SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

CEFAZOLIN - FRESENIUS

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Cefazolin (as sodium cefazolin) 1000 mg

Excipient(s) with known effect: Each vial contains 48.4 mg of sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for I.V/I.M injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Cefazolin - Fresenius is indicated in the treatment of the following serious infections due to susceptible organisms:

Respiratory Tract Infections: Due to *S.Aureus* (methicillin sensitive).

Species for which acquired resistance can be a problem: *S. pneumoniae*, *H.influenzae,* and group A beta-hemolytic streptococci.

Injectable benzathine penicillin is considered to be the drug of choice in treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever.

Data establishing the efficacy of Cefazolin - Fresenius in the subsequent prevention of rheumatic fever are not available at present.

Urinary Tract Infections: Due to *E coli*.

Skin and Skin Structure Infections: Due to *S. Aureus* (methicillin sensitive).

Species for which acquired resistance can be a problem: group A beta-hemolytic streptococci, and other strains of streptococci.

Biliary Tract Infections: Due to E coli, S. aureus. Species for which acquired resistance can be a problem: various strains of streptococci.

Bone and Joint Infections: Due to *S. aureus*.

Genital Infections: (i.e., prostatitis, epididymitis) due *to E. Coli.*

Septicemia: Due to, S. *aureus* (methicillin sensitive), *E coli.* Species for which acquired resistance can be a problem: S. *pneumonia.*

Endocarditis: Due to *S. aureus* (methicillin sensitive).

Species for which acquired resistance can be a problem: group A beta-hemolytic streptococci.

Perioperative Prophylaxis: The prophylactic administration of Cefazolin - Fresenius preoperatively, intraoperatively, and postoperatively may reduce the incidence of certain postoperative infections in patients undergoing surgical procedures which are classified as contaminated or potentially contaminated (e.g., vaginal hysterectomy, and cholecystectomy in high-risk patients such as those older than 70 years, with acute cholecystitis, obstructive jaundice, or common duct bile stones).

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

4.2 Posology and Method of Administration

Posology:

Usual Adult dosage:

Type of Infection Dose frequency	**Dose**	**Frequency**	
Moderate to severe infections	500 mg to 1 gram	every 6 to 8 hours	
Mild infections caused by susceptible gram -positive cocci	250 mg to 500 mg	every 8 hours	
Acute, uncomplicated urinary tract infections	1 gram	every 12 hours	
Pneumococcal pneumonia	500 mg	every 12 hours	
Severe, life -threatening infections (e.g.,endocarditis , septicemia)*	1 gram to 1.5 grams	every 6 hours	

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

Perioperative Prophylactic Use: To prevent postoperative infection in contaminated or potentially contaminated surgery, recommended doses are:

a. 1 gram IV or IM administered 1/2 hour to 1 hour prior to the start of surgery.

b. For lengthy operative procedures (e.g., 2 hours or more), 500 mg to 1 gram IV or IM during surgery (administration modified depending on the duration of the operative procedure),

c. 500 mg to 1 gram IV or IM every 6 to 8 hours for 24 hours postoperatively.

It is important that (1) the preoperative dose be given just (1/2 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-Fresenius 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. The prophylactic administration of Cefazolin - Fresenius should usually be discontinued within a 24- hour period after the surgical procedure. In surgery where the occurrence of infection may be particularly devastating (e.g., open-heart surgery and prosthetic arthroplasty), the prophylactic administration of Cefazolin-Fresenius may be continued for 3 to 5 days following the completion of surgery.

If there are signs of infection, specimens for cultures should be obtained for the identification of the causative organism so that appropriate therapy may be instituted

Dosage Adjustment for Patients with Reduced Renal Function: Cefazolin-Fresenius may be used in patients with reduced renal function with the following dosage adjustments:

Crearinine clearance (ml /min)	Serum creatinine (mg%)	Dosage
55 or greater	1.5 or less	Full doses
35 to 54	1.6 to 3.0	Full doses restricted to at least 8 hour intervals
11 to 34	3.1 to 4.5	1/2 of the usual dose every 12 hours
10 or less	4.6 or greater	1/2 of the usual dose every 18 to 24 hours

All reduced dosage recommendations apply after an initial loading dose appropriate to the severity of the infection. Patients undergoing peritoneal dialysis see section 5.2 Pharmacokinetic Properties.

Pediatric Dosage: In pediatric patients, a total daily dosage of 25 to 50 mg per kg (approximately 10 to 20 mg per pound) of body weight, divided into 3 or 4 equal doses, is effective for most mild to moderately severe infections. Total daily dosage may be increased to 100 mg per kg (45 mg per pound) of body weight for severe infections. Since safety for use in premature infants and in neonates has not been established, the use of Cefazolin-Fresenius in these patients is not recommended.

Pediatric Dosage Guide		
Weight	**25 mg/kg /day**	**25 mg /kg /day**

		Divided into 3 doses		**Divided into 4 doses**	
Lbs	Kg	Approximate Single dose mg/q8h	Vol.(ml)needed With dilution of 125 mg/ml	Approximate Single Dose mg/q6h	Vol.(ml) needed with dilution of 125 mg/ml
10	4.5	40 mg	0.35 ml	30 mg	0.25 ml
20	9.0	75 mg	0.60 ml	55 mg	0.45 ml
30	13.6	115 mg	0.90 ml	85 mg	0.70 ml
40	18.1	150 mg	1.20 ml	115 mg	0.90 ml
50	22.7	190 mg	1.50 ml	140 mg	1.10 ml

Weight		**50 mg/kg /day Divided into 3 doses**		**50 mg /kg /day Divided into 4 doses**	
lbs	Kg	Approximate Single dose mg/q8h	Vol.(ml)needed With dilution of 225 mg/ml	Approximate Single Dose mg/q6h	Vol.(ml) needed with dilution of 225 mg/ml
10	4.5	75 mg	0.35 ml	55 mg	0.25 ml
20	9.0	150 mg	0.70 ml	110 mg	0.50 ml
30	13.6	225 mg	1.00 ml	170 mg	0.75 ml
40	18.1	300 mg	1.35 ml	225 mg	1.00 ml
50	22.7	375 mg	1.70 ml	285 mg	1.25 ml

In pediatric patients with mild to moderate renal impairment (creatinine clearance of 70 to 40 ml /min.), 60 percent of the normal daily dose given in equally divided doses every 12 hours should be sufficient. In patients with moderate impairment (creatinine clearance of 40 to 20 mL/min.), 25 percent of the normal daily dose given in equally divided doses every 12 hours

should be adequate. Pediatric patients with severe renal impairment (creatinine clearance of 20 to 5 mL/min.) may be given 10 percent of the normal daily dose every 24 hours. All dosage recommendations apply after an initial loading dose.

Method of Administration:

Cefazolin may be administered by deep intramuscular injection, intravenously or by infusion.

IM Administration:

Intramuscular injection is contraindicated in children under the age of 30 months.

Dilute 1000mg of Cefazolin in 4 ml Lidocaine 0,5 % and administer by deep intramuscular injection. The reconstituted solution with 4 ml Lidocaine 0,5 % is stable for 24 hours below 25°C or 72 hours in the refrigerator (2° C - 8° C).

Reconstituted solution may present a yellow coloration that does not imply that the product potency is adversely affected.

IV Administration:

Cefazolin can be given by direct injection (bolus) or by continuous or intermittent infusion.

Do not use intravenously the solution reconstituted with lidocaine hydrochloride, which is specific for intramuscular administration.

Direct (bolus) IV injection:

Dilute 1000mg of Cefazolin in 10 ml of Water for injections or 4ml Sodium chloride 0.9% and administer slowly (3 to 5 minutes), directly in the vein or in the infusion system.

The reconstituted solution with 10 ml of Water for injections is stable for 24 hours below 25°C or 72 hours in the refrigerator (2° C - 8°C).

The reconstituted solution with 4 ml of Sodium chloride 0.9% is stable for 12 hours below 25°C or 72 hours in the refrigerator (2° C - 8°C).

Intermittent or continuous IV infusion.

Dilute 1000mg dosage of Cefazolin in 100 ml in one of the following intravenous solutions:

- Sodium chloride 0.9%
- Dextrose 5%

In these intravenous solutions, Cefazolin is stable for 12 hours below 25°C.

4.3 Contraindications

- Hypersensitivity to the active substance, other cephalosporins or to any of the excipients listed in section 6.1.
- History of previous immediate and/or severe hypersensitivity reaction to a penicillin or to any other type of beta-lactam drug.

- Hypersensitivity to lidocaine (I.M administration)

<u>Simultaneous administration is Contraindicated</u>

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 diarrhea 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. Antiperistaltic 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 (48 mg per 1 g cefazolin).

- Paediatric population

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.

- Important information about some of the ingredients:
This medicinal product contains 48.4 mg sodium per vial, equivalent to 2.4 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interactions with other medicinal products and other forms of interactions

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 Test

Laboratory tests for urinary glucose concentrations may give false positive reading 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 tests 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 in 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 colonization

					with resistant bacteria or yeasts (oral thrush, monoliasis vaginalis)
Blood and lymphatic system disorders		Thrombocytopenia, neutropenia, leucopenia, eosinophilia, agranulocytosis, haemolytic anaemia, granulocytosis, leukocytosis, monocytosis, lymphocytopenia, basophilia	Coagulation disorders, haemorrhages*		
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/ and emailed to the

Registration Holder's Patient Safety Unit at: drugsafety@neopharmgroup.com.

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 cephalosporin may induce convulsions.

Overdose may be associated with the following abnormal laboratory test results: elevated creatinine, BUN, liver enzyme 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 withrenal 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 by 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.

Mechanism 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 breakpoints * (exemption: *Staphylococcus* spp.) [2)]	≤1 mg/l	> 2 mg/l

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

[2)] The susceptibility of *staphylococcus* spp. in 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 with time for the selected species and local information on resistance is desirable, particularly when treating severe infections. Asnecessary, 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)[0]
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*ɜ
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 of with amikacin disulfate, amobarbital sodium, ascorbic acid, bleomycin sulphate, calcium glucoheptonate, calcium gluconate, cimetidine hydrochloride, colistin methane sulfonate sodium, erythromycin glucoheptonate, kanamycin sulfate, oxytetracyclin 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

Store below 25°C.

From a microbiological point of view, unless the method of opening and 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.

Chemical and physical in-use stability has been demonstrated as follows:

- In-use stability after reconstitution for I.M administration / Direct (bolus) I.V injection:

Diluent and volume	Purpose of use	Stability after reconstitution
4 ml lidocaine 0.5%	I.M administration	24 h below 25°C or 72 h in the refrigerator (2°C - 8°C).
10 ml water for injections	Direct I.V injection	24 h below 25°C or 72 h in the refrigerator (2°C-8°C).
4 ml sodium chloride 0.9%	Direct I.V injection	12 h below 25° C or 72 h in the refrigerator (2°C- 8°C).

- In-use stability after reconstitution for intermittent I.V infusion in 100 ml of Sodium chloride 0,9% / Dextrose 5% has been demonstrated for 12 hours below 25°C.
- Obtained solutions should be protected from light.

6.5 Nature and contents of container

Sterile powder is packaged in glass vials with 1000 mg of sodium cefazolin.

Pack sizes: 1,5,10,50 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and handling

Do not use after the expiry date which is stated on the carton.

Reconstituted solutions should be inspected visually. Only clear solutions free of visible particles should be used.

Keep out of the reach and sight of children.

7. MARKETING AUTHORISATION HOLDER

NEOPHARM (ISRAEL) 1996 LTD

Hashiloach 6, POB 7063 Petach Tiqva 4917001.

8. MANUFACTURER

LABESFAL - LABORATORIOS ALMIRO S.A,

Fresenius Kabi Group,

Lagedo, 3465- 157 Santiago de Besteiros, Portugal.

9. MARKETING AUTHORISATION NUMBER

149-89-33775-00

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