Pan-Cefazolin 1 g

Powder for solution for injection

1. NAME OF THE MEDICINAL PRODUCT

Pan-Cefazolin 1 g

Powder for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Cefazolin (as sodium) 1 g

3. PHARMACEUTICAL FORM

Powder for IM or IV use.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Cefazolin is indicated for the treatment of infections due to susceptible organisms and also perioperatively for prophylaxis.

Treatment includes:

Respiratory tract infections due to Streptococcus pneumoniae (formerly Diplococcus pneumoniae), Klebsiella species, Haemophilus influenzae, Staphylococcus aureus (penicillin-sensitive and penicillin-resistant), group A beta-haemolytic streptococci, streptococci of the nasopharynx.

Urinary tract infections due to Escherichia coli, Klebsiella species, Proteus mirabilis and some strains of enterobacter and enterococci.

Skin and Skin structure infections due to Staphylococcus aureus (penicillin-sensitive and penicillin-resistant), group A beta-haemolytic streptococci and other strains of streptococci.

Biliary tract infections due to Escherichia coli, various strains of streptococci, Proteus mirabilis, Klebsiella species and Staphylococcus aureus.

Bone and Joint infections due to Staphylococcus aureus.

Genital infections due to Escherichia coli, Proteus mirabilis, Klebsiella species and some strains of streptococci.

Septicemia due to Streptococcus pneumoniae (formerly Diplococcus pneumoniae), Proteus mirabilis, Escherichia coli and Klebsiella species.

Endocarditis due to Staphylococus aureus (penicillin-sensitive and penicillin-resistant) and group A beta-haemolytic streptococci.

Perioperative prophylaxis:

The prophylactic administration of cefazolin perioperatively (preoperatively, intraoperatively and postoperatively) may reduce the incidence of certain postoperative infections in patients undergoing surgical procedures (hysterectomy, gastrointestinal surgery) that are classified as contaminated or potentially contaminated.

The perioperative use of cefazolin may also be effective in surgical patients in whom infection at the operative site would present a serious risk (open-heart surgery and prosthetic arthroplasty).

4.2 Posology and method of administration

Cefazolin may be administered IM or IV after reconstitution; total daily dosage is the same for either route of administration (IM or IV).

Usual Adult Dosage:

Pneumococcal pneumonia: 0.5 g every 12 hours.

Mild infection 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 (endocarditis, septicaemia): 1 g to 1.5 g every 6 hours.

Maximum daily dose is up to 6 g; however, doses of up to 12 g have been prescribed in rare cases.

Dosage adjustment in renal failure (guidelines):

In patients with impaired renal function, the doses should be adjusted according to creatinine clearance or serum creatinine levels (see table).

After an initial loading dose:

CREATININE ml/min	SERUM CREATININE mg/100 ml	DOSAGE
≥55	≤1.5	Full dosage
35-54	1.6 to 3.0	Full dosage restricted to at least 8 hours intervals
11-34	3.1 to 4.5	½ of the usual dose every 12 hours
10 or less	4.6 or more	½ of the usual dose every 18 to 24 hours

Usual Children's Dosage:

In children, a total daily dosage of 25 mg to 50 mg/kg body weight, divided into 3 to 4 equal doses, is effective for most mild to moderately severe infections. Total daily dosage may be increased to 100 mg/kg body weight in severe infections.

Paediatric dosage guide:

Weight in kg	25 mg/kg/day divided into 3 doses (approx. single dose (mg/every 8h)	25 mg/kg/day divided into 4 doses (approx. single dose (mg/every 6h)
4.5	40 mg	30 mg
9.0	75 mg	55 mg
13.6	115 mg	85 mg
18.1	150 mg	115 mg
22.7	190 mg	140 mg

Weight in kg	50 mg/kg/day divided into 3 doses (approx. single dose (mg/every 8h)	50 mg/kg/day divided into 4 doses (approx. single dose (mg/every 6h)
4.5	75 mg	55 mg
9.0	150 mg	110 mg
13.6	225 mg	170 mg
18.1	300 mg	225 mg
22.7	375 mg	285 mg

Dosage adjustment in children with renal failure (guidelines):

In children with mild to moderate renal impairment (creatinine clearance of 70 to 40 ml/min), 60% of the normal daily dose given in equally divided doses every 12 hours should be sufficient.

In children with moderate impairment (creatinine clearance of 40 to 20 ml/min), 25% of the normal daily dose given in equally divided doses every 12 hours should be sufficient.

In children with severe impairment (creatinine clearance of 20 to 5 ml/min), 10% of the normal daily dose given every 24 hours should be adequate.

All dose recommendations apply after an initial loading dose is administered.

Perioperative prophylactic use:

To prevent postoperative infection in contaminated or potentially contaminated surgery the recommended doses are:

- 1 g IV or IM administered half an hour to one hour prior to initiation of surgery
- for lengthy operative procedures (2 hours or longer) 0.5-1.0 g IV or IM during surgery (administration modified according to the duration of the operative procedure)
- 0.5 to 1.0 g IV or IM administered every 6 to 8 hours for 24 hours postoperatively

If exposure to infectious organisms is likely, cefazolin should be administered at appropriate intervals during surgery to provide sufficient levels of antibiotic.

If surgery in which infection may be particularly devastating (open-heart surgery and prosthetic arthroplasty), the prophylactic administration of cefazolin may be continued for 3 to 5 days after the completion of surgery. In other cases, prophylactic administration should usually be discontinued within 24h after the surgical procedure, because of the risk of adverse reactions.

If there are signs of infection, specimens for culture should be obtained for identification of the causative organisms so that appropriate therapy may be initiated.

Method of Administration:

Parenteral drug should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

IV administration:

IV administration: Cefazolin may be given either as a direct IV injection or as a continuous or intermittent IV infusion.

Intravenous injection: Reconstitute 1 g cefazolin with 5 ml – 10 ml Water for Injection. The resulting solution must be injected slowly over a period of 3-5 minutes and it may be administered directly into vein or through tubing.

Intravenous infusion: The administration can be continuous or intermittent. In intermittent intravenous infusion cefazolin can be administered along with primary intravenous fluid management programs in a volume control set or in a separate secondary IV container.

Reconstituted 1 g cefazolin vial may be diluted in 50-100 ml of one of the following intravenous solutions: 0.9% Sodium Chloride Injection, 5% or 10% Dextrose Solution, 5% Dextrose in Lactated Ringer's Injection, 5% Dextrose and 0.9% Sodium Chloride Injection (also may be used with 5% Dextrose and 0.45% or 0.2% Sodium Chloride Injection), Lactated Ringer's Injection, 5% or 10% Invert Sugar in Water for Injection, Ringer's Injections.

IM administration

Cefazolin can be given by deep intramuscular injection.

Do not use in children less than 30 months old (solvent with lidocaine hydrochloride). Dilute cefazolin with the solvent and inject in deep intramuscular injection. Once reconstituted, the solution is stable for 24 hours at ambient temperature. The solution may be yellowish. Use 3 ml of 0.5% lidocaine.

4.3 Contraindications

Known hypersensitivity to cephalosporin antibiotics.

4.4 Special warnings and special precautions for use

Warnings:

Before therapy with cefazolin, careful inquiry should be made concerning previous hypersensitivity reactions to cephalosporins, penicillin or other drugs. Serious anaphylactic reactions may require epinephrine or other emergency measures, and the drug should be discontinued.

Use in infants: Safety of use in premature and in infants under 1 month of age has not been established and the use of cefazolin in these patients is not recommended.

Do not inject through IV route the forms intended for IM injection containing lidocaine.

Precautions:

In case of renal impairment, dosage should be adapted according to creatinine clearance or creatinemia.

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

Repeated evaluation of the patient's condition is essential.

Antibiotics (including cephalosporins) should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Pseudomembranous colitis has been reported with virtually all antibiotics (including cephalosporins); therefore, it is important to consider its diagnosis in patients who develop diarrhoea in association with antibiotic use. Treatment with broad-spectrum antibiotics alters normal flora of the colon and may permit overgrowth of clostridia. Studies indicate a toxin produced by Clostridium Difficile is one

primary cause of antibiotic-associated colitis.

Mild cases of pseudomembranous colitis may respond to drug discontinuation alone. Moderate to severe cases should be managed with fluid, electrolyte and protein supplementation as indicated.

When the colitis is not relieved by drug discontinuation or when it is severe, oral vancomycin is the treatment of choice for antibiotic-associated pseudomembranous colitis produced by Clostridium Difficile. Other cases of colitis should also be considered.

4.5 Interactions with other medicinal products and other forms of interaction

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

Specific problems with INR imbalance

Many cases of an increase in activity of oral anticoagulants have been reported in patients receiving antibiotics. The pronounced infectious or inflammatory context, the patient's age and general condition appear as risk factors. Under these circumstances, it appears difficult to differentiate between the infectious disease and its treatment in occurrence of an imbalance in the INR. However, certain classes of antibiotics are more often involved: in particular this involves fluoroquinolones, macrolides, tetracyclines, cotrimoxazole and certain cephalosporins.

Laboratory test

Development of a positive Coombs' test has been reported during treatment with the cephalosporin antibiotics. This may occur in patients treated with cefazolin.

A false positive reaction may occur on testing for glucose in the urine with reducing substances, but this can be avoided with the use of methods that are specific to gluco-oxidase.

4.6 Pregnancy and lactation

Use IN PREGNANCY: Safety of use in pregnancy has not been established.

Use in Nursing Mothers: Caution should be taken when cefazolin is administered to a nursing mother. However, if diarrhoea, candidiasis, or a skin rash occurs, breast-feeding (or drug use) should be stopped.

4.7 Effects on the ability to drive and use machines

This medicine is presumed to be safe or unlikely to produce an effect.

4.8 Undesirable effects

- Allergic reactions: skin rash, fever, anaphylaxis, eosinophilia, itching, Stevens-Johnson syndrome and toxic epidermal necrolysis (Lyell's syndrome) may rarely occur. If any of these reactions appear, appropriate measures including discontinuation of cefazolin should be considered.
- Gastro-intestinal reactions: diarrhoea, nausea, anorexia, vomiting, oral candidiasis. Symptoms of pseudomembranous colitis (severe abdominal or stomach cramps and pain; abdominal tenderness; watery and severe diarrhoea, which may also be bloody; fever) during or after antibiotic treatment; nausea, oral candidiasis, diarrhoea, stomach cramps, anorexia.
- Haematological reactions: eosinophilia, leukopenia, neutropenia, reversible thrombocytopenia.
- Hepatic disorders: slight elevation of SGOT & SGPT transaminases and alkaline phosphatases (usually transient).
- Nephrotoxicity: renal function impairment has been reported with the same group of antibiotics, in particular when concomitantly used with aminoglycosides and strong diuretics. Transient rise in BUN.
- Other reactions: pain at intramuscular injection site has occurred infrequently, phlebitis at the site of injection has been reported, genital, anal pruritus, including vulvular pruritus, genital moniliasis and vaginitis.
- Pain at the injection site (IM) with possible induration.

4.9 Overdose

Symptoms of cefazolin overdose include pain, inflammation, and phlebitis at the site of injection. When used at high doses, dizziness, paresthesia, and headache have been reported. Metabolic encephalopathy (disturbance of consciousness, motion disorders, seizures) may occur, in particular in patients with renal impairment.

Accidental cefazolin overdose requires immediate discontinuation of the drug and anticonvulsant therapy should be prescribed if seizures occur.

In severe cases of overdose, in particular in patients with renal impairment, haemodialysis combined with haemoperfusion may be considered as a last resort, although their efficacy has not been proven.

5. PHARMACOLOGICAL PROPERTIES

Antibacterial betalactam antibiotic of the first generation injectable cephalosporins, (ATC Code: J01DA04; (J:Anti-infective agents).

5.1 Pharmacodynamic properties

Critical concentrations separate susceptible strains from intermediately susceptible strains of microorganisms, and the intermediately susceptible from resistant strains:

S≤8 mg/L and R>32 mg/L.

For certain species, the prevalence of known resistance can vary depending on geography and time. Therefore, it is useful to have information on local prevalence of resistance, especially for treatment of serious infections. Such data can only be used as a guide to probability of susceptibility of a given bacterial strain to this antibiotic.

5.2 Pharmacokinetic properties

Cefazolin can be administered by IV or IM route.

Administration of an IV continuous infusion (to healthy volunteers) for 1 hour, firstly of doses of cefazolin of 3.5 mg/kg/body weight (i.e. approximately 250 mg) and then of cefazolin doses of 1.5 mg/kg/body weight during the next 2 hours (approximately 100 mg) made it possible to achieve steady-state concentrations of approximately 28 µg/mL during the third hour of infusion.

Serum concentrations (µg/ml) after IM administration of a dose of 500 mg and 1 g						
Time	30 min	1 h	2 h	4 h	6 h	8 h
500 mg IM	36.2	36.8	37.9	15.5	6.3	3.0
1 g IM	60.1	63.8	63.8	29.3	13.2	7.1
Serum concentrations (µg/ml) after IV administration of a dose of 1 g						
Time	5 min	15 min	30 min	1 h	2 h	4 h
1 g IV	188.4	135.8	106.8	73.7	45.6	16.5

In patients with normal renal function, elimination half-life is approximately 100 minutes.

Therapeutic levels are reached in the pleural fluid, joint fluid and ascetic fluid.

In patients without biliary tract obstruction, cefazolin concentrations in gallbladder tissues and in bile are high and are markedly higher than serum levels.

Conversely, in patients with biliary obstruction, biliary antibiotic concentrations are significantly lower than those in the serum.

Cefazolin rapidly crosses the placental barrier to the cord blood and amniotic fluid. Cefazolin is excreted in very small amounts into human breast milk.

Under physiological conditions, protein binding is approximately 85-90%.

Distribution into the cerebrospinal fluid is low.

Biotransformation

Cefazolin is not metabolised.

Excretion

Cefazolin is excreted unchanged (active form), predominantly in the urine, and to a very limited extent in the bile.

Following intramuscular injection of 500 mg, between 56% and 89% of the administered dose is recovered within 6 hours, and 80% to nearly 100% in 24 hours.

Following intramuscular injection of 500 mg and 1 g, cefazolin concentrations achieved in the urine (0-6 hours) are 1000/2000 µg/mL and 2000/4000 µg/mL, respectively.

5.3 Preclinical safety data

Reproduction studies conducted in rats at doses of 500 mg and 1 g/kg of cefazolin did not demonstrate any decrease in fertility or foeto-toxic effect of the medicinal product.

Mutagenicity studies and long-term studies to evaluate the carcinogenicity potential of cefazolin have not been performed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cefazolin does not contain any excipients.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 4.2.

6.3 Shelf life

2 years.

6.4 Storage

Store below 25°C, protected from light in the original package.

After reconstitution – from a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2-8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.5 Nature and content of container

Pan-Cefazolin 1 g of powder in a vial (glass); box of 25

6.6 Special precautions for handling and removal

No special requirements.

7. MANUFACTURER:

PANPHARMA
Z.I. du Clairay – Luitré
35133 FOUGÉRES - FRANCE

8. LICENSE HOLDER AND IMPORTER:

Pharmalogic Ltd.,
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9. REGISTRATION NO.:

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