**CEFAZOLIN SANDOZ®**

**NAME OF THE MEDICINE**
Active: Cephazolin sodium; sodium content is 48.3mg/g of cephazolin sodium

**Chemical structure of cephazolin sodium**

![Chemical structure of cephazolin sodium](image)

Chemical name:
(6R,7R)-3-[(5-methyl-1,3,4-thiadiazol-2-yl)thiomethyl]-8-oxo-7-[2-(1H-tetrazol-1-yl)acetamido]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate.

**Molecular formula:** C\(_{14}\)H\(_{13}\)N\(_8\)NaO\(_4\)S\(_3\)
**Molecular weight:** 476.5
**CAS:** 27164-46-1

**DESCRIPTION**
Cephazolin sodium is a white to off-white crystalline powder with a solubility in water of greater than or equal to 100mg/mL. Cefazolin Sandoz powder for injection contains cephazolin sodium as a single ingredient.

**PHARMACOLOGY**

**Pharmacodynamics**
Semi-synthetic cephalosporin for parenteral administration.

**Microbiology**
*In vitro* tests demonstrate that the bactericidal action of cephalosporins results from inhibition of cell wall synthesis. Cephazolin 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 sp.*, *Enterobacter aerogenes*, *Haemophilus influenzae*. Most strains of *Enterobacter cloacae* and indole-positive proteus (*P. vulgaris*, *P. morganii*, *P. rettgeri*) are resistant. Methicillin resistant staphylococci, *serrata*, *pseudomonas*, *Acinetobacter calcoaceticus* (formerly *Mima* and *Herellea* sp.) are almost uniformly resistant to cephazolin.

**Susceptibility tests**
Dilution or diffusion techniques – either quantitative (MIC) or breakpoint, should be used following a regularly updated, recognised and standardised method (e.g. NCCLS). Standardised susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures.
A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone, which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable, other therapy should be selected.

Pharmacokinetics
Table 1 demonstrates the blood levels and duration of cephazolin following intramuscular administration.

<table>
<thead>
<tr>
<th>Dose</th>
<th>Time after dose (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.5</td>
</tr>
<tr>
<td>250mg</td>
<td>15.5</td>
</tr>
<tr>
<td>500mg</td>
<td>36.2</td>
</tr>
<tr>
<td>1g*</td>
<td>60.1</td>
</tr>
</tbody>
</table>

*Average of two studies

Clinical pharmacology studies in patients hospitalised with infections indicate that cephazolin produces mean peak serum levels approximately equivalent to those seen in normal volunteers. In a study (using normal volunteers) of constant intravenous infusion with dosages of 3.5mg/kg for one hour (approximately 250mg) and 1.5mg/kg for the next two hours (approximately 100mg) cephazolin produced a steady serum level at the third hour of approximately 28\(\mu\)g/mL. Table 2 shows the average serum concentration after intravenous injection of a single 1g dose; average half-life was 1.4 hours.

<table>
<thead>
<tr>
<th>Dose</th>
<th>Time after dose (minutes)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5</td>
</tr>
<tr>
<td>1g</td>
<td>188.4</td>
</tr>
</tbody>
</table>

Controlled studies on adult normal volunteers receiving 1g four times daily for ten days, monitoring complete blood count, AST, ALT, bilirubin, alkaline phosphatase, serum urea, creatinine, and urinalysis, indicated no clinically significant changes attributed to cephazolin. Cephazolin is excreted unchanged in the urine. Following intramuscular injection of 500mg, 56 to 89% of the administered dose was recovered within six hours and 80 to nearly 100% was recovered in 24 hours. Cephazolin achieves peak urine concentrations greater than 1,000\(\mu\)g/mL and 4,000\(\mu\)g/mL respectively following 500mg and 1g intramuscular doses. When cephazolin is administered to patients with unobstructed biliary tracts, high concentrations, well over serum levels, occur in the gall bladder 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. Cephalozolin readily crosses the placental barrier into the cord blood and amniotic fluid. Cephalozolin is present in very low concentrations in the milk of breastfeeding mothers.

INDICATIONS
Treatment of the following serious infections due to susceptible organisms:

- Respiratory tract infections due to Strep. pneumoniae, Klebsiella sp., 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. Cephalozolin is effective in the eradication of streptococci from the nasopharynx; however, data establishing the efficacy of cephalozolin in the subsequent prevention of rheumatic fever are not available at present.
- Genitourinary tract infections due to E. coli, P. mirabilis, Klebsiella sp. 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 Strep. pneumoniae, Staph. aureus (penicillin sensitive and penicillin resistant), P. mirabilis, E. coli and Klebsiella sp.
- 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 cephalozolin.

CONTRAINDICATIONS
Known allergy to the cephalosporin group of antibiotics or previous experience of a major allergy to penicillin (see PRECAUTIONS).

Lignocaine should not be used as a diluent for intramuscular injection in patients who are hypersensitive to lignocaine.

PRECAUTIONS
Before cephalozolin 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 cephalozolin, should be administered cautiously to any patient who has demonstrated some form of allergy, particularly to drugs. If an allergic reaction to cephalozolin 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 cephalozolin. A toxin produced by 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 Cl. difficile should
be considered. Fluids, electrolytes and protein replacement should be provided when indicated.

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

Prolonged use of cepheozolin 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.

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

Tremulousness, headache, agitation, light-headedness, sensation of seeing flashing lights have been reported after patients receiving cepheozolin intraventricularly for the treatment of infected ventricular shunts. Cephazolin is not to be used via this route for the treatment of shunt infections.

**History of gastrointestinal disease**
Cephazolin, as with all cephalosporins, should be prescribed with caution in individuals with a history of gastrointestinal disease.

**Impaired renal function**
As with other beta-lactam antibiotics, seizures may occur if inappropriately high doses are administered to patients with impaired renal function. When cepheozolin is administered to patients with low urinary output because of impaired renal function, lower daily dosage is required (see DOSAGE AND ADMINISTRATION).

Encephalopathy has been reported with the use of cepheozolin in patients with renal failure. The symptoms have included tonic-clonic seizures, lethargy, disorientation, memory loss, asterixis and multifocal myoclonus. Toxicity has been attributed to increased cepheozolin serum levels and increased permeability of the blood brain barrier caused by uraemia. The dose of cepheozolin should be reduced or the dosing interval increased in patients with renal failure.

**Use in pregnancy (Category B1)**
Safety of this product for use during pregnancy has not been established in human clinical trials. Studies in animals are inadequate or lacking, but available data show no evidence of an increased occurrence of foetal damage. Studies of cord blood show prompt transfer of cepheozolin across the placenta. Drug levels in cord blood were approximately ¼ to ⅓ maternal drug levels.

**Use in lactation**
Cephazolin is present in very low concentrations in the milk of nursing mothers. Caution should be exercised when cepheozolin is administered to a nursing mother.

**Use in infants**
Safety for use in premature infants and infants under one month of age has not been established.
**Carcinogenicity**  
Long term studies in animals to determine the carcinogenic potential of cephazolin have not been performed.

**Genotoxicity**  
Mutagenicity studies have not been performed.

**Interactions with other medicines**  
Probenecid - Probenecid may decrease renal tubular secretion of cephalosporins when used concurrently, resulting in increased and more prolonged cephalosporin blood levels.

Aminoglycoside antibodies – Coadministration of aminoglycoside antibiotics with cephalosporins could produce additive nephrotoxic effects. Use of these agents should be avoided in patients with prior renal insufficiency. If coadministration of these two antibiotic classes is necessary, patients should be monitored for evidence of nephrotoxicity.

Live typhoid vaccine – Antibiotics which possess bacterial activity against *Salmonella typhi* organisms may interfere with the immunological response to the live typhoid vaccine. Allow 24 hours or more to elapse between the administration of the last dose of the antibiotic and the live typhoid vaccine.

Warfarin – Patients receiving oral anticoagulant therapy with warfarin should be closely monitored using the prothrombin time ratio or international normalised ratio (INR) during concurrent therapy with cephazolin. Adjustment of the warfarin dosage to maintain the desired anticoagulant effect may be necessary. An alternative would be to use a cephalosporin which does not possess hypoprothrombinemic properties.

**Effects on Laboratory tests**  
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.

Several cases of positive direct and indirect antiglobulin (Coombs’) tests have been reported following cephazolin therapy. These may also occur in neonates whose mothers received cephazolin prior to delivery.

**ADVERSE EFFECTS**  
The following reactions have been reported.

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

**Haematological**  
The most common blood disorder associated with cephazolin has been eosinophilia. Neutropenia, leucopenia, thrombocytopenia, thrombocytopenia and positive direct and indirect Coombs’ tests have occurred.

**Hepatic and renal**  
Isolated transient rise in AST, ALT, 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 cephazolin (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 candidiasis and vaginitis.

DOSAGE AND ADMINISTRATION
Cephazolin may be administered intramuscularly or intravenously after reconstitution. The intrathecal administration of cephazolin 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 water for injections, sodium chloride 0.9% injection or lignocaine 0.5% injection according to the dilution table (Table 3). 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. Cephazolin should be injected into a large muscle mass.

<table>
<thead>
<tr>
<th>Vial size</th>
<th>Solvent to be added</th>
<th>Approx. avail. volume</th>
<th>Approx. average concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>500mg</td>
<td>2.0mL</td>
<td>2.2mL</td>
<td>225mg/mL</td>
</tr>
<tr>
<td>1g</td>
<td>2.5mL</td>
<td>3.0mL</td>
<td>330mg/mL</td>
</tr>
</tbody>
</table>

Intravenous administration
Cephazolin 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 500mg, 1g or 2g of cephazolin in a minimum of 10 mL of water for injections. 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: sodium chloride 0.9% injection, glucose 5% or 10% injection, glucose 5% in lactated Ringer's injection, glucose 5% and sodium chloride 0.9% injection (also may be used with glucose 5% and sodium chloride 0.4 or 0.2% injection), lactated Ringer's injection, invert syrup 5 or 10% in water for injections, Ringer's injection, Normosol-M in glucose 5%, Ionosol B with glucose 5%, Plasma-Lyte with glucose 5%.

Intermittent intravenous infusion
Cephazolin can be administered along with primary intravenous fluid management programs in a volume control set or in a separate, secondary intravenous bottle. Reconstituted cephazolin 500mg, 1g or 2g may be diluted in 50 to 100 mL of water for injections or one of the previously listed 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 cephazolin.

**Continuous intravenous infusion**
The total daily dose of cephazolin, diluted and well mixed with at least 50mL of water for injections, may be added to an intravenous bottle containing one of the previously listed parenteral fluids. Alternatively, fill up the Cefazolin Sandoz 2g infusion bottle with 50 to 100mL of the listed intravenous solution. The choice of saline or glucose solution and the volume to be employed are dictated by fluid and electrolyte management.

**Dosage**

**Adults**
Usual dosage for mild Gram-positive infections is cephazolin 250 to 500mg every eight hours.

In mild to moderate infections of the respiratory tract caused by *Strep. pneumoniae*, or mild to moderate infections of the genitourinary tract caused by susceptible organisms, a dosage of 500mg to 1g every twelve hours may be used.

In moderate or severe infections the usual adult dosage is cephazolin 500mg to 1g every six to eight hours. Cephazolin has been administered in dosages of 6g/day in serious infections such as endocarditis.

In patients with renal impairment, cephazolin is not readily excreted. After a loading dose of 500mg, the recommendations in Table 4 for maintenance dosage may be used as a guide.

**Table 4**

<table>
<thead>
<tr>
<th>Renal function</th>
<th>Serum urea* (mg%)</th>
<th>Creatinine clearance (mL/min)</th>
<th>Serum creatinine (micromol/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>Mild to moderate infection</td>
<td>250-500mg 12 hourly</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Moderate to severe infection</td>
<td>0.5-1.25g 12 hourly</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3-5</td>
</tr>
<tr>
<td>Moderate impairment</td>
<td>35-49</td>
<td>40-20</td>
<td>181-310</td>
<td></td>
<td>125-250mg 12 hourly</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>250-600mg 12 hourly</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6-12</td>
</tr>
<tr>
<td>Severe impairment</td>
<td>50-75</td>
<td>20-5</td>
<td>311-620</td>
<td></td>
<td>75-150mg 24 hourly</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>150-400mg 24 hourly</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>15-30</td>
</tr>
<tr>
<td>Essentially no function</td>
<td>&gt; 75</td>
<td>&lt; 5</td>
<td>&gt; 620</td>
<td></td>
<td>37.5-75mg 24 hourly</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>75-200mg 24 hourly</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>30-40</td>
</tr>
</tbody>
</table>

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

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

Since safety for use in premature infants and in infants aged under one month has not been established, the use of cephazolin in these patients is not recommended.

### Table 5

**Part A: Paediatric dosage guide for 25mg/kg/day dose**

<table>
<thead>
<tr>
<th>kg</th>
<th>25mg/kg/day divided into 3 doses</th>
<th>25mg/kg/day divided into 4 doses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Approximate single dose (mg/8 hours)</td>
<td>Volume needed with dilution of 125mg/mL</td>
</tr>
<tr>
<td>4.5</td>
<td>40mg</td>
<td>0.35mL</td>
</tr>
<tr>
<td>9.0</td>
<td>75mg</td>
<td>0.6mL</td>
</tr>
<tr>
<td>13.6</td>
<td>115mg</td>
<td>0.9mL</td>
</tr>
<tr>
<td>18.1</td>
<td>150mg</td>
<td>1.2mL</td>
</tr>
<tr>
<td>22.7</td>
<td>190mg</td>
<td>1.5mL</td>
</tr>
</tbody>
</table>

### Part B: Paediatric dosage guide for 50mg/kg/day dose

<table>
<thead>
<tr>
<th>kg</th>
<th>50mg/kg/day divided into 3 doses</th>
<th>50mg/kg/day divided into 4 doses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Approximate single dose (mg/8 hours)</td>
<td>Volume needed with dilution of 225mg/mL</td>
</tr>
<tr>
<td>4.5</td>
<td>75mg</td>
<td>0.35mL</td>
</tr>
<tr>
<td>9.0</td>
<td>150mg</td>
<td>0.7mL</td>
</tr>
<tr>
<td>13.6</td>
<td>225mg</td>
<td>1.0mL</td>
</tr>
<tr>
<td>18.1</td>
<td>300mg</td>
<td>1.35mL</td>
</tr>
<tr>
<td>22.7</td>
<td>375mg</td>
<td>1.7mL</td>
</tr>
</tbody>
</table>

Cefazolin Sandoz contains no antimicrobial preservative. It is for single use in one patient only. Discard any residue. To reduce microbiological hazard, use as soon as practicable after initial reconstitution. If storage is necessary, store at 2° to 8°C for not more than 24 hours.
OVERDOSAGE

Contact the Poisons Information Centre on 13 11 26 for advice on management of overdose.

Symptoms
Toxic signs and symptoms following an overdose of cefazolin 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 may 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, the possibility of multiple drug overdoses, interaction among drugs and unusual drug kinetics should be considered.

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.

PRESENTATION AND STORAGE CONDITIONS
Vials (rubber stoppered); 1.0g: 1*, 5* or 10 vials per pack
Infusion bottles; 2.0g: 1, 5* or 10* infusion bottles per pack

Powder for injection
Reconstituted solution
Store below 25°C. Protect from light and moisture.
Store at 2° to 8°C. Refrigerate. Do not freeze.
(Use within 24 hours after initial reconstitution.)

*Not currently marketed in Australia

NAME AND ADDRESS OF THE SPONSOR
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19 Harris Street
Pyrmont NSW 2009
Australia
Tel: 1800 634 500

POISON SCHEDULE OF THE MEDICINE
Schedule 4 – Prescription Only Medicine
Date of first inclusion in the Australian Register of Therapeutic Goods (the ARTG):
14/03/2002

Date of most recent amendment: 12/03/2012