This leaflet format has been determined by the Ministry of Health and the content thereof has been checked and approved in October 2018

1. NAME OF THE MEDICINAL PRODUCT

Cefazolin-VIT

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Cefazolin-VIT- powder for solution for injection
Each vial contains 1.048 g cefazolin as sodium salt (equivalent to 1 g cefazolin) The sodium content of each vial is 2.2 mmol (50.6mg per 1 g cefazolin).
For a full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection

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 B - hemolytic streptococci.
- Cefazolin-VIT is effective in the eradication of streptococci from the nasopharynx.
  However data establishing the efficacy of Cefazolin-VIT 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-VIT.
- Perioperative prophylaxis: The prophylactic administraton of Cefazolin-VIT 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-VIT 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 pathogen sensitivity and the severity of the disease.

Adults
The recommended dosage for adults is shown in the table below:

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

In individual cases, dosages of up to 12 g have been given.

In adult patients with renal dysfunction, the following dosage schedule should be observed:

Creatinine clearance (ml/min x 1.73 m^2)	Serum creatinine (mg/100 ml)	Daily dose	Dosing interval
$\geq$ 55	$\leq$1.5	normal dose	unchanged
35-54	1.6-3.0	normal dose	12-hour interval
11-34	3.1-4.5	half the normal dose	12-hour interval
$\leq$10	$\geq$4.6	quarter of the normal dose	24-hour interval

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

In perioperative use to prevent infection, the dose depends on the type and duration of the surgical procedure. The following dosages are recommended:
30 minutes to one hour before surgery, a starting dose of 1 g to 2 g is administered IV or IM. For surgery of longer duration (2 hours or more), a further 500 mg to 1 g is administered IV or IM during the operation. The dose level and time of administration depend on the nature and duration of the surgical procedure. Postoperatively, 500 mg to 1 g are given IV or IM over 24 hours at intervals of 6 to 8 hours.

If possible infections might be particularly dangerous for the patient (e.g. following heart surgery or major orthopaedic procedures such as joint replacement), it is advisable to continue postoperative administration of cefazolin for 24 to 48 hours after surgery.

Elderly patients
No dose adjustment is necessary for elderly patients with normal renal function.

Children and adolescents
A total daily dose of 25 - 50 mg/kg BW, divided in 3 - 4 single doses, is effective for most mild to moderately severe infections.
For severe infections, the total dose can be increased to the maximum recommended dose of 100 mg/kg BW.

Dosage *instructions for infants. toddlers and children (guideline values)*

Body weight	25 mg/kg daily in 3 doses		25 mg/kg daily in 4 doses	
	Dosing interval approx. 8 hours	Volume to be withdrawn at a concentration of 125 mg/ml	Dosing interval 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	0.7ml
18.0 kg	150 mg	1.2 ml	115 mg	0.9ml
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 interval approx. 8 hours	Volume to be withdrawn at a concentration of 225 mg/ml	Dosing interval 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	0.7ml	110 mg	0.5 ml
13.5 kg	225 mg	1.0 ml	170 mg	0.75 ml
18.0 kg	300mg	1.35 ml	225 mg	1.0 ml
22.5 kg	375 mg	1.7 ml	285 mg ·	1.25 ml

Full-term newborn infants: Safety of use in full-term newborn infants has not been established (see section 4.4).

Children with renal dysfunction

Creatinine clearance (ml/min x 1.73 m^2)	Cefazolin dose (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 BW at the start of the therapy. As the serum cefazolin level is reduced by 35% to 65% during dialysis, a dose of 3 to 4 mg cefazolin/kg BW is administered in the subsequent dialysis-free interval (dialysis interval =72 hours).

Duration of treatment
The duration of treatment depends on the course of the disease. As is customary with antibiotic therapy, cefazolin should be given for a further 2-3 days after the patient has become afebrile or proof is obtained that the pathogens have been eliminated.

Method of administration
The prepared solution is administered deep into the muscle or intravenously (see also section 6.6).

Intramuscular use
· For intramuscular use, the medicine should be dissolved in water for injections. Intramuscular doses (maximum 1 g) should be injected into a large muscle mass. IM administration should be used only for uncomplicated infections. Reconstitution takes place with water for injections according to the following dilution table.

Volume of solvent	Vial size
4ml	1 g

Intravenous use
For preparation of solutions for IV injection or infusion, the powder is dissolved in water for injections.
Cefazolin-VIT- powder for solution for injection:
For each gram of powder, at least 4 ml of the solvent must be used.
Preparation of solution for IV infusion: The reconstituted solution (prepared as described above) has to be transferred into a suitable infusion bag or bottle with 50 - 100 ml of 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 IV infusion (over 20 to 30 minutes).

Direct intravenous injection
Up to a dose of 1g, Cefazolin-VIT can be administered by slow IV injection (over 3 - 5 minutes) directly into a vein or through the cannula.

4.3 Contraindications

This medicinal product must not be used in cases of known hypersensitivity to cefazolin or other cephalosporins and in patients who have previously shown immediate and/or severe hypersensitivity reactions to penicillin or to any other beta-lactam antibiotic.

4.4 Special warnings and precautions for use

Particular caution is required in patients with an allergic diathesis, with bronchial asthma or hay fever. Prior to administering Cefazolin-VIT, previous hypersensitivity reactions to other beta-lactams (penicillins or cephalosporins) must be investigated.

In patients exhibiting allergic reactions, the product must be discontinued and appropriate symptomatic therapy instituted. Serious acute hypersensitivity reactions may require adrenaline (epinephrine) and other emergency measures, including oxygen, i.v. fluids, i.v. antihistamines, corticosteroids, pressor amines and airway management, as clinically indicated.

Cross-allergy with other cephalosporins and occasional cross-allergies with penicillins must be borne in mind. In cases of known hypersensitivity to penicillin, cross-allergy with other beta- lactams, e.g. cephalosporins, must be taken into account. cross-hypersensitivity among beta- lactam antibiotics has been clearly documented and may occur in up to 10% of patients with a history of penicillin allergy.

Severe hypersensitivity reactions (anaphylaxis) with occasional fatal outcomes have been reported in patients undergoing treatment with beta-lactam antibiotics (see section 4.8). These reactions are more likely to occur in persons with a history of known hypersensitivity to beta- lactam antibiotics.

In patients with impaired renal function, the dosage and/or dosing frequency must be adjusted to the degree of renal dysfunction (see section 4.2). As with other β-lactam antibiotics, seizures may occur if inappropriately high doses are administered to patients with impaired renal function.
While cefazolin only rarely causes renal impairment, monitoring of renal function is nonetheless recommended, especially in severely ill patients receiving maximum doses and patients
under concomitant treatment with other potentially nephrotoxic medicinal products, such as aminoglycosides or potent diuretics (e.g. furosemide).

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

Coagulation disorders may rarely occur during treatment with cefazolin. At risk are patients with risk factors leading to vitamin K deficiency or affecting other coagulation mechanisms (parenteral nutrition, malnutrition, impaired hepatic and renal function, thrombocytopenia). The same applies to comorbidities (e.g. haemophilia, gastrointestinal ulcers) that can trigger or aggravate haemorrhages. Prothrombin values should therefore be monitored in such cases. If these values are reduced, vitamin K replacement should be given (10 mg/week).

In the event of severe and persistent diarrhoea, antibiotic-associated pseudomembranous colitis should be considered, which can be life-threatening. Cefazolin should therefore be discontinued immediately in such cases and appropriate therapy instituted. Antiperistaltic agents are contraindicated.

During long-term use of cefazolin, non-sensitive pathogens may proliferate. Patients should therefore be carefully monitored. If superinfection occurs, appropriate measures should be taken. Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by Clostridium difficile is a primary cause of “antibiotic-associated colitis.”

In patients with hypertension or heart failure, the sodium content of the solution for injection must be taken into account (50.6 mg per 1g cefazolin).

Children and adolescents
Cefazolin-VIT should not be administered to premature and newborn infants of less than one month of age, as no experience is available and the safety of such use has not been demonstrated.

Not for intrathecal use.
Prescribing Cefazolin-VIT in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant administration contraindicated
Antibiotics
Cefazolin-VIT must not be administered together with antibiotics with bacteriostatic activity (e.g. tetracyclines, sulphonamides, erythromycin, chloramphenicol), as antagonistic effects have been observed during *in vitro* tests.

Concomitant administration not recommended
Probenecid
Renal clearance of Cefazolin-VIT is reduced when probenecid is co-administered.

Precautions

Vitamin K1
Some cephalosporins such as cefamandole, cefazolin and cefotetan may interfere with the metabolisation of vitamin K1, particularly in cases of vitamin K1 deficiency. Substitution of vitamin K1 may therefore be necessary.

Anticoagulants
Cephalosporins may, in very rare cases, lead to coagulation disorders (see section 4.4.). If oral anticoagulants or high heparin doses are adjuvantly administered, coagulation values must be monitored.
Nephrotoxic substances
It cannot be ruled out that the nephrotoxic effect of antibiotics (e.g. aminoglycosides, colistin, polymyxin B) and diuretics (e.g. furosemide) may be aggravated. If co-administered with cefazolin, renal function tests should be carefully monitored.

Laboratory tests

Laboratory tests may give a false-positive response for urine glucose if Benedict's solution, Fehling's solution or Clinitest® tablets are used, but not when enzyme-based detection methods are applied.
The indirect and direct Coombs' test can also give false-positive results. This may also apply to newborn infants whose mothers have been receiving cephalosporins.

Oral contraceptives
Cefazolin may influence the efficacy of hormonal contraceptives. For this reason, use of additional birth control methods besides hormonal contraceptives is recommended during a course of treatment with Cefazolin-VIT.

4.6 Fertility, pregnancy and lactation

Pregnancy
To date, there. is insufficient experience for the use of Cefazolin-VIT during human pregnancy. Hence, Cefazolin-VIT should only be used during pregnancy after careful benefit/risk assessment. This applies particularly to the first trimester. Cefazolin-VIT crosses the placenta.

Lactation
Cefazolin-VIT is excreted in human milk at low concentrations. In breast-fed infants, sensitisation and changes in the intestinal flora and *Candida* infections may occur. In these cases, breast- feeding should be suspended during treatment.

4.7 Effects on ability to drive and use machines

Cefazolin-VIT has no influence or negligible influence on the ability to drive and use machines. However, some adverse reactions (e.g. vertigo, headache, paraesthesia, agitation, seizures; see section 4.8) may affect the ability to concentrate and reaction times and may therefore impair the ability to drive or use machines.

4.8 Undesirable effects

The undesirable effects are categorised 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 classes	Common	Uncommon	Rare	Very rare	Not known
Infections and Infestations					Long-term treatment or repeated use can lead to superinfections or colonisation with resistant bacteria or yeast-like fungi (oral thrush, vaginal candidiasis)

System organ classes	Common	Uncommon	Rare	Very rare	Not known
Blood and lymphatic system disorders		Thrombocytopenia, neutropenia, leukopenia, eosinophilia, agranulocytosis, haemolytic anaemia	Coagulation disorders, haemorrhages*		Leukocytosis, granulocytosis, monocytosis, lymphocytopenia, basophilia, reduced haemoglobin and/or haematocrit, aplastic anaemia, pancytopenia
Immune system disorders	Allergic skin reactions such as erythema, generalized exanthema, Urticaria and pruritus	Serious hypersensitivity reactions such as Angioderma and drug fever		Life-threatening anaphylactic shock**	Erythema exsudativum multiforme. Interstitial pneumonia or pneumonitis, Lyell´s syndrome, Stevens-Johnson syndrome
Nervous system disorders					Headache, dizziness, malaise, tiredness, vertigo, paraesthesia, excitation of the central nervous system, hyperactivity, nervousness or anxiety, sleeplessness, sleepiness, weakness, hot flushes, colour perception changes and confused states, myoclonus, seizures§ convulsive fits§, aseptic meningitis,
Gastrointestinal disorders	Diarrhoea, nausea, loss of appetite, flatulence, abdominal pain#				Pseudomembranous colitis+

System organ classes	Common	Uncommon	Rare	Very rare	Not known
Hepatobiliary disorders		Mild, transient elevation of AST, ALT and alkaline phosphatase		Reversible hepatitis and cholestatic jaundice	Raised GGT, bilirubin and/or LDH
Renal and urinary disorders			Interstitial nephritis and other renal disorders$		Transient rise in BUN levels (blood, urea, nitrogen) and serum creatinine concentrations, nephrotoxicity$
General disorders and administration site conditions		Phlebitis, thrombophlebitis			Chest pains, pleural effusion, dyspnoea or respiratory distress, cough, rhinitis, raised or lowered serum glucose concentration, genital and anal pruritus, genital moniliasis, vaginitis, pain from IM administration. Photosensitive phenomena have been described

* At risk are patients with risk factors leading to vitamin K deficiency or affecting other coagulation mechanisms as well as patients with disorders that can trigger or aggravate haemorrhages.
** Symptom, which may require appropriate immediate emergency measures.
§ Particularly in the event of an overdose or unadjusted dosage in patients with renal impairment.
# In most cases, the symptoms are mild in nature and often resolve, if not during, then after discontinuation of treatment.
+ In the event of severe and persistent diarrhoea during or after treatment with Cefazolin-VIT, a doctor must be consulted, as this may a sign of a severe condition (pseudomembranous colitis), which must be treated immediately (e.g. with vancomycin oral 250 mg 4 times daily). The patient must refrain from all self-medication with antiperistaltic agents.
$ Mostly occurring in severely ill patients receiving several medicinal products.

Reporting of suspected adverse reactions

Reporting of suspected adverse reactions after authorization 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

4.9 Overdose

Symptoms of overdose:
An overdose can cause pain, inflammatory reactions and phlebitis at the injection site. Administration of very high parenteral cephalosporin doses can result in vertigo, paraesthesia and headache. Particularly in patients with renal disease, seizures may occur following an overdose with cephalosporins.
The following abnormal laboratory test results may occur after an overdose: elevated creatinine values, BUN, liver enzyme values and bilirubin; positive Coombs' test; thrombocytosis and thrombocytopenia, eosinophilia, leukopenia and prolongation of the prothrombin time.

Treatment of an overdose:
If seizures occur, the product must be discontinued immediately. Treatment with anticonvulsants may be indicated. Vital body functions and relevant laboratory parameters must be very carefully

monitored. In the event of a severe overdose, a combination of haemodialysis and haemoperfusion may be beneficial if other treatments are unsuccessful, although supportive data to this are lacking. Peritoneal dialysis is ineffective.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: other beta-lactam antibiotics, 1st-generation cephalosporins

ATC code: J01DB04

Mode of action
The mechanism of action of cefazolin is based on inhibition of bacterial cell wall synthesis (in the growth phase), due to blockade of penicillin-binding proteins (PBPs), e.g. transpeptidases. This results in a bactericidal action.

Pharmacokinetic/pharmacodynamic relationship
Efficacy largely depends on the length of time during which the active substance level remains above the minimum inhibitory concentration (MIC) of the pathogen.

Resistance mechanisms
Resistance to cefazolin can be due to the following mechanisms:
- Inactivation by beta-lactamases: cefazolin is largely stable against penicillinases of Gram-positive bacteria, although it has only low stability against numerous plasmid- encoded beta-lactamases, e.g. extended-spectrum beta-lactamases (ESBLs) or chromosome-encoded beta-lactamases of the AmpC type.
- Reduced affinity of PBPs to cefazolin: acquired resistance in pneumococci and other streptococci is due to modifications of PBPs present as a result of a mutation. However, the formation of an additional PBP with reduced affinity for cefazolin is responsible for resistance in methicillin (oxacillin)-resistant staphylococci.
- In Gram-negative bacteria, insufficient penetration of cefazolin through the outer cell wall can lead to insufficient PBP inhibition.
- Cefazolin can be actively transported from the cell by efflux pumps.

Cefazolin is partially or completely cross-resistant with other cephalosporins and penicillins. Breakpoints
Cefazolin is tested using the standard dilution series. The following minimum inhibitory concentrations for susceptible and resistant germs have been established:

EUCAST (European Committee on Antimicrobial Susceptibility Testing) breakpoints (2011- 01-05, version 1.3):

Pathogen	**Susceptibility**	**Resistance**
Staphylococcus spp.	--*	--*
Streptococcus group *A, B,* C, G	--**	--**
Other streptococci §	< 0.5 mg/1	> 0.5 mg/1
Non-species-specific breakpoints	1 mg/1	> 2 mg/1

* Susceptibility of staphylococci to cefazolin can be derived from their susceptibility to cefoxitin.
** Beta-lactam susceptibility of. group A, B, C and G beta-haemolytic streptococci can be derived from their susceptibility to penicillin.
§ For endocarditis, see national or international endocarditis guidelines for Streptococci *viridans* breakpoints.

Susceptibility
For individual species, the prevalence of acquired resistance may vary geographically and over time. Therefore, local information on the resistance situation is required, particularly for the adequate treatment of severe infections. If, based on the local resistance situation, the efficacy of cefazolin is questionable, expert therapeutic advice should be sought.

Usually susceptible species
Gram-positive aerobes
Staphylococcus aureus (methicillin-sensitive)°
Staphylococcus saprophyticus °
Streptococcus agalactiae°
Streptococcus pneumoniae
Streptococcus pyogenes °
Species, in which acquired resistance may pose a problem during use
Gram-positive aerobes
Staphylococcus aureus
Staphylococcus epidermidis +
Staphylococcus haemolyticus +
Staphylococcus hominis +
Staphylococcus pneumoniae (penicillin-intermediate)
Gram-negative aerobes
Escherichia coli

Haemophilus influenzae $
Klebsiella oxytoca
Klebsiella pneumoniae
Proteus mirabilis
Naturally resistant species.
Gram-positive aerobes
Enterococcus spp.
Staphylococcus aureus (methicillin-sensitive)
Staphylococcus pneumoniae (penicillin-resistant)
Gram-negative aerobes
Acinetobacter baumannii
Citrobacter freundii
Enterobacter spp.
Morganella morganii
Moraxella catarrhalis
Proteus vulgaris
Pseudomonas aeruginosa
Serratia marcescens
Stenotrophomonas maltophilia
Anaerobes
Bacteroides fragilis
Other micro-organisms
Chlamydia spp.
Chlamydophila spp.
Legionella spp.
Mycoplasma spp.

° Susceptibility is assumed in the primary literature, standard works and therapeutic recommendations.
$ Natural susceptibility of most isolates lies within the intermediate range.
+ The rate of resistance is over 50% in at least one region.
oo No current data available; in studies (more than 5 years old), the proportion of resistant strains is stated to be> 50%.Outside the hospital setting, the resistance rate is< 10%.

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

5.2 Pharmacokinetic properties

Cefazolin-VIT is administered parenterally. Peak plasma levels are reached after IM injection within 30 to 75 minutes.

Plasma concentrations (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

Plasma concentrations (µg/ml} after intravenous administration of 1g

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

Approximately 65% – 92% of cefazolin is bound to plasma proteins. Cefazolin has good penetration into tissue such as skeletal muscles, myocardium, bone, bile and gallbladder, endometrium and vagina. Cefazolin penetrates the placental barrier and is also excreted in human milk. Diffusion into cerebrospinal fluid and aqueous humour is inadequate.

Cefazolin is not metabolised. It is excreted in the microbiologically active form mainly via the kidneys by means of glomerular filtration. A small moiety is excreted via the bile. The plasma elimination half- life is approximately two hours; in patients with renal insufficiency, the plasma half-life may be prolonged.

5.3 Preclinical safety data

Repeated administration of cefazolin to dogs and rats using different routes of injection over a period of one to six months showed no significant effects on biochemical and haematological values. Signs of neurotoxicity were seen in some studies.
After IM injection, cefazolin is only poorly tolerated at the injection site.
In studies on rabbits, the kidney appeared to be the target organ, though not in rats and dogs. Cefazolin showed no teratogenic activity and did not affect general reproductive functions. No studies are available concerning mutagenicity and carcinogenicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None.

6.2 Incompatibilities

Cefazolin is incompatible with amikacin disulphate, amobarbital sodium, ascorbic acid, bleomycin sulphate, calcium glucoheptonate, calcium gluconate, cimetidine hydrochloride, colistin methanesulphonate sodium, erythromycin glucoheptonate, kanamycin sulphate, oxytetracycline hydrochloride, pentobarbital sodium, polymyxin B sulphate and tetracycline hydrochloride

6.3 Shelf life

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

After reconstitution:
From a microbiological point of view, the ready-to-use solution 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.

6.4 Special precautions for storage

Powder for solution for injection or infusion:
Store below 25°C. Keep the container 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.

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

Nature
10 ml Clear Colorless type III glass vial with Bromobutyl rubber stopper type I and aluminum flip-off cap
The vials contain white or almost white powder.

Contents
Vials in packs of: 10 per box.

6.6 Special precautions for disposal and other handling

Use only freshly prepared, clear and colourless solutions. For single withdrawal only.
Any unused solution should be discarded.

The prepared solution should be visually inspected for particles and discolouration prior to administration.
The prepared solution is clear.

7. MANUFACTURER

ACS DOBFAR S.p.A. Nucleo Industriale S.Atto, S.Nicolò a Tordino, 64100 Teramo, Italy

8. REGISTRATION HOLDER

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

9. MARKETING AUTHORISATION NUMBER

160 81 35045 00

General classification for supply
Medicinal product subject to medical prescription only.