SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Cefazolin 1g Powder for solution for injection/infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 1g cefazolin (as cefazolin sodium).

Excipient(s) with known effect
This medicinal product contains 2.2mmol (or 50.6 mg) sodium per vial.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for injection/infusion.

White or almost white powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Cefazolin 1g Powder for solution for injection/infusion is indicated for the treatment of the following infections caused by cefazolin-susceptible micro-organisms:

- skin and soft tissue infections
- bone and joint infections.

Perioperative prophylaxis. For surgical operations with increased risk of infections with anaerobic pathogens, e.g. colorectal surgery, a combination with an appropriate drug with activity against anaerobes is recommended.

The use of cefazolin should be limited to cases where parenteral treatment is needed.

Susceptibility of causative organism to the treatment should be tested (if possible), although therapy may be initiated before the results are available.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

The dosage as well as the method of administration are dependent on the location and severity of the infection and on the clinical and bacteriological progress. Local therapeutic guidance should be taken into consideration.

Adults and adolescents (above 12 years of age and ≥ 40 kg bodyweight)

• Infections caused by sensitive micro-organisms: 1 g - 2 g cefazolin per day divided into 2-3 equal doses.
• Infections caused by moderately sensitive micro-organisms: 3 g - 4 g cefazolin per day divided into 3-4 equal doses.

In severe infections, doses of up to 6 g per day can be administered in three or four equal doses (one dose every 6 or 8 hours).

Special dosage recommendations
Peri-operative prophylaxis
• To prevent postoperative infection in contaminated or potentially contaminated surgery, recommended doses are: 1 g cefazolin 30 – 60 minutes before surgery
• In case of long surgical interventions (2 hours or more) additional 0.5 - 1 g cefazolin during the intervention.
• Prolonged continuation of administration beyond the surgical intervention should be supported by national official guidance.

It is important that (1) the preoperative dose be given just (30 min 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; and (2) cefazolin 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.

Adult patients with renal impairment
Adults with renal impairment may need a lower dose to avoid overlapping. This lower dose may be guided by determining blood levels. If not possible, the dosage can be established based on creatinine clearance.

Cefazolin maintenance therapy in patients with renal impairment

Creatinine clearance (mL / min)	Serum creatinine (mg / dL)	Dosage
≥ 55	≤ 1.5	Normal dose and normal dosage interval
35 – 54	1.6 – 3.0	Normal dose, every 8 hours
11-34	3.1 – 4.5	Half of the normal dose every 12 hours

≤ 10	≥ 4.6	Half of the normal dose every 18 – 24 hours

In haemodialysis patients, the treatment schedule depends on the dialysis conditions.

Guidelines for adult dosage
Reconstitution table for intramuscular injection

Content per vial	Amount of diluent to be added	Approximate concentration
1 g	2.5 mL	330 mg / mL

Reconstitution table for intravenous injection

Content per vial	Minimum amount of diluent to be added	Approximate concentration
1 g	4 mL	220 mg / mL

Paediatric population:
Infections caused by sensitive microorganisms
A dose of 25-50 mg / kg body weight divided into two to four equal doses per day is recommended (one dose every 6, 8 or 12 hours).

Infections caused by moderately sensitive microorganisms
A dose of up to 100 mg / kg body weight divided in three or four equal doses is recommended (one dose every 6 or 8 hours).

Prematures and infants below the age of 1 month
Since safety of use in prematures and infants below the age of one month has not been determined, the use of Cefazolin 1g Powder for solution for injection/infusion in these patients is not recommended. See also section 4.4.

Guidelines for paediatric dosage

Intravenous injection
1 g vial: The content of 1 vial (1000 mg cefazolin) is dissolved in 4 mL of a compatible solvent (i.e. concentration approx. 220 mg / mL). The respective volume of this solution to be used is indicated in Table 1 in addition to the dose in mg.

Intravenous administration of lidocaine solutions must be strictly avoided.

Table 1: Appropriate volumes for intravenous and intramuscular injection for paediatric patients for Cefazolin 1 g powder for solution for injection/infusion.

Body weight	**Strength**	**5 kg**	**10 kg**	**15 kg**	**20 kg**	**25 kg**
Divided dose every 12 hours at	1-g vial	63 mg;	125 mg;	188 mg;	250 mg;	313 mg;

25 mg / kg body weight/ day		0.29 mL	0.57 mL	0.85 mL	1.14 mL	1.42 mL
Divided dose every 8 hours at 25 mg / kg body weight/ day	1-g vial	42 mg;	85 mg;	125 mg;	167 mg;	208 mg;
		0.19 mL	0.439 mL	0.57 mL	0.76 mL	0.94 mL
Divided dose every 6 hours at 25 mg / kg body weight/ day	1-g vial	31 mg;	62 mg;	94 mg;	125 mg;	156 mg;
		0.14 mL	0.28 mL	0.43 mL	0.57 mL	0.71 mL
Divided dose every 12 hours at 50 mg / kg body weight / day	1-g vial	125 mg	250 mg;	375 mg;	500 mg;	625 mg;
		0.57 mL	1.14 mL	1.7 mL	2.27 mL *	2.84 mL *
Divided dose every 8 hours at 50 mg / kg body weight/ day	1-g vial	83 mg;	166 mg;	250 mg;	333 mg;	417 mg;
		0.438 mL	0.75 mL	1.14 mL	1.51 mL	1.89 mL
Divided dose every 6 hours at 50 mg / kg body weight/ day	1-g vial	63 mg;	125 mg;	188 mg;	250 mg;	313 mg;
		0.29 mL	0.57 mL	0.85 mL	1.14 mL	1.42 mL
Divided dose every 8 hours at 100 mg / kg body weight/ day	1-g vial	167 mg;	333 mg;	500 mg;	667 mg;	833 mg;
		0.76 mL	1.51 mL	2.27 mL *	3.03 mL *	3.79 mL *
Divided dose every 6 hours at 100 mg / kg body weight/ day	1-g vial	125 mg;	250 mg;	375 mg;	500 mg;	625 mg;
		0.57 mL	1.14 mL	1.7 mL	2.27 mL *	2.84 mL *

* For intramuscular administration, when the calculated volume of each individual administration exceeds 2 mL, it is preferable to select a dosage scheme with more divided doses throughout the day (3 or 4) or divide the volume to be administered into equal parts between two different injection sites.

For volumes inferior of 1 mL, please use a 0.5 mL syringe for better accuracy of dosing.

Intramuscular injection

The content of 1 vial (1000 mg cefazolin) is dissolved in 4 mL of a compatible solvent (i.e. concentration approx. 220 mg / mL) and appropriate volume (as indicated in table 1) is withdrawn from the reconstituted solution and administered by intramuscular injection.

For administration in children younger than 30 months of age, cefazolin should not be dissolved in lidocaine solution (see section 4.4).

Intravenous infusion
The dosage can be given as intravenous infusion, using the reconstituted and further diluted solution (10 mg / mL) described in section 6.6.

Paediatric patients with renal impairment
Children with renal impairment (like adults) may need a lower dose to avoid overlapping.
This lower dose may be guided by determining blood levels. If not possible, the dosage may be determined based on creatinine clearance, according to the following guidelines.

In children with moderate impairment (creatinine clearance 40 – 20 mL / min), 25% of the normal daily dose, divided into doses every 12 hours are sufficient.
In children with severe impairment (creatinine 20 – 5 mL / min) will be 10% of normal daily dose, given every 24 hours are sufficient.
All these guidelines are valid after an initial starting dose. See also section 4.4.

Elderly patients:
In elderly patients with normal renal function no dosage adjustment is necessary.

Method of administration
Cefazolin 1g Powder for solution for injection/infusion may be administered as a deep IM injection or by slow intravenous injection or intravenous infusion after dilution.
The volume and type of diluent to be used for the reconstitution is dependent upon the method of administration.
For instructions on the reconstitution of the medicinal product before administration, please see section 6.6.

If lidocaine is used as a solvent, the resulting solution should never be administered intravenously (see section 4.3). The information in the Summary of Product Characteristics of lidocaine should be considered.

Duration of treatment
The duration of the treatment depends on the severity of the infection as well as on the clinical and bacteriological progress.

4.3 Contraindications

- Hypersensitivity to cefazolin sodium.
- History of severe hypersensitivity (e.g. anaphylactic reaction) to other beta-lactam antibiotics (penicillins, monobactams and carbapenems).

Contraindications to lidocaine must be excluded before intramuscular injection of cefazolin when lidocaine solution is used as a solvent (see section 4.4). See information in the Summary of Product Characteristics of lidocaine, especially

contraindications. Cefazolin solutions containing lidocaine should never be administered intravenously.

4.4 Special warnings and precautions for use

Hypersensitivity
Before therapy is initiated, it must be ascertained that the patient has shown no previous hypersensitivity following administration of cephalosporins, penicillins or other medicinal substances. Cefazolin should be administered with caution in patients with a tendency to allergies. Cross-allergies between penicillins and cephalosporins have been documented.

As with all beta-lactam antibacterial agents, severe hypersensitivity reactions including fatal outcome have uncommonly been reported. In the event of severe hypersensitivity reactions, treatment with cefazolin must be discontinued immediately and adequate emergency measures must be initiated. Prior to administration, it should be determined whether the patient has a past history of severe hypersensitivity reactions to cefazolin, other cephalosporins or any other type of beta-lactam agent. Cefazolin should be used with caution in patients with a history of hypersensitivity reactions to other beta-lactams categorized as non-serious.

Antibiotic-associated pseudomembranous colitis
In cases of severe and persistent diarrhoea, considerations should be given to the possibility of antibiotic- related pseudomembranous colitis. This condition can be life-threatening and therefore, treatment with cefazolin should be stopped immediately and appropriate therapy should be administered; antiperistaltic agents are contraindicated. See also section 4.8 Undesirable effects.

Renal impairment
In patients with renal impairment, the dose and/or dosing frequency should be adjusted to the degree of renal dysfunction (see section 4.2). Although cefazolin rarely causes renal dysfunction, it is recommended that renal function be monitored, especially in severely ill patients receiving maximum doses and in patients receiving potentially nephrotoxic agents, such as aminoglycosides or potent diuretics (e.g. furosemide), at the same time.

Intrathecal use
Not for intrathecal administration. Severe intoxication of the central nervous system (including convulsions) has been reported following intrathecal administration of cefazolin.

Bacterial resistance and superinfections
Long-term treatment of cefazolin can result in cefazolin-resistant bacteria. Patients should be closely monitored for potential superinfections. If these occur, appropriate measures should be taken.

Coagulation disorders
Treatment with cefazolin may lead to coagulation disorders in exceptional cases. Risk factors are vitamin K deficiency in patients or the effect of other coagulation mechanisms (parenteral nutrition, malnutrition, impaired hepatic and renal function, thrombocytopenia). Blood clotting may also be impaired in the case of associated diseases (haemophilia, gastric and duodenal ulcers) that may cause or aggravate

bleeding. Therefore, patients with these conditions should be monitored for their prothrombin time. If there is a significant reduction, a vitamin K supplement (10 mg / week) should be administered.

Hypertension or heart failure
In patients with hypertension or heart failure the sodium content of the solution for injection should be taken into account.

Use of lidocaine
In case a lidocaine solution is used as a solvent, cefazolin solutions must only be used for intramuscular injection. Contraindications to lidocaine, warnings and other relevant information as detailed in the Summary of Product Characteristics of lidocaine must be considered before use (see section 4.3).

The lidocaine solution should never be administered intravenously.

Paediatric population
Premature babies and infants below the age of one month
Cefazolin must not be given to preterm babies and infants below the age of one month, as there has been no adequate relevant experience to date.

This medicinal product contains 50.6 mg sodium per vial (1,000 mg), equivalent to 2.5% of the WHO recommended maximum daily intake of 2 g sodium for an adult.
To be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

Antibiotics
The potential for antagonistic effects that have been observed *in vitro* with antibiotics with a bacteriostatic action (e.g. tetracyclines, sulphonamides, erythromycin, chloramphenicol) should be considered when these antibiotics are to be co-administered with cefazolin.

Probenecid
The renal clearance of cefazolin is reduced with concomitant administration of probenecid.

Vitamin K1
Some cephalosporins such as cefamandole, cefazolin and cefotetan can cause interference in vitamin K1 metabolism, especially in cases of vitamin K1 deficiency. This may require vitamin K1 replacement.

Anticoagulants
Cephalosporins can, in very rare cases, lead to coagulation disorders (section 4.4). During concomitant use with anticoagulants (e.g. warfarin or heparin) in high doses, coagulation parameters must be monitored. In a large number of cases, an increase in oral anticoagulant activity has been reported in patients receiving antibiotics. Infection and inflammation, age and general condition of the patient are likely to constitute risk factors.

Under these circumstances, it is difficult to establish which role the infectious disease and its treatment play when INR imbalance occurs. However, some classes of antibiotics are more implicated, particularly fluoroquinolones, macrolides, cyclins, cotrimoxazole and some cephalosporins.

Nephrotoxic substances
It cannot be excluded that the nephrotoxic effect of antibiotics (e.g. aminoglycosides, colistin, polymyxin B), iodine-containing contrast agents, organoplatinum compounds, high-dose methotrexate, some antiviral drugs (e.g. aciclovir, foscarnet), pentamidine, ciclosporin, tacrolimus and diuretics (e.g. furosemide) is increased.
When co-administered with cefazolin, kidney function tests must be carefully monitored.

Laboratory tests
In laboratory tests, there may be a false-positive reaction for urinary glucose when using Benedict's solution or Fehling's solution in patients treated with cefazolin. Cefazolin has no effect on enzymatic measurements of glucose in urine.
The indirect and direct Coombs' test can also give false-positive results. This may also apply to newborn babies whose mothers have been receiving cephalosporins.

4.6 Fertility, pregnancy and lactation

Pregnancy
Animal studies do not indicate direct or indirect harmful effects on reproductive toxicity.

Cefazolin 1g Powder for solution for injection/infusion should only be administered in pregnancy, especially during the first trimester, after careful benefit-risk assessment because there is insufficient experience and cefazolin crosses the placenta.
It is preferable to avoid the use of cefazolin during pregnancy, unless it is absolutely necessary.

Breastfeeding
Cefazolin is excreted in maternal milk at very low concentrations and thereforeit should only be used after careful benefit/risk assessment. If diarrhoea or candidiasis should occur in the infant during breastfeeding, the mother should not breastfeed her infant during treatment, or else treatment with cefazolin should be discontinued.

Fertility
Animal studies have shown no effects on fertility.

4.7 Effects on ability to drive and use machines

Cefazolin has no
influence on the ability to drive and use machines. However, adverse reactions may occur (see also section 4.8) which may affect the ability to drive and use machines.

4.8 Undesirable effects

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. The frequencies of adverse reactions are categorized as:
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).

MedDRA System Organ Class	Frequency	Adverse reaction
Infections and infestations	Uncommon	Oral candidiasis
	Rare	Genital candidiasis (monoliasis), vaginitis. As with any antibiotic, prolonged use can lead to overgrowth of non-susceptible bacteria. Rhinitis
Blood and lymphatic system disorders	Rare	Leukopenia, granulocytopenia, neutropenia, thrombocytopenia, leukocytosis, granulocytosis, monocytosis, lymphocytopenia, basophilia and eosinophilia were observed in blood counts. These effects are rare and reversible.
	Very rare	Coagulation (blood-clotting) disorders with subsequent bleeding (see section 4.4).
Immune system disorders	Uncommon	Pyrexia
	Very rare	Anaphylactic shock (swelling of the larynx with narrowing of the airways, increased heart rate, shortness of breath, decrease in blood pressure, swollen tongue, anal pruritus, genital pruritus, face edema)
Metabolism and nutrition disorders	Rare	Hyperglycaemia, hypoglycaemia
Nervous system disorders	Uncommon	Seizures (in patients with renal dysfunction treated with inappropriately high doses).
	Rare	Dizziness
Vascular disorders	Uncommon	Thrombophlebitis
Respiratory, thoracic and mediastinal disorders	Rare	Pleural effusion, dyspnoea or respiratory distress, cough
Gastrointestinal	Common	Nausea, vomiting, diarrhoea

disorders	Rare	Anorexia
	Very rare	Pseudomembranous colitis (this complication must be treated immediately if the diarrhoea is associated with antibiotic therapy.)
Hepatobiliary disorders	Rare	Transient elevation of aspartate aminotransferase, alanine aminotransferase or alkaline phosphatase, gamma-glutamyl transferase, bilirubin and/or lactate dehydrogenase, transient hepatitis and transient cholestatic jaundice.
Skin and subcutaneous tissue disorders	Common	Rash
	Uncommon	Erythema, erythema multiforme, urticaria, angioedema
	Rare	Toxic epidermal necrolysis, Stevens-Johnson syndrome
Renal and urinary disorders	Rare	Nephrotoxicity, interstitial nephritis, undefined nephropathy, proteinuria, transient elevation of blood urea nitrogen (BUN), usually in patients concomitantly treated with other potential nephrotoxic agents.
Reproductive system and breast disorders	Very rare	Vulvovaginal pruritus
General disorders and administration site conditions	Common	Pain at the intramuscular injection site, sometimes with induration
	Rare	Malaise, fatigue, chest pain

A physician should be consulted in the event of severe and persistent diarrhoea during or after treatment with cefazolin, as such diarrhoea may be a symptom of a serious disease (pseudomembranous colitis) that must be treated immediately. Patients should not, under any circumstances, take antiperistaltic agents as self-medication (see section 4.4).

Prolonged use of cephalosporins may result in overgrowth of cefazolin-resistant bacteria, especially *Enterobacter, Citrobacter, Pseudomonas, Enterococcus* and *Candida.* This may lead to superinfections or potential colonization with resistant organisms or yeasts (see section 4.4).

Studies
Transient elevation of AST, ALT, blood urea and alkaline phosphatase without clinical evidence of renal or hepatic damage.

Animal data has shown that cefazolin has a potentially nephrotoxic effect. Although this has not been demonstrated in humans, the possibility should however be taken into account, especially in patients receiving high doses over a prolonged period. Interstitial nephritis and unspecified nephropathy have been reported in rare cases. The patients affected were seriously ill and were receiving several medications. The role of cefazolin in the development of interstitial nephritis or other nephropathies has not been established.

In rare cases, the following have been reported during treatment:

- Decreased haemoglobin and/or haematocrit levels, anaemia, agranulocytosis, aplastic anaemia, pancytopenia and haemolytic anaemia.

The following cases have been reported during treatment with certain cephalosporins:

- Nightmares, dizziness, hyperactivity, nervousness or anxiety, insomnia, drowsiness, weakness, flushing, impaired colour vision, confusion and epileptic 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. Healthcare professionals are asked to report any suspected adverse reactions via Yellow Card Scheme, Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms of overdose

An overdose can cause pain, inflammatory reactions and phlebitis at the injection site. Parenteral administration of high doses of cephalosporins can cause dizziness, paraesthesia and headache. Following overdose with cephalosporins, convulsions may occur especially in patients with renal disease.

Following an overdose, the following abnormal laboratory values may occur: increase in creatinine levels, BUN, liver enzymes and bilirubin, a positive Coombs' test, thrombocythaemia and thrombocytopenia, eosinophilia, leukopenia and prolongation of prothrombin time.

Treatment of overdose

If convulsions occur, administration of the drug should be discontinued immediately. Treatment with antiepileptics may be indicated. Vital body functions and parameters should be monitored closely. In case of a severe overdose where the patient is no longer responsive to other treatments, haemodialysis with haemoperfusion may be effective, although this has not been proven.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use, other beta-lactam antibacterials, first generation cephalosporins,
ATC code: J01DB04

Mechanism of action

All cephalosporins (beta-lactam antibiotics) inhibit cell wall synthesis and are selective inhibitors of peptidoglycan synthesis. The first step is binding of the drug to cell receptors (penicillin-binding proteins). After this binding, the transpeptidase reaction is blocked and peptidoglycan synthesis is inhibited. This process leads to bacterial lysis.

PK/PD relationship

For cephalosporins, the most important pharmacokinetic-pharmacodynamic index correlating with in vivo efficacy is the percentage of the dosing interval during which the free active substance concentration is above the minimum inhibitory concentration of the pathogen concerned (%T>MIC).

Mechanism of resistance

Beta-lactam antibiotics contain a so-called beta-lactam ring which is essential for the antimicrobial effect. If this ring is split open, it loses its antibiotic effect. Various bacteria have enzymes (beta-lactamases) that can split open this ring, thus they become resistant to this type of antibiotic.

As with all cephalosporins and other beta-lactam antibiotics, various mechanisms of resistance may be acquired by groups of bacteria: changes in the target (penicillin-binding proteins, PBPs), enzymatic degradation of the central structure by beta-lactamases and altered access to the target. There is cross-resistance between cephalosporins and penicillins. Gram-negative microorganisms contain inducible chromosomal-bound beta-lactamases such as *Enterobacter* spp., *Serratia* spp., *Citrobacter* spp. and *Providence* spp.; these should be regarded as resistant to cefazolin despite in vitro susceptibility.

Microbiological susceptibility

The prevalence of acquired resistance for certain strains can vary depending on geographical location and the time of testing. Therefore, information on the local resistance situation is desirable, especially when treating severe infections. If, due to the local resistance situation, efficacy is questionable, expert advice should be sought.

Commonly susceptible species
Aerobe Gram-positive *Staphylococcus aureus* (methicillin-sensitive)
Species for which acquired resistance may be a problem
Haemophilus influenzae *Staphylococcus epidermidis* (methicillin-sensitive) *Streptococcus pneumoniae*
Inherently resistant organisms

Citrobacter spp. *Enterobacter* spp. *(Enterobacter cloacae, Enterobacter aerogenes)* *Morganella morganii* *Proteus stuartii* *Proteus vulgaris* *Pseudomonas aeruginosa* *Serratia* spp. *Staphylococcus aureus,* methicillin-resistant *Indole-positive Proteus* spp *Klebsiella pneumoniae* *Proteus mirabilis*

5.2 Pharmacokinetic properties

Absorption and distribution

- IM administration:

In human pharmacology, the serum levels of cefazolin and duration of action after intramuscular administration are given in the following table.

Dosage (g)	Serum concentration (µg/mL)					
	30 min	1 h	2 h	4 h	6 h	8 h
0.25	15.5	17.0	13.0	5.1	2.5	<1.5
0.50	36.2	36.8	37.9	15.5	6.3	3.0
1.0*	60.1	63.8	54.3	29.3	13.2	7.1

*- Average of two studies

- IV administration:

Upon continuous IV infusion (in healthy subjects) of cefazolin at a dose of 3.5 mg/kg for one hour, followed by a dose of 1.5 mg/kg for the next 2 hours, serum levels of about 28 mg/mL were seen in the third hour.

- The average serum concentrations obtained after IV administration of a single dose of 1 g are presented in the following table.

Serum concentration (µg / mL)					
5 min	15 min	30 min	1 hr	2 hr	4hr
188.4	135.8	106.8	73.7	45.6	16.5

Cefazolin has a mean half-life of about 1.8 hours, which may increase by as much as 15-30 hours in cases of severe renal dysfunction and may be higher in cases of anuria.

Peak plasma concentrations are 63.6 mg/L and 188.4 mg/L, which were achieved after 1-2 hours of continuous IV infusion at a dose of 1 g. The half-life is 100 minutes.
When cefazolin is administered to patients without bile duct obstruction, concentrations far exceeding serum levels occur in the gallbladder tissue and bile.

Cefazolin readily crosses the placental barrier. The amounts of cefazolin in breast milk are low.

The rate of protein binding is 85-90% for human serum under physiological conditions. Diffusion of cefazolin in the cerebrospinal fluid is low.

Biotransformation

Cefazolin is not metabolised.

Elimination

Cefazolin is mainly excreted via the urine, with a small percentage via the bile. Following intramuscular injection of 500 mg, 56% to 89% of the administered dose is eliminated renally within six hours and 80% to almost 100% within 24 hours. Following intramuscular administration of 500 mg and 1 g cefazolin, peak urinary concentrations of more than 1,000 and more than 4,000 µg/mL, respectively, are achieved.

5.3 Preclinical safety data

The acute toxicity of cefazolin is low.
Repeated administration of cefazolin to dogs and rats via different routes of injection over a period of 1 to 6 months showed no significant effects on biochemical and haematological values Renal toxicity was observed after repeated doses in rabbits, but not in dogs and rats. Cefazolin showed no teratogenic or embryotoxic activity.
No studies on mutagenicity and carcinogenicity are available.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None.

6.2 Incompatibilities

Cefazolin is incompatible with amikacin disulfate, amobarbital-sodium, ascorbic acid, bleomycin sulphate, calcium gluceptate, calcium gluconate, cimetidine hydrochloride, colistimethate-sodium, erythromycin gluceptate, kanamycin sulphate, oxytetracyclin hydrochloride, pentobarbital-sodium, polymyxin-B-sulphate and tetracycline hydrochloride.

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

3 years.

After reconstitution/dilution

Chemical and physical stability has been demonstrated for 12 hours at 25 °C and for up to 24 hours at 2-8 °C.

From a microbiological point of view, unless the method of opening/reconstitution/dilution precludes the risk of microbial contamination, 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 the times stated above for the chemical and physical in-use stability.

6.4 Special precautions for storage

Store below 30°C.
Keep the vials in the outer carton in order to protect from light.
For storage conditions after reconstitution / dilution of the medicinal product , see section 6.3.

6.5 Nature and contents of container

20 mL Type III colorless glass vial closed with bromobutyl Type I rubber closures and sealed with aluminium caps with a flip-top plastic cover.

The medicinal product is supplied in pack sizes of 1, 10 or 50 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Preparation of the solution

For each route of administration see the table for addition volumes and solution concentrations, which may be useful when fractional doses are required.

Intramuscular injection
Cefazolin 1g Powder for solution for injection/infusion:
Reconstitute Cefazolin 1g Powder for solution for injection/infusion with one of the following compatible diluents according to the dilution table that follows:

- water for injection
- 10% glucose solution
- 0.9% sodium chloride solution
- 0.5% lidocaine HCl solution

Shake well until contents of the vial are fully dissolved and inject as deep IM injection.

Reconstitution table for intramuscular injection

Content per vial	Amount of diluent to be added	Approximate concentration
1 g	2.5 mL	330 mg / mL

For the amount of diluent to be added for paediatric population please refer to section 4.2 - Guidelines for paediatric dosage.

Use of lidocaine:
In case a lidocaine solution is used as a solvent, cefazolin solutions must only be used for intramuscular injection. Contraindications to lidocaine, warnings and other relevant information as detailed in the Summary of Product Characteristics of lidocaine must be considered before use.

The lidocaine solution should never be administered intravenously.
IM injection with lidocaine as solvent is indicated for children over 30 months old.

Intravenous injection

Reconstitute Cefazolin 1g Powder for solution for injection/infusion with one of the following compatible diluents according to the dilution table that follows:

- water for injections
- (0.9%) sodium chloride solution or
- 5% glucose solution
- 10% glucose solution

Reconstitution table for intravenous injection

Content per vial	Minimum amount of diluent to be added	Approximate concentration
1 g	4 mL	220 mg / mL

Cefazolin is to be injected slowly over three to five minutes. In no case should the solution be injected in less than 3 minutes. This should be done directly into the vein or into the tube from which the patient receives intravenous solution. Single doses exceeding 1 g should be given as intravenous infusion over 30 to 60 minutes.

Guidelines for paediatric dosage:
1 g vial: The content of 1 vial (1000 mg cefazolin) is dissolved in 4 mL of a compatible solvent (i.e. concentration approx. 220 mg/mL). The respective volume of this solution to be used is indicated in table 1 in addition to the dose in mg.

For the amount of diluent to be added for paediatric population please refer to section 4.2 - Guidelines for paediatric dosage. For volumes inferior of 1 mL, please use a 0.5 mL syringe for better accuracy of dosing.

Intravenous infusion

Cefazolin 1g Powder for solution for injection/infusion should first be reconstituted with one of the diluents detailed as compatible for intravenous injection.

Further dilution should take place with one of the following compatible diluents according to the dilution table that follows:

- sodium chloride 0.9% solution
- glucose 5%
- Ringer's solution
- lactated Ringer's solution
- water for injections

Dilution table for intravenous infusion

Content per vial	Reconstitution	Dilution	Approximate concentration
	Minimum amount of diluent to be added	Amount of diluent to be added	
1 g	4 mL	50 mL – 100 mL	20 mg / mL – 10 mg / mL

Cefazolin 1 g Powder for solution for injection/infusion solutions containing lidocaine should never be administered intravenously.

As for all parenteral medicinal products, inspect the reconstituted solution visually for particulate matter and discoloration prior to administration. The solution should only be used if the solution is clear and practically free from particles.

The reconstituted product is for single use only.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Noridem Enterprises Ltd.
Evagorou & Makariou,
Mitsi Building 3, Office 115,
1065 Nicosia, Cyprus

8 MARKETING AUTHORISATION NUMBER(S)

PL 24598/0053

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 10/12/2018
Date of latest renewal: 27/09/2023

10 DATE OF REVISION OF THE TEXT

11/09/2024