SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
CEZOL 1 g IM/IV Powder for Solution for Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Active substance:
Vial:
Each vial contains 1048.32 mg cefazolin sodium equal to 1000 mg cefazolin.

Ampoule:
Each diluent ampoule contains 4 ml water for injection.

Excipients:
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Powder for solution for injection and diluent

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
CEZOL is indicated in the treatment of the following infections due to susceptible microorganisms:
- Respiratory tract infections
- Urinary system infections
- Skin and soft tissue infections
- Biliary tract infections
- Bone and joint infections
- Genital infections
- Septicemia
- Endocarditis
- Perioperative prophylaxis

4.2 Posology and method of administration
Posology/frequency and duration of administration
CEZOL may be administered by intramuscular, intravenous injection or intravenous infusion after reconstitution. The dosage and route of administration must be determined based on age, body weight of patient, the type of infection and sensitivity of organism caused to infection.

Adults

The type of infection	Dose	Frequency of administration
Moderate to severe infections	500 mg - 1 g	Every 6-8 h
Mild infections caused by susceptible gram positive cocci	250-500 mg	Every 8 h
Acute uncomplicated urinary tract infections	1 g	Every 12 h
Pneumococcal pneumonia	500 mg	Every 12 h
Severe, life-threatening infections (e.g. endocarditis, septicemia)*	1 g-1.5 g	Every 6 h

*In rare instances, doses up to 12 g per day have been used.

Perioperative prophylactic use
To prevent postoperative infection in contaminated or potentially contaminated surgery, the recommended doses are as follows:

a. 1 gram intravenously or intramuscularly administered ½ to 1 hour prior to the start of surgery.
b. For lengthy operative procedures (e.g. 2 hours or longer), 500 mg to 1 g intravenously or intramuscularly during surgery (administration modified according to the duration of the operative procedure)
c. 500 mg to 1 gram intravenously or intramuscularly every 6 to 8 hours for 24 hours postoperatively.

It is important that the preoperative dose be given just (½ to 1 hour) prior to the start of surgery so that adequate antibiotic levels are present in the serum and tissues at the time of initial surgical incision. Additionally, CEZOL may be administered, if necessary, at appropriate intervals during surgery to provide sufficient levels of the antibiotic at the anticipated moments of greatest exposure to infective organisms.
In surgery such as open-heart surgery and prophylactic arthroplasty where the occurrence of infection may be particularly devastating, the prophylactic administration may be continued for 3 to 5 days following the completion of surgery.

Method of administration:
CEZOL may be administered by intramuscular, intravenous injection or intravenous infusion after reconstitution. It should not be used by intrathecal administration.

Preparation of Parenteral Solution and Administration
Parenteral drug products should be shaken well after reconstituted, and inspected visually for particulate matter prior to administration. If particulate matter is evident in prepared solution, it must not be used.

Intramuscular administration
CEZOL 1 g IM/IV Powder for Solution for Injection should be dissolved in 4 ml water for injection (accompanying diluent) or 3 ml 0.5% lidocaine hydrochloride solution to prepare intramuscular injection. The prepared solution should be injected into a large muscle mass (e.g. gluteal region). Solutions prepared with lidocaine hydrochloride should never be administered intravenously**.**

Intramuscular administration should be used only when intravenous administration is difficult and the following precautions should be exercised:
- The duration of intramuscular therapy should be kept to the absolute minimum. Repeated injections at the same site should be avoided. Repeated injections should be avoided in low birth weight infants, newborns, infants or children.
- Do not inject at innervated sites.
- If insertion of the injection needle evokes intense pain, or if blood flows back into the syringe, withdraw the needle immediately and inject at a different site.
- Solutions prepared for intramuscular administration must not be used for intravenous injection.
- Intramuscular injection may cause pain or induration at the injection site.

Intravenous administration
Solutions prepared with lidocaine hydrochloride should never be administered intravenously.

As intravenous doses may cause vascular pain or thrombophlebitis, the rate of injection should be as

slow as possible to avoid such complications. Careful reconstitution, injection site selection and using proper injection technique should be implemented.

Intravenous injection
CEZOL 1 g IM/IV Powder for Solution for Injection should be dissolved with 4 ml water for injection (accompanying diluent), or 0.9% sodium chloride solution, or 5% dextrose solution as diluent to prepare intravenous administration. Prepared solution may be injected slowly (3 to 5 minutes) directly into a vein or through latex tubing for patients receiving parenteral fluids.

Intravenous infusion
After preparation as indicated in the intravenous injection section, CEZOL 1 g IM/IV Powder for Solution for Injection may be administered by intermittent or continuous infusion by diluting it in a volume of 50-100 ml with any of the following solutions:
0.9% sodium chloride
5% dextrose in lactated Ringer
5% dextrose + 0.9% sodium chloride
5% dextrose + 0.45% sodium chloride
5% dextrose + 0.2% sodium chloride
Lactated Ringer
Ringer's solution
5% sodium bicarbonate solution

Additional information on special populations

Renal impairment
In patients with renal impairment, dosage may be adjusted as described following after an initial loading dose appropriate to the severity of the infection. In patients with a creatinine clearance ≥55 ml/min or serum creatinine ≤1.5 mg/dl, dose adjustment is not required. Patients with a creatinine clearance between 35-54 ml/min or serum creatinine between 1.6-3 mg/dl can also be given full doses but dosage should be restricted to at least 8 hour intervals. Patients with a creatinine clearance between 11-34 ml/min or serum creatinine between 3.1-4.5 mg/dl should be given half the usual dose every 12 hours. Patients with a creatinine clearance ≤10 ml/min or serum creatinine ≥4.6 mg/dl should be given half the usual dose every 18 to 24 hours.

Hepatic impairment
If hepatic side effects are seen during treatment, the medicine should be discontinued.

Pediatric population
In children, a total daily dosage of 25 to 50 mg/kg of body weight, divided into 3 or 4 equal doses, is effective for most mild to moderately severe infections. Total daily dosage may be increased to 100 mg/kg for severe infections. Since efficacy and safety for use in premature infants and in infants under 1 month of age has not been established, it is not recommended for use in these patients. Following dosage tables may be used in pediatric patients:

25 mg/kg/day

Body weight	Average dose every 8 hours	Average dose every 6 hours
4.5 kg	40 mg	30 mg
9 kg	75 mg	55 mg
13.6 kg	115 mg	85 mg
18.1 kg	150 mg	115 mg
22.7 kg	190 mg	140 mg

50 mg/kg/day

Body weight	Average dose every 8 hours	Average dose every 6 hours
4.5 kg	75 mg	55 mg
9 kg	150 mg	110 mg
13.6 kg	225 mg	170 mg
18.1 kg	300 mg	225 mg
22.7 kg	375 mg	285 mg

Dosage in pediatric patients with renal impairment
Dosage should be adjusted as following after an initial normal loading dose: In pediatric patients with mild to moderate renal impairment (creatinine clearance of 70-40 ml/min) 60% of the normal daily dose divided into two doses every 12 hours is sufficient. In children with moderate impairment (creatinine clearance of 40-20 ml/min), 25% of the normal daily dose divided into two doses every 12 hours is sufficient. In pediatric patients with severe renal impairment (creatinine clearance of 20-5 ml/min), 10% of the normal daily dose every 24 hours should be given.

Geriatric population
In elderly patients, caution should be exercised in the following conditions. Medicine should be used with caution; dose and dose intervals of patients, should be carefully determined according to clinical monitoring.
- In elderly patients, side effects due to reduced physiological functions tend to be more frequent.
- Caution should be exercised in elderly because of bleeding tendency due to vitamin K deficiency.

4.3 Contraindications
It should not be used in patients with hypersensitivity to cephalosporin group of antibiotics.
It should also not be used in individuals who are hypersensitive to amide-type local anesthetics and in those with heart block.

4.4 Special warnings and precautions for use
Before therapy with CEZOL is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to cefazolin, cephalosporins, penicillins or other medicines. If CEZOL is given to penicillin-sensitive patients, caution should be exercised because cross-hypersensitivity among beta-lactam antibiotics has been documented and may occur in up to 10% of patients with a history of penicillin allergy. If an allergic reaction occurs, CEZOL treatment should be stopped. In severe acute hypersensitivity reactions, other emergency treatments may be necessary depending on the clinical situation, including adrenaline and oxygen, intravenous fluids, intravenous antihistamines, corticosteroids, pressoramines, and maintaining an open airway. All emergency facilities should be prepared before administration, and patients should be kept under careful observation throughout the administration and until the drug is administered.

Caution should be exercised in the following patients groups:
- Patients with a personal or familial history to bronchial asthma, rash, or urticaria.
- Patients with severe renal impairment
- Patients with poor oral nutrition, patients receiving parenteral nutrition, or patients in debilitated states (since vitamin K deficiency may develop in these patients, careful examination should be performed)
- Elderly patients

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including cefazolin. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

After pseudomembranous colitis has been diagnosed, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an oral antibacterial drug clinically effective against *Clostridium difficile*.

Caution should be exercised during long-term cefazolin therapy as overgrowth of non-susceptible organisms may occur.

Cefazolin should be used in lower doses in patients with decreased urine output due to decreased renal function (see section 4.2).

As with other beta-lactam antibiotic treatments, convulsions may occur if very high doses are administered to patients with impaired renal function (see section 4.2).

Cefazolin should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Cephalosporins may be associated with a fall in prothrombin activity. Those at risk include patients with renal or hepatic impairment or poor nutritional state, as well as patients receiving a protracted course of antimicrobial therapy, and patients previously stabilized on anticoagulant therapy. Prothrombin time should be monitored in patients at risk and exogenous vitamin K administered as indicated.

Safety and efficacy of cefazolin in premature infants and neonates have not been established. See section 4.2 for use in babies older than 1 month.

This medicinal product contains 2.2 mmol (or 50.6 mg) sodium in each ampoule. To be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

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

If concomitant used with cefazolin, effects of warfarin may be increased. Combined use of cefazolin with diuretics may increase renal impairment.

Effects of BCG and Typhoid vaccine may be decreased by cefazolin.

Interaction with laboratory tests
A false-positive reaction for glucose in the urine may occur with Benedict's solution, Fehling's solution or with Clinitest tablets however a false-positive reaction has not been observed with enzyme-based tests.

Positive direct and indirect antiglobulin (Coombs) tests have occurred. These may also occur in neonates whose mothers received cephalosporins before delivery.

Additional information on special populations
There is no study conducted with special populations.

4.6 Pregnancy and lactation
General recommendation
Pregnancy category: B

Women of childbearing potential/Birth control (Contraception)
There is no suggestion as to use of the medicine for women of childbearing potential and women currently using a birth control (contraceptive) method.

Pregnancy
Since there are no adequate number of controlled studies in pregnant women, it should not be used during pregnancy unless necessary.
When cefazolin has been administered prior to caesarean section, drug levels in cord blood have been approximately one quarter to one third of maternal drug levels. However, no adverse effects of cefazolin on the fetus were detected.

Breast-feeding
It has been reported that cefazolin is secreted in breast milk. It is therefore advisable to avoid taking this product in breastfeeding women. If use of the product is judged to be essential, breastfeeding must be discontinued during treatment.

Reproductive ability/Fertility
Animal studies have revealed no direct or indirect harmful effects on pregnancy/embryonal/fetal development/parturition or post-natal development (See section 5.3).

4.7 Effects on ability to drive and use machines
There is no known effect on the ability to drive and use machines.

4.8 Undesirable effects
The frequency of adverse reactions is classified as follows:
Very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1000, <1/100); rare (≥1/10,000, <1/1000); very rare (<1/10,000); not known (cannot be estimated from the available data)

Blood and lymphatic system disorders:
Common: Granulocytopenia, eosinophillia
Rare: Pancytopenia, agranulocytosis, hemolytic anemia or thrombocytopenia, Vitamin K deficiency, Vitamin B deficiency

Nervous system diseases:
Not known: Convulsion

Respiratory, thoracic and mediastinal disorders:
Rare: Interstitial pneumonia or PIE syndrome

Gastrointestinal diseases:
Common: Nausea, vomiting
Rare: Severe colitis (pseudomembranous colitis)

Skin and subcutaneous tissue disorders:
Common: Skin rash, urticaria, skin redness
Rare: Mucocutaneous ocular syndrome (Stevens-Johnson syndrome) or toxic epidermal necrolysis (Lyell's syndrome)

Hepato-biliary disorders:
Common: Increase in AST (GOT), ALT (GPT) or ALP
Rare: Hepatitis

Renal and urinary tract infection:
Common: Increase in BUN
Rare: Severe renal impairment (such as acute kidney failure), increased blood creatinine

General disorders and administration side diseases:
Rare: Shock, anaphylactoid reactions, candidiasis, headache, dizziness, general fatigue, vitamin B deficiency (glossitis, stomatitis, anorexia, or neuritis)

*In the event of such reactions observed during treatment, therapy should be discontinued and appropriate measures should be taken.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is essential. It allows continued monitoring of the benefit/risk ratio of the medicinal product. Healthcare professionals should report any suspected adverse reaction via the national reporting system.

4.9 Overdose and treatment
Signs and symptoms: The administration of large doses of parenteral cephalosporins may cause dizziness, paresthesia, and headaches. Convulsions may occur with some cephalosporins, particularly in patients with renal impairment in whom accumulation is likely to occur. In laboratory tests, elevations in creatinine, BUN, liver enzymes and bilirubin level, a positive Coombs' test, thrombocytosis, thrombocytopenia, eosinophilia, leucopenia, and prolongation of the prothrombin time may occur.

Treatment: Supportive therapy should be instituted in managing severe overdosage. Hematologic, renal, and hepatic functions as well as coagulation should be monitored until the patient is stabilized. In particular, malnutrition, prolonged duration of the treatment, hepatic or renal impairment may lead to increase in the INR. If convulsion occurs, treatment should be discontinued promptly. Anticonvulsant therapy may be administered if clinically indicated.

In cases of severe overdosage, especially in a patient with renal failure, hemodialysis and hemoperfusion may be considered; however, no data supporting such therapy are available.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Cephalosporin group antibacterial
ATC code: J01DB04

Cefazolin is a bactericidal first-generation cephalosporin antibiotic that affects the final stage of bacterial cell wall synthesis in Gram-negative and Gram-positive bacteria.

Microbiological properties

In vitro tests demonstrate that the bactericidal action of cephalosporins results from inhibition of cell wall synthesis. Cefazoline is active against the following organisms *in vitro* and in clinical infections:
Staphylococcus aureus (including penicillinase-producing strains), *Staphylococcus epidermidis* (methicillin-resistant staphylococci are uniformly resistant to cefazolin), Group A beta-hemolytic streptococci and other strains of streptococci (many strains of enterococci are resistant), *Streptococcus pneumonia, Escherichia coli, Proteus mirabilis, Klebsiella* species*, Enterobacter aerogenes, Haemophilus influenza.*

Most strains of indole positive *Proteus* (*Proteus vulgaris*), *Enterobacter cloacae*, *Morganella morganii*, and *Providencia rettgeri, Serratia, Pseudomonas,* are resistant to cefazolin.

5.2 Pharmacokinetic properties

General properties

Absorption:
After intramuscular administration of cefazolin to healthy volunteers, the mean serum concentrations were 37 µg/ml at 1 hour and 3 µg/ml at 8 hours following a 500 mg dose, and 64 µg/ml at 1 hour and 7 µg/ml at 8 hours following a 1 g dose.

Studies have shown that following intravenous administration of cefazolin to healthy volunteers, mean serum concentrations peaked at approximately 185 µg/ml and were approximately 4 µg/ml at 8 hours for a 1 g dose.

In a study using healthy volunteers of constant intravenous infusion with dosages of 3.5 mg/kg for 1 hour (approximately 250 mg) and 1.5 mg/kg the next 2 hours (approximately 100 mg), cefazolin produced a steady serum level at the third hour of approximately 28 µg/ml.

Studies in patients hospitalized with infections indicate that cefazolin produces mean peak serum levels approximately equivalent to those seen in healthy volunteers.

Distribution and Biotransformation
Bile levels in patients without obstructive biliary disease can reach or exceed serum levels by up to 5 times; however, in patients with obstructive biliary disease, bile levels of cefazolin are considerably lower than serum levels (<1 µg/ml).

In synovial fluid, the level of cefazolin becomes comparable to that reached in serum at about 4 hours after drug administration.

Studies of cord blood show prompt transfer of cefazolin across the placenta. Cefazolin is present in very low concentrations in the milk of nursing mothers.

Cefazolin is barely metabolized in the liver.

Elimination
The serum half-life for cefazolin is approximately 1.8 hours following intravenous administration and approximately 2 hours following intramuscular administration.
Cefazolin is excreted unchanged in the urine. In the first 6 hours approximately 60% of the drug is excreted in the urine and this increases to 70% to 80% within 24 hours. Cefazolin achieves peak urine concentrations of approximately 2,400 µg/ml and 4,000 µg/ml respectively following 500 mg and 1 g intramuscular doses.

In patients undergoing peritoneal dialysis (2 l/h.), cefazolin produced mean serum levels of 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). Intraperitoneal administration of cefazolin is usually well tolerated.

5.3 Preclinical safety data
Animal studies have revealed no direct or indirect harmful effects on pregnancy/embryonal/fetal development/parturition or post-natal development.

Acute toxicity (LD_{50} g/kg)

	Mice		Rats	
	Male	**Female**	**Male**	**Female**
Intravenous	5.4	5	3.3	3
Intraperitoneal	6.2	6.2	7.4	7.6
Subcutaneous	7.6	9	11	10

Subacute and chronic toxicity
Doses up to 4000 mg/kg/day were administered subcutaneously, intraperitoneally or intravenously to Spraque Dawley rats and beagle dogs for 1-6 months, but no abnormal findings were observed other than mild local damage at the injection site.

Carcinogenicity/Mutagenicity/Teratogenicity
No long-term animal studies and mutagenicity studies have been performed to determine the carcinogenic potential of CEZOL.
In fetal organogenesis period no teratogenic effects were observed in ICR mice and Sprague-Dawley rats subcutaneously or intravenously administered with 250-4000 mg/kg/day cefazolin and in white Japanese rabbits subcutaneously administered with 64-125 mg/kg/day cefazolin.

Effects on the kidneys
No evidence of renal abnormality has been revealed in subacute and chronic toxicity studies performed on rats and dogs; however, renal toxicity has been observed in white Japanese rabbits when they are administered subcutaneously with doses of 500 mg/kg/day or greater, or intravenously with doses of 250 mg/kg/day or greater.

6. PHARMACEUTICAL PARTICULARS
6.1 List of excipients

In each diluent ampoule:
Water for injection

6.2 Incompatibilities
Mixing of the reconstituted solution with other antibiotics (including aminoglycosides) is not recommended before administration.

6.3 Shelf life
Shelf life is 48 months.

6.4 Special precautions for storage
Before reconstitution, store at room temperature below 25°C, protected from light.
After reconstitution the product should be used immediately.

6.5 Nature and contents of container
In the box, 1 colorless Type III glass vial, closed with rubber stopper and sealed with aluminum cap and 1 colorless Type I glass ampoule containing 4 ml water for injection as diluent.
Each carton box contains 1 vial and 1 diluent ampoule.

6.6 Special precautions for disposal and other handling
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORIZATION HOLDER
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8. MARKETING AUTHORIZATION NUMBER
195/19

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION
Date of first authorization : 17.04.2000
Date of last renewal : 17.04.2010

10. DATE OF REVISION OF THE TEXT