Cefazolin-VIT

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Cefazolin-VIT

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Cefazolin-VIT powder for solution for injection or infusion.
Each vial contains 1.048 g cefazolin sodium (equivalent to 1.0 g cefazolin).

Excipient(s) with known effect:
The sodium content of each vial is 2.2 mmol (50.6 mg).

3. PHARMACEUTICAL FORM

Powder for solution for injection or infusion.
The powder is white or almost white.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of serious infections caused by susceptible organisms and also perioperatively for prophylaxis.
Treatment Respiratory tract:
Respiratory tract infections due to streptococcus pneumoniae (formerly diplococcus pneumoniae), klebsiella species, haemophilus influenzae, staphylococcus aureus (penicillin-sensitive and penicillin-resistant) and group A beta-hemolytic streptococci.
Cefazolin is effective in the eradication of streptococci from the nasopharynx. However, data establishing the efficacy of cefazolin in the subsequent prevention of rheumatic fever are not available at present.
Urinary tract:
Infections due to escherichia coli, klebsiella species, proteus mirabilis and some strains of Enterobacter and enterococci.
Skin and skin structure:
-hemolytic beta Infections due to Staphylococcus aureus (penicillin-sensitive and penicillin-resistant) group A 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 (i.e. prostatitis epididymitis) due to escherichia coli, proteus mirabilis, klebsiella species and some strains of enterococci.
Septicemia due to streptococcus pneumoniae (formerly diplococcus pneumoniae), staphylococcus aureus (penicillin-sensitive and penicillin-resistant), proteus mirabilis, escherichia coli and klebsiella species.
Endocarditis caused by staphylococcus aureus (penicillin-sensitive and penicillin-resistant) and group A beta-hemolytic streptococci.
Appropriate culture and susceptibility studies should be performed to determine the susceptibility of the causative organism to cefazolin.
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 (e.g. hysterectomy, gastrointestinal surgery and transurethral prostatectomy) 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 (e.g. open-heart surgery and prosthetic arthroplasty).

4.2 Posology and method of administration

Posology
The dosage depends on the susceptibility of the pathogens, and the severity of the disease.

Adults
The usual dosage in adults is shown in the following table:

Type of infection	Dose	Dosing interval	Total daily dose
Mild infections (caused by Gram-positive pathogens)	500 mg	every 8 hours	1.5 g
	1 g	every 12 hours	2 g
Uncomplicated urinary tract infections	1 g	every 12 hours	2 g
Moderate to severe infections (caused by Gram-negative pathogens)	1 g	every 6 - 8 hours	3 g – 4 g
Life-threatening infections	1 g -1.5 g	every 6 hours	4 g – 6 g

In individual cases, doses of up to 12 g were administered.

In adult patients with renal insufficiency, the dosage regimen below should be followed:

Creatinine clearance (ml/min/1.73 m²)	Serum creatinine (mg/100 ml)	Total daily dose	Dosing interval
≥ 55	≤1.5	usual dose	unchanged
35-54	1.6-3.0	usual dose	12-hour interval
11-34	3.1-4.5	half the usual dose	12-hour interval
≤ 10	≥ 4.6	quarter the usual dose	24-hour interval

In patients undergoing haemodialysis, the dosage regimen depends on the conditions of dialysis.

For perioperative use to prevent infections, doses depend on the type and duration of surgery. The doses below are recommended:
30 minutes to 1 hour prior to surgery an initial dose of 1 g to 2 g is administered I.V. or I.M. For longer surgeries (2 hours or more) another dose of 500 mg to 1 g is administered I.V. or I.M. intraoperatively. The dose level and the timing depend on the type and duration of surgery.
Postoperatively, 500 mg to 1 g are administered I.V. or I.M. at intervals of 6 to 8 hours for 24 hours.

If potential infections are likely to be very dangerous for the patient (e.g. after cardiac surgery or major orthopaedic surgery such as total joint replacement), it is advisable to continue postoperative dosing for 24 up to 48 hours.

Elderly patients
No dose adjustments are needed in elderly patients with normal renal function.

Paediatric population
A total daily dose of 25 - 50 mg/kg body weight divided in 3 - 4 single doses, is effective in most mild to moderate infections.
In severe infections, the total dose may be increased to the maximum recommended dose of 100 mg/kg body weight.

Dose instructions for infants, toddlers and children (indicative values)

Body weight	25 mg/kg daily in 3 doses		25 mg/kg daily in 4 doses	
	dosing intervals of approx. 8 hours	volume to be withdrawn at a concentration of 125 mg/ml	dosing intervals of approx. 6 hours	volume to be withdrawn at a concentration of 125 mg/ml
4.5 kg	40 mg	0.35 ml	30 mg	0.25 ml
9.0 kg	75 mg	0.6 ml	55 mg	0.45 ml

13.5 kg	115 mg	0.9 ml	85 mg	0.7 ml
18.0 kg	150 mg	1.2 ml	115 mg	0.9 ml
22.5 kg	190 mg	1.5 ml	140 mg	1.1 ml

Body weight	50 mg/kg daily in 3 doses		50 mg/kg daily in 4 doses	
	dosing intervals of approx. 8 hours	volume to be withdrawn at a concentration of 225 mg/ml	dosing intervals of approx. 6 hours	volume to be withdrawn at a concentration of 225 mg/ml
4.5 kg	75 mg	0.35 ml	55 mg	0.25 ml
9.0 kg	150 mg	0.7 ml	110 mg	0.5 ml
13.5 kg	225 mg	1.0 ml	170 mg	0.75 ml
18.0 kg	300 mg	1.35 ml	225 mg	1.0 ml
22.5 kg	375 mg	1.7 ml	285 mg	1.25 ml

Neonates: Safety of use in neonates has not been established (see section 4.4).

Children with renal insufficiency

Creatinine clearance (ml/min/1.73 m^2)	Dose of cefazolin (mg/kg)	Dosing interval (h)
> 50	7 (up to 500 mg/dose)	6-8
25-50	7	12
10-25	7	24-36
< 10	7	48-72

Children undergoing haemodialysis are given 7 mg/kg body weight at the beginning of treatment. As cefazolin serum levels drop by 35% to 65% during dialysis, a dose of 3 to 4 mg/kg body weight is administered between dialysis sessions (dialysis interval = 72 hours).

Duration of treatment

The duration of treatment depends on the course of the disease. In keeping with the general principles of antibiotic therapy, cefazolin should be continued for at least 2 to 3 days after the fever has subsided or proof is obtained for the eradication of the pathogens.

Method of administration

The prepared solution is administered by deep intramuscular or intravenous injection.
See also section 6.6.

Intramuscular administration

For I.M. administration the medicine should be dissolved in water for injections.
Intramuscular doses (max. 1 g) should be injected into a large muscle mass.

The I.M. administration should only be used for uncomplicated infections.
Reconstitute with water for injections according to the following dilution table:

Vial size	Volume of solvent
1 g	4 ml

Intravenous administration
For preparation of solutions for I.V. injection or infusion, the powder is dissolved in water for injections.
Cefazolin-VIT- powder for solution for injection or infusion:
For each gram of powder, at least 4 ml of the solvent must be used.
Preparation of solution for I.V. infusion: The reconstituted solution (prepared as described above) has to be transferred into a suitable infusion bag or bottle with 50-100 ml of one the following diluents:
- 0.9% Sodium Chloride
- Lactated Ringer's Injection
- 5% Glucose and 0.9% Sodium Chloride
- 10% Glucose Injection
- 5% Glucose Injection

Intermittent intravenous infusion
Higher daily doses (4-6 g in 2-3 single doses) are administered by I.V. infusion (over 20 to 30 minutes).

Direct intravenous injection
Up to a dose of 1 g cefazolin may be administered by slow I.V. injection (3-5 minutes) made directly into a vein or through the cannula.

For instructions on reconstitution of the medicinal product before administration, see section 6.4.

4.3 Contraindications

Hypersensitivity to the active substance or other cephalosporins or to any of the excipients.
History of previous immediate and/or severe hypersensitivity reaction to a penicillin or to any other type of beta-lactam drug.

Simultaneous administration is Contraindicated
Antibiotics
Cefazolin must not be used together with antibiotics which have a bacteriostatic mode of action (e.g. tetracyclines, sulfonamides, erythromycin, chloramphenicol) since antagonistic effects were observed in *in-vitro* tests (see section 4.5).

4.4 Special warnings and precautions for use

- Special precaution should be exercised in patients with an allergic diathesis, with bronchial asthma or hay fever. Before the administration of cefazolin previous hypersensitivity reactions to other beta-lactams (penicillins or cephalosporins) should be investigated.
- In patients developing allergic reactions the drug should be discontinued and appropriate symptomatic treatment should be instituted. Cross allergies with other cephalosporins and occasionally occurring cross allergies with penicillins should be considered. In cases of known hypersensitivity to penicillins, a cross-allergy to other beta-lactams such as cephalosporins should be taken into account.
- Serious and occasionally fatal hypersensitivity reactions (anaphylaxis) have been reported in patients treated with beta-lactam antibiotics (see section 4.8). These reactions are more likely to occur in individuals with a history of beta-lactam hypersensitivity.
- In the case of severely impaired renal function with a glomerular filtration rate below 55 ml/min, accumulation of cefazolin can be expected; therefore, the dose should be reduced accordingly or the dosing interval extended (see section 4.2). Although cefazolin seldom causes renal impairment, it is recommended to monitor the renal function, especially in severely ill patients, who are administered maximum doses and in patients who receive other potentially nephrotoxic drugs concomitantly, such as aminoglycosides or potent diuretics (e.g. furosemide).
- In rare cases, coagulation disorders may occur during cefazolin treatment. Patients at risk are those with risk factors causing vitamin K deficiency or affecting other coagulation mechanisms (parenteral nutrition, dietary deficiencies, impaired hepatic and renal function, thrombocytopenia). Blood clotting may also be disrupted in case of associated diseases (e.g. haemophilia, gastric and duodenal ulcers) causing or aggravating haemorrhages. Prothrombin time should, therefore, be monitored in patients presenting with these diseases. If these values are reduced, vitamin K (10 mg/week) should be supplemented.
- *Antibiotic-related pseudomembranous colitis*
  Cases of antibiotic-associated colitis have been reported in almost all antibiotics, the severity of which can range from mild to life threatening (see section 4.8). Therefore, it is important to be mindful of this diagnosis in patients who experience diarrhoea during or after using an antibiotic. In the event of antibiotic-associated colitis, cefazolin should be discontinued immediately, a doctor consulted, and appropriate treatment initiated. Anti-peristaltic medicinal products are contraindicated in this situation.
- With long-term use of cefazolin, non-sensitive pathogens can get out of control. Close monitoring of the patient is therefore essential. If a superinfection occurs during treatment, appropriate measures must be taken.
- *Long-term or high-dose therapy*
  Regular check of organ system functions, including renal, hepatic and hematopoietic function, is advisable during long-term or high-dose treatment. Elevated liver enzymes and changes in blood cells have been reported (see section 4.8).
- In patients with hypertension or heart failure the sodium content of the solutions for injection should be taken into account (50.6 mg per 1 g cefazolin).
- <u>Paediatric population</u>
  Cefazolin should not be administered to premature and newborn infants of less than 1 month

of age as no data is available and the safety of use has not been established.

- *Intrathecal administration*

  Not for intrathecal administration. Severe central nervous system intoxications (including convulsions) were reported following intrathecal administration of cefazolin.

- **Cefazolin-VIT** contains sodium

  This medicinal product contains 50.6 mg sodium per vial, equivalent to 2.5 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

Simultaneous administration is Contraindicated

Antibiotics

Cefazolin must not be used together with antibiotics which have a bacteriostatic mode of action (e.g. tetracyclines, sulfonamides, erythromycin, chloramphenicol) since antagonistic effects were observed in *in-vitro* tests.

Concomitant administration is not recommended

Probenecid

The renal clearance of cefazolin is reduced when probenecid is co-administered.

Precautions

Vitamin K1

Some cephalosporins such as cefamandol, cefazolin and cefotetan may interfere with the metabolism of vitamin K1, especially in cases of vitamin K1 deficiency. This may require vitamin K1 supplementation.

Anticoagulants

Cephalosporins may very rarely lead to blood coagulation disorders (see section 4.4). If oral anticoagulants or high dosage heparin are concomitantly used, coagulation parameters should be monitored.

Nephrotoxic agents

An increase in nephrotoxic effects of antibiotics (e.g. aminoglycosides, colistin, polymyxin B) and diuretics (e.g. furosemide) cannot be ruled out. Renal values should be carefully monitored when these medicinal products are co-administered with cefazolin.

Laboratory tests

Laboratory tests for urinary glucose concentrations may give false positive readings if based on Benedict's solution, Fehling's solution or Clinitest® tablets. However, cefazolin does not affect enzyme-based tests.

Both the indirect and the direct Coombs test may also give false positive readings, e.g. in newborns whose mothers received cephalosporins.

4.6 Fertility, pregnancy and lactation

Pregnancy
To date there is insufficient experience on use of cefazolin during pregnancy in humans, therefore it should only be used during pregnancy, especially during the first trimester, after careful benefit-risk evaluation. Cefazolin crosses the placenta.

Lactation
Cefazolin is excreted into human milk at low concentration. Cefazolin can cause sensitization and change in the intestinal flora, as well as candida infections in breast-fed infants. In these cases, breast-feeding should be stopped during treatment.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, there may be side effects (e.g. allergic reactions, dizziness) which may affect the ability to drive and use machines (see section 4.8).

4.8 Undesirable effects

The meaning of the named frequencies is as follows: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data):

System organ class	Common	Uncommon	Rare	Very rare	Not known
Infections and infestations			Rhinitis		Long-term or repeated use may lead to superinfection or colonisation with resistant bacteria or yeasts (oral thrush, monoliasis vaginalis)
Blood and lymphatic system disorders		Thrombocytopenia, neutropenia, leucopenia, eosinophilia, agranulocytosis,	Coagulation disorders, haemorrhages*		

		haemolytic anaemia, granulocytosis, leukocytosis, monocytosis, lymphocytopenia, basophilia			
Immune system disorders	Allergic skin reactions such as erythema, urticaria and pruritus	Severe hypersensitivity reactions such as angioedema and drug-induced fever		Life threatening anaphylactic shock **	
Metabolism and nutrition disorders			Hyperglycaemia, hypoglycaemia		
Nervous system disorders			dizziness		convulsions §
Respiratory, thoracic and mediastinal disorders			Pleural effusion, dyspnoea or respiratory distress, cough		
Gastrointestinal disorders	Diarrhoea, nausea, vomiting, loss of appetite				Pseudomembranous colitis +
Skin and subcutaneous tissue disorders	Rash	Erythema multiforme, angioedema	Toxic epidermal necrolysis, Stevens-Johnson syndrome		
Hepatobiliary disorders		Slight, transient elevation of AST, ALT and alkaline phosphatase	Temporary increase in GGT, bilirubin and/or LDH	Reversible hepatitis and cholestatic jaundice	
Renal and urinary disorders			Interstitial nephritis and other kidney diseases $		
General disorders and administration site conditions		Phlebitis, thrombophlebitis	Malaise, fatigue, chest pain		

* Patients at risk for these effects are those with vitamin K deficiency or other factors leading to coagulation disturbances and patients with diseases that induce or intensify bleedings.
** which may necessitate immediate intensive care.
§ Especially in case of overdosing or unadjusted dosing in renal failure.
# In most cases, the symptoms are only mild and often disappear during or after the treatment.
+ In cases of severe and persistent diarrhoea during or after the treatment with cefazolin a physician should be consulted because this could be the symptom of a serious disease (pseudomembranous colitis) that must be treated immediately (e.g. with oral vancomycin 250 mg qid). The patients should refrain from any self-medication with peristalsis-inhibiting drugs.
$ Mostly in severely ill patients receiving additional drugs.

In cases of severe and persistent diarrhoea during or after the treatment with cefazolin, a physician should be consulted because this could be the symptom of a serious disease (pseudomembranous colitis) that must be treated immediately. The patients should refrain from any self-medication with peristalsis inhibiting medicinal products (see section 4.4). Prolonged use of a cephalosporin may result in the overgrowth of cefazolin-resistant bacteria, especially Enterobacter, Citrobacter, Pseudomonas, Enterococci, or Candida.

Studies
Transient increase in SGOT, SGPT, blood urea and alkaline phosphatase without clinical evidence of renal or hepatic damage. Animal data has shown that a potential nephrotoxicity with cefazolin exists. Although not demonstrated in humans, this possibility should nevertheless be considered especially in patients receiving high doses administered over longer periods. Interstitial nephritis and undefined nephropathies have been reported in rare cases. The patients affected were seriously ill and had several medications administered. The role of cefazolin in the development of interstitial nephritis and other nephropathies has not been established.

In rare cases the following have been reported:
Decreased haemoglobin and/or hematocrit, anaemia, aplastic anaemia, pancytopenia and haemolytic anaemia.

The following cases have been reported during treatment with certain cephalosporins:
Nightmares, vertigo, hyperactivity, nervousness or anxiety, insomnia, drowsiness, weakness, hot flushes, disturbed colour vision, confusion and epileptogenic activity.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il

4.9 Overdose

Symptoms of overdose:

Overdosing may cause pain, inflammatory reactions and phlebitis at the injection site. If administered in very high parenteral doses, cephalosporins may cause vertigo, paresthesias and headache. Particularly in patients with renal disease, overdosing of cephalosporins may induce convulsions.
Overdose may be associated with the following abnormal laboratory tests results: Elevated creatinine, BUN, liver enzymes and bilirubin; positive Coombs test; thrombocytosis and thrombocytopenia, eosinophilia, leukopenia as well as prolonged prothrombin time.

Treatment of overdose*:*
In case of seizures, administration of the medicinal product should be discontinued immediately. Antiepileptic medicinal products may be appropriate. Vital body functions and parameters should be monitored closely. In the event of severe overdose, especially in patients with renal impairment, a combination of haemodialysis and haemoperfusion may be useful if the patient fails to respond to other treatments. However, no corresponding supporting data are available. Peritoneal dialysis is not effective.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other beta-lactam antibacterials, first-generation cephalosporins.

ATC-Code: J01DB04

Mode of action:
The bactericidal activity of cefazolin results from the inhibition of bacterial cell wall synthesis (during the growth phase) caused by an inhibition of penicillin-binding proteins (PBPs) like transpeptidases.

Pharmacokinetics and pharmacodynamics relationship:
The extent of the bactericidal activity depends on the period of time during which the serum level of the active substance exceeds the minimum inhibitory concentration (MIC) of the pathogen.

Mechanisms of resistance:

A resistance to cefazolin may be caused by the following mechanisms:
- inactivation by beta-lactamases. Cefazolin exhibits a wide stability against penicillinases of gram-positive bacteria, but only a minor stability against numerous plasmid encoded beta-lactamases, e.g. extended-spectrum beta-lactamases (ESBLs) or by chromosomal encoded beta-lactamases of the AmpC type.
- reduced affinity of PBPs to cefazolin. The acquired resistance of Pneumococci and other Streptococci is caused by modifications of already existing PBPs as a consequence of a

mutation process. By contrast, the creation of an additional PBP with reduced affinity to cefazolin is responsible for resistance in methicillin-(oxacillin-)resistant Staphylococcus.
- inadequate penetration of cefazolin through the outer cell membrane of gram-negative bacteria can lead to insufficient inhibition of the PBPs.
- the presence of transport mechanism (efflux pumps) being able to actively transport cefazolin out of the cell.

A partial or complete cross resistance of cefazolin occurs with other penicillins and cephalosporins.

Breakpoints:

The common dilution series is used for testing cefazolin. The following minimum inhibitory concentrations were defined for susceptible and resistant germs:

EUCAST (European Committee on Antimicrobial Susceptibility Testing) break points (2011-01-05, version 10.0):

Pathogen	**Susceptibility**	**Resistance**
1 *Enterobacterales* (only Infections of the urinary tract) [1)]	≤ 0.001 mg/l	> 4 mg/l
2 *Staphylococcus* spp.	[2)]	- [2)]
3 *Streptococcus* spp. (Groups A, B, C, G) [3)]	[3)]	- [3)]
4 Streptococci "Viridans" group	≤ 0.5 mg/l	> 0.5 mg/l
5 Non species-related break points * (exemption: *Staphylococcus* spp.) [2)]	≤ 1 mg/l	> 2 mg/l

[1)] exclusively for *E. coli* and *Klebsiella* spp. (exept for *K. aerogenes*).

[2)] The susceptibility of *Staphylococcus* spp. is inferred from the Oxacillin resp. Cefoxitin susceptibility. Methicillin (Oxacillin/Cefoxitin)-resistant staphylococci are rated resistant against cephalosporines independently of the outcome of the susceptibility testing.

[3)] The beta-lactam susceptibility of streptococcus groups A, B, C and G is inferred from the penicillin susceptibility.

* Based on pharmacokinetic data.

Susceptibility:

The prevalence of acquired resistance may vary geographically and over time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the efficacy of cefazolin in at least some types of infections is questionable.

Commonly susceptible species
Gram-positive aerobes

Staphylococcus aureus (methicillin-susceptible)°
Staphylococcus saprophyticus°
Streptococcus agalactiae°
Streptococcus pneumoniae
Streptococcus pyogenes°
Gram-negative aerobes
Citrobacter koseri
Species for which acquired resistance may be a problem
Gram-positive aerobes
*Staphylococcus aureus*ə
Staphylococcus epidermidis^{+}
Staphylococcus haemolyticus^{+}
Staphylococcus hominis^{+}
Staphylococcus pneumoniae (penicillin-intermediate)
Gram-negative aerobes
Escherichia coli$^{\%}$
Haemophilus influenzae
Klebsiella oxytoca$^{+\%}$
Klebsiella pneumoniae$^{\%}$
Proteus mirabilis$^{\%}$
Inherently resistant species
Gram-positive aerobes
Enterococcus spp.

Staphylococcus aureus (methicillin-resistant)
Staphylococcus pneumoniae (penicillin-resistant)
Gram-negative aerobes
Acinetobacter spp.
Citrobacter freundii
Enterobacter spp.
Legionella spp.
Morganella morganii
Moraxella catarrhalis
Proteus vulgaris
Pseudomonas aeruginosa
Serratia marcescens
Stenotrophomonas maltophilia
Anaerobes
Bacteroides fragilis
Others
Chlamydia spp.
Chlamydophila spp.
Mycoplasma spp.

° Literature data, reference books and therapy guidelines support susceptibility.
+ In at least one region the resistance rate is > 50%.
ɜ In the community the resistance rate is < 10%.
% ESBL producing strains are always resistant.

Further information:
Penicillin-resistant *Streptococcus pneumoniae* are cross-resistant to cephalosporins such as cefazolin.

5.2 Pharmacokinetic properties

Cefazolin is administered parenterally. Maximum serum levels after I.M. injection are reached after 30 to 75 minutes.

Serum concentration (µg/ml) after intramuscular administration

Dose	30 min	1 h	2 h	4 h	6 h	8 h
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

Serum concentration (µg/ml) after intravenous administration of 1 g

5 min	15 min	30 min	1 h	2 h	4 h
188.4	135.8	106.8	73.7	45.6	16.5

About 65-92 % of cefazolin is bound to plasma proteins. Cefazolin penetrates very well into tissues including skeletal muscle, myocardial tissue, bone tissue, bile and gallbladder tissue, endometrium and vaginal tissue. Cefazolin crosses the placenta barrier and is also excreted into human milk. Diffusion into cerebrospinal fluid and aqueous fluid is not sufficient.

Cefazolin is not metabolized. Most of the administered dose undergoes glomerular filtration and is eliminated with the urine in a microbiologically active form. A smaller part is excreted by bile. The plasma elimination half-life is about 2 hours; in patients with renal impairment, this time can be prolonged.

5.3 Preclinical safety data

Repeated administration of cefazolin in dogs and rats with different routes of injection for 1 to 6 months did not show significant effects on biochemical and haematological parameters.
In some studies signs of neurotoxicity were revealed.
After intramuscular injection, cefazolin is poorly tolerated at the injection site.
During studies in rabbits, the kidney appeared as the target organ; this was not the case in rats and dogs.
Cefazolin did not show teratogenic activity and did not affect general reproductive functions.
There are no studies available about mutagenicity and carcinogenicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None

6.2 Incompatibilities

Cefazolin is incompatible with amikacin disulfate, amobarbital sodium, ascorbic acid, bleomycin sulfate, calcium glucoheptonate, calcium gluconate, cimetidine hydrochloride, colistin methane sulfonate sodium, erythromycin glucoheptonate, kanamycin sulfate, oxytetracycline hydrochloride, pentobarbital sodium, polymyxin B sulfate, tetracycline hydrochloride.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Powder for solution for injection: Store below 25°C. Keep in the outer carton in order to protect from light.

After reconstitution:
The chemical-physical stability of the reconstituted product in WFI for I.M. and I.V. administration is maintained for 24 hours at 25 ± 2°C and 10 days at 5 ± 3°C.

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 5 ± 3°C, unless reconstitution has taken place in controlled and validated aseptic conditions.

After dilution:
Chemical and physical in-use stability has been demonstrated for 36 hours if stored at 30 ± 2°C and for 96 hours if stored at 5 ± 3°C for the following diluents normally used for intravenous infusion:
- 0.9% Sodium Chloride
- Lactated Ringer's Injection
- 5% Glucose and 0.9% Sodium Chloride
- 10% Glucose Injection
- 5% Glucose Injection

6.5 Nature and contents of container

Cefazolin-Vit is packed in a 10 ml type III colorless glass vials, sealed with a type I bromobutyl rubber stopper and an aluminum flip-off cap.
Each pack contains 10 vials.

6.6 Special precautions for disposal and other handling

Only use freshly prepared, clear and colourless solutions.
For single use only.
Any unused solution should be discarded.
Inspect the reconstituted solution visually for particulate matter and for discoloration prior to administration. The reconstituted solution is clear.

7. MANUFACTURER

ACS DOBFAR S.P.A.,
Via Alessandro Fleming 2,
37135, Verona, Italy.

8. LICENSE HOLDER AND IMPORTER:

Vitamed Pharmaceutical Industries Ltd.,
6 Hatahana St., P.O.B. 114, Binyamina 3055002, Israel.

9. LICENSE NUMBER:

160-81-35045-00

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