CLEAN PROPOSED PROFESSIONAL INFORMATION

SCHEDULING STATUS: S4

PROPRIETARY NAMES (AND DOSAGE FORM)

ZEFKOL 0,5 g INJECTION (powder for injection)

ZEFKOL 1,0 g INJECTION (powder for injection)

COMPOSITION

Each ZEFKOL 0,5 g Injection vial contains cefazolin sodium equivalent to 500 mg cefazolin.

Each ZEFKOL 1,0 g Injection vial contains cefazolin sodium equivalent to 1 g cefazolin.

ZEFKOL (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 per 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

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* (*in vitro* activity does not necessarily imply *in vivo* sensitivity):

Staphylococcus aureus (including penicillinase-producing strains),

Staphylococcus epidermidis,

Methicillin-resistant staphylococci are uniformly resistant to cefazolin,

Group A ß-haemolytic streptococci and other strains of streptococci (many strains of enterococci are resistant),

Streptococcus pneumonia,

Escherichia coli,

Proteus mirabilis,

Klebsiella species,

Enterobacter aerogenes and

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.

Pharmacokinetics

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

Table 1: Serum concentration after intramuscular administration

Dose	Serum Concentrations (µg/ml)					
	½ hr	1 hr	2 hr	4 hr	6 hr	8 hr
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 1 hour (approximately 250 mg), followed by 1,5 mg/kg for the next 2 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 concentration 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 6 hours and 80 % to nearly 100 % in 24 hours. Following the intramuscular administration of 0,5 g 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 l/hr), mean serum levels of cefazolin were approximately 10 and 30 µg/ml after 24 hours' instillation of a dialyzing solution containing 50 mg/l and 150 mg/l respectively. Mean peak levels were 29 µg/ml (range 13 to 44 µg/ml) with 50 mg/l (3 patients) and 72 µg/ml (range 26 to 142 µg/ml) with 150 mg/l (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 mean peak 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.

INDICATIONS

ZEFKOL 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 ß-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 ß-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 ß-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 ZEFKOL.

Peri-operative prophylaxis: The prophylactic administration of ZEFKOL 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 ZEFKOL should be discontinued within a 24-hour period after the surgical procedure.

CONTRA-INDICATIONS

ZEFKOL is contra-indicated in patients with a known hypersensitivity to the cephalosporin group of antibiotics.

Pregnancy and lactation, as safety has not been established.

Premature babies and infants under 1 month of age, as safety has not been established.

WARNINGS AND SPECIAL PRECAUTIONS

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

SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY OCCUR. ZEFKOL 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 medicines.

Prolonged use of ZEFKOL 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. 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 ZEFKOL.

Risk-benefit should be considered in patients with renal function impairment as cefazolin is mainly excreted renally. A reduced dosage is recommended when ZEFKOL is administered to patients with low urinary output because of impaired renal function (see 'Dosage and directions for use').

Prothrombin time INR should be monitored in patients with hepatic or renal impairment, or poor nutritional state, as well as patients receiving protracted course of antimicrobial therapy, and patients previously stabilised on anticoagulant therapy.

The intrathecal administration of ZEFKOL is not an approved route of administration for this antibiotic; there have been reports of severe central nervous system (CNS) toxicity including seizures when ZEFKOL was administered in this manner.

Driving and using machinery

Patients should exercise caution before driving, operating hazardous machinery or performing hazardous tasks, as their physical and/or mental abilities may be impaired.

INTERACTIONS

Used concurrently, probenecid may decrease renal tubular secretion of cephalosporins, resulting in increased and more prolonged cephalosporin blood levels.

PREGNANCY AND LACTATION

Safety in pregnancy and lactation has not been established.

Cefazolin readily crosses the placental barrier into the umbilical cord blood and amniotic fluid. Cefazolin is excreted in breast milk. Adequate and well-controlled studies have not been done.

DOSAGE AND DIRECTIONS FOR USE

ZEFKOL may be administered after reconstitution by deep intramuscular injection or by slow intravenous injections over 3 to 5 minutes or by intravenous infusion. The total daily dosages are the same for either route of administration.

The intrathecal administration of ZEFKOL is not an approved route of administration for this antibiotic; there have been reports of severe CNS toxicity, including seizures, when ZEFKOL was administered in this manner.

Intramuscular administration: Reconstitute with sterile water for injection, bacteriostatic water for injection or 0,9 % sodium chloride injection, according to Table 3. Shake well until dissolved. ZEFKOL should be injected into a large muscle mass.

Table 3: Dilution table

Vial size	Diluent to be added	Approximate available volume	Approximate average concentration
0,5 g	2 ml	2,2 ml	225 mg/ml
1 g*	3 ml	3,5 ml	285 mg/ml

*The 1 g vial should be reconstituted only with sterile water for injection or bacteriostatic water for injection.

Intravenous administration: ZEFKOL may be administered by intravenous injection or by continuous or intermittent infusion.

Intermittent intravenous infusion: ZEFKOL may be administered along with primary intravenous fluid management programmes in a volume control set or in a separate, secondary IV bottle. Reconstituted ZEFKOL 0,5 g or 1,0 g may be diluted in 50 ml to 100 ml of one of the following intravenous solutions:

0,9 % Sodium chloride injection

5 % or 10 % Dextrose injection

5 % Dextrose in lactated Ringer's injection

5 % Dextrose and 0,9 % sodium chloride injection (may also be used with 5 % dextrose and 0,45 % or 0,2 % sodium chloride injection)

Lactated Ringer's injection

Ringer's injection

Plasma-Lyte with 5 % dextrose

Intravenous injection: (administer solution directly into a vein or through tubing): Dilute reconstituted ZEFKOL 0,5 g or 1,0 g in a minimum of 10 ml of sterile water for injection. Inject solution slowly over a period of 3 to 5 minutes. Do not inject in less than 3 minutes.

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:

ZEFKOL may be used in patients with reduced renal function with the following dosage adjustments:

Patients with a creatinine clearance of ≥ 55 ml/min or 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.

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 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, ZEFKOL 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/day divided into 3 doses		25 mg/kg/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/day divided into 3 doses		50 mg/kg/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

SIDE EFFECTS

The following side effects have been reported:

Immune system disorders

Frequent: Eosinophilia.

Less frequent: Hypersensitivity reactions: drug fever, skin rash, vulvar pruritus, reactions resembling serum sickness and anaphylaxis have occurred.

Blood and lymphatic system disorders

Less frequent: Neutropenia, leucopenia, agranulocytosis and thrombocytopenia. There may be positive direct and indirect Coombs' tests although haemolytic anaemia less frequently occurs.

Frequency unknown: The presence of the methylthiadiazolethinol side-chain might be associated with causing hypoprothrombinaemia and bleeding disorders, aplastic anaemia, haemorrhage and pancytopenia.

Nervous system disorders

Frequent: Headache.

Less frequent: Dizziness.

Frequency unknown: Confusion and stupor may occur. Convulsions and other signs of CNS toxicity have been associated with high doses, especially in patients with severe renal impairment.

Ear and labyrinth disorders

Less frequent: Hearing loss.

Gastro-intestinal disorders

Frequent: Abdominal or stomach cramps. Nausea and vomiting have been reported. Anorexia, diarrhoea and oral candidiasis (oral thrush) have been reported.

Less frequent: Symptoms of pseudomembranous colitis (diarrhoea) may appear either during or after ZEFKOL treatment as a result of overgrowth of non-susceptible organisms. Dyspepsia, flatulence.

Hepato-biliary disorders

Frequency unknown: 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, toxic epidermal necrolysis, Stevens-Johnson syndrome or erythema multiforme, skin rash.

Renal and urinary disorders

Less frequent: Increased levels of urea may occur, and are not always associated with clinical evidence of renal impairment. Interstitial nephritis and other renal disorders have been reported. 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: Genital and anal pruritus, genital moniliasis and vaginitis. Vaginal candidiasis.

General disorders and administration site disorders

Less frequent: Pain on intramuscular injection, sometimes with induration, has occurred. Phlebitis at the site of injection has been noted.

Frequency unknown: Superinfections.

Investigations

Less frequent: Transient leukopenia, neutropenia, agranulocytosis, thrombocytopenia, eosinophilia, lymphocytosis and thrombocytosis have been seen.

Frequency unknown: 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' test) have occurred; these may occur in neonates whose mothers received cephalosporins before delivery.

Broad spectrum antibiotics should be prescribed with caution in individuals with a history of gastro-intestinal disease, particularly colitis.

Serum values of alanine aminotransferase (ALT), alkaline phosphatase, aspartate aminotransferase (AST or lactate dehydrogenase (LDH) may be increased.

Serum bilirubin, blood urea or creatinine concentrations may be increased.

Carnitine or haematocrit values may decrease during therapy.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

The administration of inappropriately large doses of parenteral cephalosporins may cause dizziness, paraesthesiae, 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.

If seizures occur, the medicine should be discontinued promptly: anticonvulsant therapy may be administered if clinically indicated.

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 are available.

IDENTIFICATION

ZEFKOL 0,5 g and 1,0 g Injection is a white or almost white powder.

PRESENTATION

A clear glass vial sealed with a rubber stopper and an aluminium-plastic combined cap, containing dry powder equivalent to 0,5 g or 1,0 g cefazolin, in packs of 1 or 10 vials.

STORAGE INSTRUCTIONS

Store dried powder at 15 to 25 ºC.

Reconstituted ZEFKOL diluted in sterile water for Injection, 5 % dextrose injection, 0,9 % sodium chloride injection or bacteriostatic water for injection is stable for 24 hours when stored below 25 ºC and for 10 days when stored in a refrigerator (2 to 8 ºC).

Solutions of ZEFKOL in sterile water for injection, 5 % dextrose injection, 0,9 % sodium chloride injection that are frozen immediately after reconstitution in the original container are stable for as long as 12 weeks when stored at –20 ºC. Once thawed, these solutions are stable for 24 hours when stored below 25 ºC or for 10 days when stored in a refrigerator (2 to 8 ºC). If the product is warmed, care should be taken to avoid heating it after the thawing is complete. Once thawed, the solution should not be refrozen.

Secondary diluents: Solutions of ZEFKOL for infusion in 10 % dextrose injection, 5 % dextrose in lactated Ringer's injection, 5 % dextrose and 0,9 % sodium chloride injection (may also be used with 5 % dextrose and 0,45 % or 0,2 % sodium chloride injection), lactated Ringer's injection, Ringer's injection or Plasma-Lyte with 5 % dextrose should be used within 24 hours after dilution if stored at 15 to 25 ºC, or within 96 hours if stored in a refrigerator (2 to 8 ºC). (DO NOT FREEZE ZEFKOL DILUTED WITH THE ABOVE DILUENTS).

Prior to administration, parenteral drug products should be inspected visually for particulate matter and discolouration whenever solution and container permit.

KEEP OUT OF THE REACH OF CHILDREN.

REGISTRATION NUMBERS

ZEFKOL 0,5 g Injection: 37/20.1.1/0136

ZEFKOL 1,0 g Injection: 37/20.1.1/0137

Botswana S3:

ZEFKOL 0,5 g Injection: BOT0801438

ZEFKOL 1,0 g Injection: BOT0801437

Namibia NS2

ZEFKOL 0,5 g Injection:06/20.1.1/0269

ZEFKOL 1,0 g Injection:06/20.1.1/0270

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

Acino Pharma (Pty) Ltd

106, 16th Road

Midrand

1686

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