PRODUCT INFORMATION

KEFZOL
(cephazolin, as cephazolin sodium)

DESCRIPTION

Kefzol (cephazolin sodium) is a semisynthetic 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 cephazolin sodium.

Cephazolin sodium is a white to off-white crystalline powder with a solubility of ≥ 100mg/mL in water.

The structural formula is as follows:

![Structural formula of Kefzol]

ACTIONS

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

- *Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant).

Group A beta-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 *Enterobacter cloacae* and indole-positive *Proteus* (*Pr. vulgaris*, *Pr. morganii*, *Pr. rettgeri*) are resistant. Methicillin-resistant staphylococci, *Serratia*, *Pseudomonas*, *Acinetobacter calcoaceticus* (formerly *Mima* and *Herellea* species) are almost uniformly resistant to cephazolin.

**Human Pharmacology** -- The following table demonstrates the blood levels and duration of cephazolin following intramuscular administration.

**TABLE 1**
SERUM CONCENTRATIONS AFTER INTRAMUSCULAR ADMINISTRATION

<table>
<thead>
<tr>
<th>Dose</th>
<th>½ hr</th>
<th>1 hr</th>
<th>2 hr</th>
<th>4 hr</th>
<th>6 hr</th>
<th>8 hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>250 mg</td>
<td>15.5</td>
<td>17.0</td>
<td>13.0</td>
<td>5.1</td>
<td>2.5</td>
<td></td>
</tr>
<tr>
<td>500 mg</td>
<td>36.2</td>
<td>36.8</td>
<td>37.9</td>
<td>15.5</td>
<td>6.3</td>
<td>3.0</td>
</tr>
<tr>
<td>1 g *</td>
<td>60.1</td>
<td>63.8</td>
<td>54.3</td>
<td>29.3</td>
<td>13.2</td>
<td>7.1</td>
</tr>
</tbody>
</table>

* Average of two studies

Controlled studies on adult normal volunteers receiving 1 g four times a day for ten days, monitoring CBC, SGOT, SGPT, bilirubin, alkaline phosphatase, serum urea, creatinine, and urinalysis, indicated no clinically significant changes attributed to cephazolin.

In a study (using normal volunteers) of constant intravenous infusion with dosages of 3.5 mg/kg for one hour (approximately 250 mg) and 1.5 mg/kg the next two hours (approximately 100 mg), cephazolin produced a steady serum level at the third hour of approximately 28 µg/mL. The following table shows the average serum concentration after I.V. injection of a single 1 g dose; average half-life was 1.4 hours.

**TABLE 2**
SERUM CONCENTRATION AFTER 1 g INTRAVENOUS DOSE

<table>
<thead>
<tr>
<th>Serum Concentrations (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 min</td>
</tr>
<tr>
<td>188.4</td>
</tr>
</tbody>
</table>

Cephazolin is excreted unchanged in the urine. Following intramuscular injection of 500 mg, 56 to 89 percent of the administered dose was recovered within six hours and 80 to nearly 100 percent was recovered in twenty-four hours. Cephazolin achieves peak urine concentrations greater than 1000 µg/mL and 4000 µg/mL respectively following 500 mg and 1 g intramuscular doses.
When cephazolin is administered to patients with unobstructed biliary tracts, high concentrations, well over serum levels, occur in the gallbladder tissue and bile. In the presence of obstruction, however, concentration of the antibiotic in bile is considerably lower than the serum level.

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

Cephazolin readily crosses the placental barrier into the cord blood and amniotic fluid. Cephazolin is present in very low concentrations in the milk of nursing mothers.

**Disc Susceptibility Tests** -- Quantitative methods that require measurement of zone diameters give the most precise estimates of antibiotic susceptibility. One such procedure* has been recommended for use with discs for testing susceptibility to cephalosporin-class antibiotics. Interpretations correlate diameters of the disc test with MIC values for Kefzol. With this procedure, a report from the laboratory of "susceptible" indicates that the infecting organism is likely to respond to therapy. A report of "resistant" indicates that the infecting organism is not likely to respond to therapy. A report of "intermediate susceptibility" suggests that the organism would be susceptible if high dosage is used or if the infection is confined to tissues and fluids (e.g. urine) in which high antibiotic levels are attained.

**INDICATIONS**

Kefzol is indicated in the treatment of the following serious infections due to susceptible organisms:

- **Respiratory tract infections** due to *S. pneumoniae*, *Klebsiella* species, *H. influenzae*, *Staph. aureus* (penicillin-sensitive and penicillin- resistant), and Group A beta-haemolytic streptococci.

- **Injectable benzathine penicillin** is considered to be the drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever.

- **Kefzol** is effective in the eradication of streptococci from the nasopharynx; however, data establishing the efficacy of Kefzol in the subsequent prevention of rheumatic fever are not available at present.

- **Genitourinary tract infections** due to *Esch. coli*, *Pr. mirabilis*, *Klebsiella* species, and some strains of *Enterobacter* and enterococci.

- **Skin and skin structure infections** due to *Staph. aureus* (penicillin-sensitive and penicillin-resistant), and Group A beta-haemolytic streptococci and other strains of streptococci.

- **Bone and joint infections** due to *Staph. aureus*.

- **Septicaemia** due to *S. pneumoniae*, *Staph. aureus* (penicillin-sensitive and penicillin-resistant), *Pr. mirabilis*, *Esch. coli* and *Klebsiella* species.
Endocarditis due to *Staph. aureus* (penicillin-sensitive and penicillin-resistant), and Group A beta-haemolytic streptococci.

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

**CONTRAINDICATIONS**

Kefzol is contraindicated in patients with known allergy to the cephalosporin group of antibiotics or who have previously experienced a major allergy to penicillin (*see PRECAUTIONS*).

**PRECAUTIONS**

Before cephazolin therapy is instituted, careful inquiry should be made concerning previous hypersensitivity reactions to cephalosporins and penicillin. Cephalosporin C derivatives should be given cautiously in penicillin-sensitive patients.

Serious acute hypersensitivity reactions may require adrenaline and other emergency measures.

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

Antibiotics, including Kefzol, should be administered cautiously to any patient who has demonstrated some form of allergy, particularly to drugs.

If an allergic reaction to Kefzol occurs, the drug should be discontinued and the patient treated with the usual agents (e.g., adrenaline or other pressor amines, antihistamines, or corticosteroids).

Antibiotic associated pseudomembranous colitis has been reported with many antibiotics including Kefzol. A toxin produced with *Clostridium difficile* appears to be the primary cause. The severity of the colitis may range from mild to life threatening. It is important to consider this diagnosis in patients who develop diarrhoea or colitis in association with antibiotic use (this may occur up to several weeks after cessation of antibiotic therapy). Mild cases usually respond to drug discontinuation alone. However, in moderate to severe cases appropriate therapy with a suitable oral antibacterial agent effective against *C. difficile* should be considered. Fluids, electrolytes and protein replacement should be provided when indicated.

Drugs which delay peristalsis, e.g. opiates and diphenoxylate with atropine (Lomotil) may prolong and/or worsen the condition and should not be used.

Prolonged use of Kefzol 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 Kefzol is administered to patients with low urinary output because of impaired renal function, lower daily dosage is required (see dosage instructions).

The intrathecal administration of Kefzol 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 cephazolin was administered in this manner.

**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 Tes-Tape (urine sugar analysis paper, Lilly).

**Use in Pregnancy** - Pregnancy Category B1 - Safety of this product for use during pregnancy has not been established.

**Use in Infants** -- Safety for use in prematures and infants under one month of age has not been established.

**ADVERSE REACTIONS**

The following reactions have been reported:

**Hypersensitivity** -- Drug fever, skin rash, vulvar pruritus, eosinophilia, itching and Stevens-Johnson syndrome have occurred.

**Blood** -- Neutropenia, leukopenia, thrombocythaemia, thrombocytopenia and positive direct and indirect Coombs tests have occurred.

**Hepatic and Renal** -- Isolated transient rise in SGOT, SGPT, serum urea and alkaline phosphatase levels has been observed without evidence of renal or hepatic impairment.

**Gastrointestinal** -- Nausea, anorexia, vomiting, diarrhoea, and oral candidiasis (oral thrush) have been reported. As with other broad-spectrum antibiotics, colitis, including rare instances of pseudomembranous colitis, has been reported in conjunction with therapy with Kefzol (see PRECAUTIONS).

**Other** -- Pain at the site of injection after intramuscular administration has occurred, some with induration. Phlebitis at the site of injection has been noted. Other reactions have included genital and anal pruritus, genital moniliasis, and vaginitis.

**DOSAGE AND ADMINISTRATION**

Kefzol may be administered intramuscularly or intravenously after reconstitution.

The intrathecal administration of Kefzol is not an approved route of administration for this antibiotic; in fact, there have been reports of severe CNS toxicity including seizures when cephazolin was administered in this manner.
Intramuscular Administration -- Reconstitute with Sterile Water for Injection, Bacteriostatic Water for Injection, or 0.9 percent Sodium Chloride Injection according to the dilution table below. Shake well until dissolved. To facilitate putting the product into solution, the vial should be warmed in the hands while shaking. Do not use the reconstituted injection solution if there is any sign of turbidity. Kefzol should be injected into a large muscle mass.

<table>
<thead>
<tr>
<th>TABLE 3</th>
<th>DILUTION TABLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vial Size</td>
<td>Diluent to Be added</td>
</tr>
<tr>
<td>1 g</td>
<td>2.5 mL</td>
</tr>
</tbody>
</table>

Intravenous Administration -- Kefzol may be administered by direct intravenous injection or by intermittent or continuous infusion. Total daily dosages are the same as with intramuscular injection.

Direct Intravenous Injection -- Dilute the reconstituted 1 g Kefzol in a minimum of 10 mL of Sterile Water for Injection. Inject solution slowly over three to five minutes. It may be administered directly into a vein or through the tubing for a patient receiving one of the following intravenous solutions:

- 0.9% Sodium Chloride Injection
- 5% or 10% Glucose Injection
- 5% Glucose in Lactated Ringer's Injection
- 5% Glucose and 0.9% Sodium Chloride Injection (also may be used with 5% Glucose and 0.4% or 0.2% Sodium Chloride Injection)
- Lactated Ringer's Injection
- 5% or 10% Invert Sugar in Sterile Water for Injection
- Ringer's Injection
- Normosol-M in 5% Glucose
- Ionosol B with Glucose 5%
- Plasma-Lyte with 5% Glucose.

Intermittent Intravenous Infusion -- Kefzol can be administered along with primary intravenous fluid management programmes in a volume control set or in a separate, secondary I.V. bottle. Reconstituted 1 g Kefzol may be diluted in 50 to 100 mL of Sterile Water for Injection or one of the above parenteral fluids, and infused over a period of three to five minutes. If a Y-type administration set is used, it is desirable to discontinue the other solution during the infusion of the solution containing Kefzol.

Continuous Intravenous Infusion -- The total daily dose of Kefzol, diluted and well mixed with at least 50 mL of Sterile Water for Injection, may be added to an I.V. bottle containing one of the above parenteral fluids. The choice of saline or glucose solution and the volume to be employed are dictated by fluid and electrolytic management.

Dosage -- In adults, usual dosage for mild gram-positive infections is 250 to 500 mg of Kefzol every eight hours. In mild to moderate infections of the respiratory tract caused by *S. pneumoniae*, or mild to moderate infections of the genitourinary tract caused by susceptible
organisms, a dosage of 500 mg to 1 g every twelve hours may be used. In moderate or severe infections, the usual adult dosage is 500 mg to 1 g of Kefzol every six to eight hours. Kefzol has been administered in dosages of 6 g per day in serious infections such as endocarditis. In patients with renal impairment, cephalozolin is not readily excreted. After a loading dose of 500 mg, the following recommendations for maintenance dosage may be used as a guide.

### TABLE 4

**MAINTENANCE DOSAGE OF KEFZOL IN ADULTS WITH REDUCED RENAL FUNCTION**

<table>
<thead>
<tr>
<th>Renal Function</th>
<th>Serum Urea* (mg%)</th>
<th>Serum Creatinine Clearance (mL/min)</th>
<th>Serum Creatinine (mmol/L)</th>
<th>Dosage</th>
<th>Serum Half-Life (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild Impairment</td>
<td>20-34</td>
<td>70-40</td>
<td>115 - 180</td>
<td>250 to 500 mg 500 mg to 1.25 g</td>
<td>3 - 5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>q 12 h</td>
<td></td>
</tr>
<tr>
<td>Moderate Impairment</td>
<td>35-49</td>
<td>40-20</td>
<td>181 - 310</td>
<td>125 to 250 mg 250 to 600 mg</td>
<td>6 - 12</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>q 12 h</td>
<td></td>
</tr>
<tr>
<td>Severe Impairment</td>
<td>50-75</td>
<td>20-5</td>
<td>311 - 620</td>
<td>75 to 150 mg 150 to 400 mg</td>
<td>15 - 30</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>q 24 h</td>
<td></td>
</tr>
<tr>
<td>Essentially No Function</td>
<td>&gt;75</td>
<td>&lt;5</td>
<td>&gt;620</td>
<td>37.5 to 75 mg 75 to 200 mg</td>
<td>30 - 40</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>q 24 h</td>
<td></td>
</tr>
</tbody>
</table>

* If used to estimate degree of renal impairment, concentrations should reflect a steady state of renal azotaemia.

In children, a total daily dosage of 25 to 50 mg per kg of body weight, divided into three or four equal doses, is effective for most mild to moderately severe infections. Total daily dosage may be increased to 100 mg per kg of body weight for severe infections. In children with mild to moderate impairment of renal function (creatinine clearance of 70-40 mL/min) 60% of the normal daily dose given in divided doses q 12 h should be sufficient. In patients with moderate impairment (creatinine clearance of 40-20 mL/min) 25% of the normal daily dose given in divided doses q 12 h should be sufficient. In children with marked impairment (creatinine clearance of 20-5 mL/min) 10% of the normal daily dose given q 24 h should be adequate. All dosage recommendations apply after an initial loading dose.

Since safety for use in premature infants and in infants under one month has not been established, the use of Kefzol in these patients is not recommended.
### TABLE 5

**PAEDIATRIC DOSAGE GUIDE**

#### Part A

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>25 mg/kg/day</th>
<th>25 mg/kg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Divided into 3 Doses</td>
<td>Divided into 4 Doses</td>
</tr>
<tr>
<td>Approximate Single Dose (mg q 8 h)</td>
<td>Vol. (mL) Needed with Dilution of 125 mg/mL</td>
<td>Approximate Single Dose (mg q 6 h)</td>
</tr>
<tr>
<td>4.5</td>
<td>40 mg</td>
<td>0.35 mL</td>
</tr>
<tr>
<td>9</td>
<td>75 mg</td>
<td>0.6 mL</td>
</tr>
<tr>
<td>13.6</td>
<td>115 mg</td>
<td>0.9 mL</td>
</tr>
<tr>
<td>18.1</td>
<td>150 mg</td>
<td>1.2 mL</td>
</tr>
<tr>
<td>22.7</td>
<td>190 mg</td>
<td>1.5 mL</td>
</tr>
</tbody>
</table>

#### Part B

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>50 mg/kg/day</th>
<th>50 mg/kg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Divided into 3 Doses</td>
<td>Divided into 4 Doses</td>
</tr>
<tr>
<td>Approximate Single Dose (mg q 8 h)</td>
<td>Vol. (mL) Needed with Dilution of 225 mg/mL</td>
<td>Approximate Single Dose (mg q 6h)</td>
</tr>
<tr>
<td>4.5</td>
<td>75 mg</td>
<td>0.35 mL</td>
</tr>
<tr>
<td>9</td>
<td>150 mg</td>
<td>0.7 mL</td>
</tr>
<tr>
<td>13.6</td>
<td>225 mg</td>
<td>1 mL</td>
</tr>
<tr>
<td>18.1</td>
<td>300 mg</td>
<td>1.35 mL</td>
</tr>
<tr>
<td>22.7</td>
<td>375 mg</td>
<td>1.7 mL</td>
</tr>
</tbody>
</table>

**OVERDOSAGE**

*Signs and Symptoms* -- Toxic signs and symptoms following an overdose of Kefzol may include pain, inflammation and phlebitis at the injection site.

The administration of inappropriately large doses of parenteral cephalosporins may cause dizziness, paraesthesias and headaches. 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, serum urea, liver enzymes and bilirubin, a positive Coombs' test, thrombocytosis, thrombocytopenia, eosinophilia, leucopenia and prolongation of the prothrombin time.

*Treatment* -- In managing overdosage, consider the possibility of multiple drug overdoses, interaction among drugs and unusual drug kinetics in your patient.
If seizures occur, the drug should be discontinued promptly; anticonvulsant therapy may be administered if clinically indicated. Protect the patient's airway and support ventilation and perfusion. Meticulously monitor and maintain, within acceptable limits, the patient's vital signs, blood gases, serum electrolytes, etc.

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.

Contact the Poisons Information Centre on 131126 for management of overdose.

**STORAGE**

Store below 30 degrees Celsius and protect from light. Upon reconstitution, Kefzol and dilutions of Kefzol in the recommended intravenous fluids are stable for 24 hours if stored under refrigeration (2-8°C). To reduce microbiological hazards, use as soon as practicable after reconstitution. Contains no antimicrobial agent. Product is for single use in one patient only. Discard any residue.

**PRESENTATION**

Kefzol 1 g (equivalent to 1 g cephazolin); pack of 10 vials.

**POISON SCHEDULE**

S4

**SPONSOR**

Aspen Pharmacare Australia Pty Ltd
34-36 Chandos St
St Leonards NSW 2065
Australia

**REFERENCES**


**DATE OF TGA APPROVAL**

Approved by the Therapeutic Goods Administration: May 11, 1995
Safety-related notification – September 29, 2003
Date of most recent amendment: 18 February 2010.