIES KAN VOORKOM. CEFAZOLIN OETHMAAN MOET GESTAAK EN DIE PASIËNT MOET MET ADRENALIEN, KORTIKOSTEROÏEDE EN ANTIHISTAMIENE BEHANDEL WORD.
Daar is kliniese en laboratoriumgetuienis van gedeeltelike kruisallergie tussen penisilliene en kefalosporiene. Dit is gemeld dat pasiënte ernstige reaksies, waaronder anafilakse, teenoor albei klasse middels ervaar het.
Pseudomembraankolitis is met talle breëspektrumantibiotika aangemeld; dit is dus belangrik om hierdie diagnose in gedagte te hou vir pasiënte wat diarree met die gebruik daarvan ontwikkel. Sodanige kolitis kan lewensbedreigend wees en geskikte maatreëls moet ingestel word, waaronder staking van die antibiotikum.
Gebruik saam met alkohol kan effekte soos die van disulfiraam veroorsaak soos maagkrampe, blosing in die gesig, hoofpyn, hipotensie, naarheid, hartkloppings, kortasemheid, sweet, tagikardie of braking.
As 'n allergiese reaksie teenoor CEFAZOLIN OETHMAAN voorkom, moet die medikasie gestaak en die pasiënt met geskikte middels, bv. adrenalien, kortikosteroïede en antihistamiene, behandel word.

Langdurige gebruik van CEFAZOLIN OETHMAAN kan tot die oorgroei van nie-vatbare organismes lei. Noukeurige kliniese toesig van die pasiënt is noodsaaklik. Indien superinfeksie tydens behandeling voorkom, moet geskikte maatreëls getref word.

As CEFAZOLIN OETHMAAN toegedien word aan pasiënte met 'n lae nieruitset vanweë swak nierfunksie, moet 'n laer dosis gegee word (kyk "Dosis en gebruiksaanwysings").

Die intratekale toediening van CEFAZOLIN OETHMAAN is nie 'n goedgekeurde roete vir toediening van hierdie antibiotikum nie; daar was inderwaarheid verslae van erge toksisiteit op die sentrale senustelsel (SSS), waaronder toevalle, toe CEFAZOLIN OETHMAAN op hierdie manier toegedien is.

Breëspektrumantibiotika moet versigtig voorgeskryf word aan individue met 'n geskiedenis van gastro-intestinale siekte, veral kolitis.

Gebruik vir kinders: Die veiligheid en effektiwiteit vir premature en babas jonger as 1 maand is nie bepaal nie.

Interaksies:
As dit saam gebruik word, kan probenesied renale tubulêre uitskeiding van CEFAZOLIN OETHMAAN vertraag en hoër en langer durende bloedvlakke van die kefalosporien veroorsaak.
CEFAZOLIN OETHMAAN kan dalk die effekte van warfarien versterk.

Interaksies met medisyne/laboratoriumtoetse:
'n Vals positiewe reaksie vir glukose in die urien kan met Benedict of Fehling se oplossings of met Clinitest-tablette verkry word, maar nie met die suikertoets met glukose-oksidase, bv. Tes-Tape, nie.

Positiewe direkte en indirekte toetse vir antiglobulien (Coombs) is verkry; dit kan ook voorkom in pasgeborenes wie se moeders kefalosporiene voor die bevalling gekry het.

Menslike Voortplanting:
Die veiligheid van hierdie produk vir gebruik tydens swangerskap is nie bepaal nie. CEFAZOLIN OETHMAAN kom in baie lae konsentrasies in die melk van voedende moeders voor.

Dosis en gebruiksaanwysings:
Nadat dit aangemaak is, kan CEFAZOLIN OETHMAAN intramuskulêr of intraveneus toegedien word. Die totale daaglikse dosis is vir albei roetes van toediening dieselfde.
Die intratekale toediening van CEFAZOLIN OETHMAAN is nie 'n goedgekeurde roete vir toediening van hierdie antibiotikum nie; daar was inderwaarheid verslae van erge toksisiteit op die SSS, waaronder toevalle, toe CEFAZOLIN OETHMAAN op hierdie manier toegedien is.

<u>*Intramuskulêre of intraveneuse toediening:*</u>
Vir intramuskulêre toediening. maak volgens Tabel 3 met 0,5 % lidokaïen aan. Skud goed totdat dit opgelos is.
CEFAZOLIN OETHMAAN moet in 'n groot spiermassa ingespuit word.
Vir intraveneuse toediening: maak volgens Tabel 3 met water vir inspuiting of 0,9 % natriumchloried aan.
Voeg 50 – 100 ml 0,9 % natriumchloriedoplossing in die infusiebottel, laat die droë stof oplos om die oplossing vir intraveneuse infusie te berei en dien stadig as infusie toe.
Voor toediening moet die aangemaakte oplossing visueel vir deeltjies en verkleuring geïnspekteer word. Die aangemaakte oplossing is helder.

Tabel 3: Tabel vir verdunning:

Grootte van flessie	***Oplosmiddel wat bygevoeg moet word***
500 mg	2 ml
1 g	4 ml

<u>*Dosis:*</u>

Gewone volwasse dosis: Die gewone volwasse dosis word in Tabel 4 gegee.

Tabel 4: Gewone volwasse dosis

Tipe infeksie	***Dosis***	***Frekwensie***
Pneumokokkale longontsteking	500 mg to 1 g	Every 6 to 12 hours
Ligte infeksies veroorsaak deur vatbare Gram-positiewe kokke	250 mg to 500 mg	Every 8 hours
Akute ongekompliseerde urienweginfeksies	1 g	Every 12 hours
Matige tot erge infeksies	500 mg to 1 g	Every 6 to 8 hours
Ernstige lewensbedreigende infeksies (bv. endokarditis, septisemie)	1 g to 1,5 g	Every 6 hours

<u>*Aanpassing in die dosis vir pasiënte met swak nierfunksie:*</u>

CEFAZOLIN OETHMAAN kan met die volgende aanpassings in die dosis vir pasiënte met swak nierfunksie gebruik word: Pasiënte met kreatinienopruiming van ≥ 55 ml/min of 'n serumvlak van ≤ 130 µmol/l kreatinien kan die volle dosis ontvang. Pasiënte met kreatinienopruiming van 35 tot 54 ml/min of 'n serumvlak van 139 tot 260 µmol/l kreatinien kan ook die volle dosis ontvang, maar die dosering moet tot intervalle van ten minste 8 uur beperk word. Pasiënte met kreatinienopruiming van 11 tot 34 ml/min of 'n serumvlak van 269 tot 390 µmol/l kreatinien moet die helfte van die gewone dosis elke 12 uur kry.

Pasiënte met kreatinienopruiming van ≤ 10 ml/min of serumvlak van ≥ 399 µmol/l kreatinien moet die helfte van die gewone dosis elke 18 tot 24 uur kry. Die aanbeveling vir alle lae dosisse geld na 'n aanvanklike ladingsdosis in ooreenstemming met die graad van die infeksie. Vir inligting oor peritoneale dialise, kyk "Menslike farmakologie".

<u>*Peri-operatiewe profilaktiese gebruik:*</u>
Om postoperatiewe infeksie na gekontamineerde of moontlik gekontamineerde abdominale histerektomie te voorkom, is die aanbevole dosisse as volg:

a. 1 g IV of IM toegedien 'n half tot 1 uur voor die aanvang van die operasie.
b. vir lang chirurgiese prosedures (bv. 2 uur of langer), 1 g IV of IM tydens die operasie (toediening aangepas volgens die duur van die chirurgiese prosedure).
c. 1 g IV of IM elke 6 tot 8 uur vir 'n maksimum van 24 uur na die operasie is gebruik.

Dit is belangrik dat:

1. Die dosis voor die operasie net voor (½ tot 1 uur) die aanvang van die operasie gegee word sodat voldoende vlakke van die antibiotikum op die tyd van die aanvanklike chirurgiese insnyding in die serum teenwoordig is.
2. As blootstelling aan infektiewe organismes waarskynlik is, moet CEFAZOLIN OETHMAAN met geskikte intervalle tydens die operasie toegedien word om te verseker dat voldoende vlakke van die antibiotikum wanneer benodig teenwoordig is.

<u>*Pediatriese dosis:*</u>
Vir kinders is 'n totale daaglikse dosis van 25 tot 50 mg/kg liggaamsmassa, verdeel in drie of vier gelyke dosisse, effektief vir die meeste matig tot matig ernstige infeksies (Tabel 5). Die totale daaglikse dosis kan vir ernstige infeksies tot 100 mg/kg liggaamsmassa verhoog word.

Vir kinders met ligte tot matige swak nierfunksie (kreatinienopruiming van 70 tot 40 ml/min) sal 60 % van die normale daaglikse dosis in verdeelde doserings elke 12 uur voldoende wees. Vir kinders met matige swak nierfunksie (kreatinienopruiming 40 tot 20 ml/min) sal 25 % van die normale daaglikse dosis gegee in verdeelde doserings elke 12 uur voldoende wees.

Vir kinders met ernstige swak nierfunksie (kreatinienopruiming 20 tot 5 ml/min) sal 10 % van die normale daaglikse dosis elke 24 uur voldoende wees. Die aanbevelings van alle dosisse geld na 'n aanvanklike ladingsdosis gegee is.

Tabel 5: Riglyne vir pediatriese dosis (500 mg-flessie met 2 ml oplosmiddel of 1 g-flessie met 4 ml oplosmiddel)

Massa	***25 mg/kg per dag in 3 dosisse verdeel***		***25 mg/kg per dag in 4 dosisse verdeel***	
kg	***Benaderde enkeldosis (elke 8 uur)***	***Volume nodig vir verdunning tot 225 mg/ml***	***Benaderde enkeldosis (elke 6 uur)***	***Volume nodig vir verdunning tot 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

Massa	***50 mg/kg per dag in 3 dosisse verdeel***		***50 mg/kg per dag in 4 dosisse verdeel***	
kg	***Benaderde enkeldosis (elke 8 uur)***	***Volume nodig vir verdunning tot 225 mg/ml***	***Benaderde enkeldosis (elke 6 uur)***	***Volume nodig vir verdunning tot 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

Vir die behandeling van infeksies deur β-hemolitiese streptokokke moet 'n terapeutiese dosis vir ten minste 10 dae gegee word.

Newe-effekte:
Die volgende newe-effekte is aangemeld:

Infeksies en infestasies:
Langdurige gebruik kan oorgroei van nie-vatbare organismes veroorsaak.

Versteurings van bloed en limfstelsel:
Minder dikwels: Hipoprotrombinemie, leukopenie, neutropenie, trombositose en agranulositose Positiewe direkte en indirekte Coombstoetse is verkry.

Versteurings van senustelsel:
Dikwels: Hoofpyn
Minder dikwels: Konvulsies (veral met hoë dosisse en in pasiënte met swak nierfunksie), duiseligheid, verwardheid en stupor.

Gastroïntestinale versteurings:
Dikwels: Buikkrampe, diarree, naarheid of braking, anoreksie en orale kandidiase (mond sproei).
Minder dikwels: Winderigheid, slegte spysvertering. Simptome van pseudomembraankolitis (diarree) kan tydens antibiotiese behandeling of daarna verskyn.

Hepatobiliêre versteurings:
Minder dikwels: Styging in die vlakke van lewerensieme (transaminases) en alkaliese fosfatase is waargeneem. Hepatitis en cholestatiese geelsug is aangemeld.

Versteurings van vel en subkutane weefsel:
Minder dikwels: Urtikarie, pruritus en veluitslag, toksiese epidermale nekrolise, multivorme eriteem of Stevens-Johnsonsindroom

Versteurings van die nier en urien
Minder dikwels: Nierdisfunksie en interstisiële nefritis

Hoër vlakke ureum kan voorkom en nie altyd saam met kliniese getuienis van swak nierfunksie nie. Die gebruik saam met kalium- en lusdiuretika of aminoglikosiede het met 'n hoër voorkoms van swak nierfunksie gepaardgegaan.

Versteurings van voortplantingstelsel en borste:
Dikwels: Vaginale kandidiase
Minder dikwels: Genitale en anale pruritus, genitale moniliase en vaginitis

Algemene versteurings en toestande by die plek van toediening:
Dikwels: 'n Algemene newe-effek van CEFAZOLIN OETHMAAN is hipersensitiwiteitsreaksies, waaronder veluitslag, urtikarie, eosinofilie, koors, reaksies soos serumsiekte en anafilakse.
Minder dikwels: Tromboflebitis by die plek van inspuiting, pyn met intramuskulêre inspuiting en soms met indurasie

Bekende simptome van oordosering en besonderhede vir die behandeling daarvan:
Die toediening van onvanpaste hoë dosisse parenterale CEFAZOLIN OETHMAAN kan duiseligheid, parestesie, hoofpyn, verwardheid en stupor veroorsaak. Stuiptrekkings kan na oordosering met sekere kefalosporiene voorkom en veral in pasiënte met swak nierfunksie in wie akkumulasie waarskynlik sal voorkom.
Abnormaliteite in laboratoriumtoetse wat na 'n oordosering kan voorkom, is onder meer stygings in die vlakke van kreatinien, ureum, lewerensieme en bilirubien, 'n positiewe Coombs se toets, trombositose of trombositopenie, eosinofilie, leukopenie en verlenging van die protrombientyd.
Behandeling: Behandeling is simptomaties en ondersteunend.
In gevalle van erge oordosering, veral in 'n pasiënt met nierversaking, kan 'n kombinasie van hemodialise en hemoperfusie oorweeg word as meer konserwatiewe behandeling misluk. Geen data wat sodanige behandeling ondersteun, is egter beskikbaar nie.

Identifikasie:
Die flessie met **CEFAZOLIN 500 mg OETHMAAN** poeier vir inspuiting is met 'n rubberprop en 'n aluminiumdoppie met 'n pienk afwipseël verseël. Dit bevat steriele poeier vir inspuiting.
Die flessie met **CEFAZOLIN 1 g OETHMAAN** poeier vir inspuiting is met 'n rubberprop en 'n aluminiumdoppie met 'n bruin afwipseël verseël. Dit bevat steriele poeier vir inspuiting.

Aanbieding:
Flessies met **CEFAZOLIN 500 mg OETHMAAN en CEFAZOLIN 1 g OETHMAAN** poeier vir inspuiting word verskaf in kartonne wat 1 of 10 flessies bevat.

Bergingsinstruksies:
Bewaar die droë poeier teen of benede 25 °C.
Aangemaakte oplossing (gereed vir gebruik): Vir 24 uur stabiel indien by 2 tot 8 °C gehou. Gooi ongebruikte oplossing weg.
Hou in die buitenste karton.
HOU BUITE DIE BEREIK VAN KINDERS.

Registrasienommers:
CEFAZOLIN 500 mg OETHMAAN poeier vir inspuiting: 31/20.1.1/0675
CEFAZOLIN 1 g OETHMAAN poeier vir inspuiting: 31/20.1.1/0676

Naam en besigheidsadres van die houer van die registrasiesertifikate:
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