03/2023

CEFAZOLIN - FRESENIUS

צפאזולין - פרזניוס

מרכיבים פעילים:

CEFAZOLIN (AS SODIUM) 1000 MG

צורת מינון:

POWDER FOR SOLUTION FOR INJECTION

רופא/ה, רוקח/ת נכבד/ה,
חברת ניאופרם (ישראל) 1996 בע"מ מבקשת להודיע על עדכון העלון לרופא של התכשיר שבנדון .
העלון עודכן בתאריך מרץ 2023 .

ההתוויה הרשומה לתכשיר בישראל:
Cefazolin - Fresenius is indicated in the treatment of serious infections due to susceptible microorganisms.

בהודעה זו מצוינים השינויים המהותיים בלבד.

מקראה לעדכונים המסומנים:
מידע שהוסר -מסומן בקו אדום חוצה ~~XXX~~
תוספת -כתב **כחול**
תוספת החמרה - כתב **כחול** -מסומן בצהוב מרקר
מידע שעבר מקום - כתב ירוק

עדכונים מהותיים נעשו בסעיפים הבאים בעלון לרופא:

4.3 Contraindications

- ~~Cefazolin Labesfal is contraindicated in patients who have~~ Hypersensitivity ~~reaction~~ to the active substance, other cephalosporins or to any of the ~~solvents/ intravenous solutions mentioned in section 4.2~~ excipients listed in section 6.1.
- ~~Hypersensitivity to cephalosporins.~~
- 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)
- ~~Do not use the IM presentation in children with less than 30 months (solvent is lidocaine chloridrate).~~

Simultaneous administration is Contraindicated

Antibiotics

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

4.4 Special warnings and precautions for use

- Special precaution should be exercised in patients with an allergic diathesis, with bronchial asthma or

hay fever. Before the administration of cefazolin previous hypersensitivity reactions to other beta-lactams (penicillins or cephalosporins) should be investigated.

- In patients developing allergic reactions the drug should be discontinued and appropriate symptomatic treatment should be instituted. Cross allergies with other cephalosporins and occasionally occurring cross allergies with penicillins should be considered. In cases of known hypersensitivity to penicillins, a cross-allergy to other beta-lactams such as cephalosporins should be taken into account.
- Serious and occasionally fatal hypersensitivity reactions (anaphylaxis) have been reported in patients treated with beta-lactam antibiotics (see section 4.8). These reactions are more likely to occur in individuals with a history of beta-lactam hypersensitivity.

~~Before therapy with Cefazolin Fresenius is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to cefazolin, cephalosporins, penicillins, or other drugs. Cephalosporin administration is formally contraindicated in patients who have had a previous immediate hypersensivity reaction to cephalosporins, if this product is given to penicillin-sensitive patients, caution should be exercised because 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. In case of doubt, medical surveillance is required during first administration in order to treat anaphylactic shock that might occur.If an allergic reaction to Cefazolin Fresenius occurs, discontinue treatment with the drug. Serious acute hypersensitivity reactions may require treatment with epinephrine and other emergency measures, including oxygen, iv fluids, iv antihistamines, corticosteroids, pressor amines, and airway management, as clinically indicated.~~

- 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 ~~Pseudomembranous colitis has been reported with nearly~~ all antibiotics ~~antibacterial agents, including cefazolin, and may range in~~, the severity of which can range from mild to life-threatening (see section 4.8). Therefore, it is important to be mindful of ~~consider~~ this diagnosis in patients who experience ~~present with~~ diarrhea

  during or after using an antibiotic ~~subsequent to the administration of antibacterial agents~~.

~~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."~~

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

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.

~~**Precautions**~~

- ~~**General:** Prolonged use of Cefazolin - Fresenius may result in the overgrowth of nonsusceptible organisms. Careful clinical observation of the patient is essential.~~
- ~~When Cefazolin - Fresenius is administered to patients with low urinary output because of impaired renal function, lower daily dosage is required. As with other ß -lactam antibiotics, seizures may occur if inappropriately high doses are administered to patients with impaired renal function (see 4.2 Posology and Method of Administration).~~
- ~~Geriatric Use: Reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely~~

~~to have decreased renal function, care should be taken in dose selection, and it maybe useful to monitor renal function.~~

- ~~Cefazolin - Fresenius, as with all cephalosporins, should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.~~
- ~~Cephalosporins may be associated with a fall in prothrombin activity. Those at risk include patients with renal or hepatic impairment or poor nutritional state, as well as patients receiving a protracted course of antimicrobial therapy, and patients previously stabilized on anticoagulant therapy. Prothrombin time should be monitored in patients at risk and exogenous vitamin K administered as indicated.~~
- ~~Prescribing Cefazolin - Fresenius 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.~~
- ~~Renal function should be monitored during treatment, in cases of association of cefazolin with other antibacterials potentially nephrotoxic (aminoglycosides in particular) or diuretics like furosemide or etacrinic acid.~~

~~Due to the poor diffusion of cefazolin through cerebrospinal fluid, this medicine is not indicated on meningitis treatment, even if caused by sensitive germs.~~

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

~~may decrease renal tubular secretion of cephalosporins when used concurrently, resulting in increased and more prolonged cephalosporin blood levels~~

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

- ~~Although no specific interaction with cefazolin has been reported, cases of nephrotoxicity after concomitant administration of other cephalosporins and aminoglycosides had been described.~~
- ~~Cefazolin has been associated with an increase of prothrombin time and haemorrhagic episodes. These effects may potentiate the effects of warfarin and other oral anticoagulants.~~

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.

~~*Drug/*~~*Laboratory Test* ~~*Interactions.*~~

Laboratory tests for urinary glucose concentrations may give ~~A~~ false positive reading if based on ~~reaction for glucose in the urine may occur with~~ Benedict's solution, Fehling's solution or ~~with~~ CLINITEST® tablets. However, ~~but not with~~ cefazolin does not affect enzyme-based tests ~~such as Clinistix®.~~

Both the ~~Positive~~ indirect and the ~~in~~direct ~~antiglobulin (~~Coombs~~)~~ tests may also give false positive readings, e.g. in newborns ~~have occurred; these may also occur in neonates~~ whose mothers received cephalosporins ~~before delivery.~~

4.6 Fertility, pregnancy and lactation

~~Cefazolin use during pregnancy and lactation should be made only when necessary because the drug crosses the placental barrier and is excreted in breast milk.~~

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.

~~The harmlessness of Cefazolin administration in premature infants and in children less than 3 months has not been established. Studies in animals have not revealed any evidence of teratogenic or fetotoxic effect.~~

~~There are, however, no adequate and well-controlled studies in pregnant women.~~

~~Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.~~

Lactation:

Cefazolin is excreted in human milk at low concentration~~. Caution should be exercised when Cefazolin - Fresenius is administered to a nursing woman.~~ 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.

~~Fertility~~

~~No data is available regarding the effects of Cefazolin - Fresenius on human fertility.~~

~~Labor and Delivery: When cefazolin has been administered prior to caesarean section, drug levels in cord blood have been approximately one quarter to one third of maternal drug levels.~~

~~The drug appears to have no adverse effect on the fetus.~~

4.7 Effects on ability to drive and use machines

~~Seizures may occur when high doses of cefazolin are given to patients with renal dysfunction.~~

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):

~~The following reactions have been reported:~~

~~Gastrointestinal: diarrhea, oral candidiasis (oral thrush), vomiting, nausea, stomach cramps, anorexia, and~~

pseudomembranous colitis. Onset of pseudo¬membranous colitis symptoms may occur during or after antibiotic treatment (see Warnings). Nausea and vomiting have been reported rarely.

Allergic: Anaphylaxis, eosinophilia, itching, drug fever, skin rash, Stevens-Johnson syndrome,

Hematologic: Neutropenia, leukopenia, thrombo¬cytopenia, thrombocythemia,

Hepatic: Transient rise in SGOT, SGPT, and alkaline phosphatase levels has been observed (without clinical evidence of liver damage).As with other ce¬phalosporins, reports of hepatitis have been received.

Renal: As with other cephalosporins, reports of increased BUN and creatinine levels, as well as renal failure, have been received.

Local Reactions: Rare instances of phlebitis have been reported at site of injection. Pain at the site of injection after intramuscular administration has occurred infrequently. Some induration has occurred.

Other Reactions: Genital and anal pruritus (inclu¬ding vulvar pruritus, genital moniliasis, and vaginitis).

Infections and infestations: As with other antibiotics, prolonged use may result in overgrowth of non-susceptible microorganisms.

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.

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4.9 Overdose

Symptoms of overdose:

Overdosing~~e~~ may ~~can~~ cause pain, inflammatory reactions and phlebitis at the injection site. If administered in ~~administration of~~ very high parenteral doses, ~~of~~ cephalosporins may ~~can~~ cause ~~result in dizziness. Shivering~~ vertigo, paresthesias and headache. Particularly in patients with renal disease, overdosing of cephalosporin may ~~overdose can~~ induce convulsions.

~~In case of seizures, administration of the drug should be discontinued immediately and anticonvulsant therapeutic should be instituted.~~

~~If overdose occurs in patients with renal insufficiency, haemodialysis may be needed.~~

Overdos~~ag~~e may be associated with ~~lead to~~ the following abnormal laboratory test results: elevated creatinine, BUN, liver enzyme ~~values~~ and bilirubin; positive Coombs test; thrombocytosis and thrombocytopenia, eosinophilia, leukopenia as well as ~~and a~~ prolonged prothrombin time.

~~Severe acute hypersensivity reactions may require administration of epinephrine, corticosteroids or other emergency~~

Treatment of overdose:

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

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Mode of action:

~~Cefazolin is a first generation cephalosporin, and like cephalosporins and penicillins, exerts anti~~ The bactericidal activity by of cefazolin results from the inhibition~~ng~~ of ~~the synthesis of the~~ bacterial cell wall synthesis (during the growth phase) caused by an inhibition of penicillin-binding proteins (PBPs) like transpeptidases.

~~Cefazolin binds with high affinity to penicillin binding proteins on the bacterial cell wall, interrupting peptidoglycan synthesis.~~

~~Transpeptidase enzym, responsible for binding glicine to pentapeptide (d-alanine) is inhibited by~~

~~cephalosporins. As a result, bacterial cell wall is destroyed.~~

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:

~~The beta-lactam antibiotics contain a so-called beta- lactam ring which is essential for the antimicrobial action. 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, different resistance mechanism acquired by groups of bacteria include: changes in targets (penicillin-binding proteins, PBPs), enzymatic degradation of the ring by beta-lactamases and changed access to the target site.~~

~~There is cross-resistance between cephalosporins and penicilins. Gram-negative microorganisms containing inducible chromosome for beta-lactamases, such as Enterobacter spp, Serratia spp, Citrobacter spp and spp Providence, should be regarded as resistant to cefazolin despite in vitro susceptibility.~~

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.

~~Susceptibility testing~~ Breakpoints:

~~Minimum inhibitory concentration (MIC) breakpoints established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) are as follows:~~

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):

~~Organism~~ 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,~~and~~ G) 3)	3)	3)

4 Streptococci "Viridans" group ~~Streptococci~~	≤ 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. ~~to cephalosporins~~ 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.

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
~~Neisseria gonorrhoeae~~
~~Group A B, C and G streptococci, ß-haemolytic~~
Gram-positive aerobes
*Staphylococcus aureus*ɘ
Staphylococcus epidermidis+ ~~(methicillin-sensitive)~~
Staphylococcus haemolyticus+
Staphylococcus hominis+
Staphylococcus pneumoniae (penicillin-intermediate)

Gram-negative aerobes
Escherichia coli%
Haemophilus influenzae
Klebsiella oxytoca+%
~~Enterobacteriaceae spp (~~*Klebsiella pneumoniae*%~~)~~
~~Enterobacteriaceae spp (~~*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. ~~(Enterobacter cloacae, Enterobacter aerogenes)~~
Legionella spp.
Morganella morganii
Moraxella catarrhalis
~~Proteus stuartii~~
~~Indole positive Proteus spp~~
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%.

ɔ In the community the resistance rate is < 10%.

% ESBL producing strains are always resistant

~~Some strains of listed species may be more or less sensitive to the product that is declared for the majority of these microorganisms. For this reason, susceptibility testing is recommended.~~

Further information:

Penicillin-resistant Streptococcus pneumoniae are cross-resistant to cephalosporins such as cefazolin.

~~Pharmacokinetic/pharmacodynamic relationship~~
~~For cephalosporins, the most important pharmacokinetic-pharmacodynamic index correlating with in vivo efficacy has been shown to be the percentage of the dosing interval that the unbound concentration remains above the minimum inhibitory concentration (MIC) of cefazolin for individual target species (i.e., %T>MIC).~~

5.2 Pharmacokinetic properties

~~Absorption and distribution:~~
~~IM administration:~~
~~After intramuscular administration of cefazolin to normal volunteers, the mean serum concentrations were 37 mcg/mL at 1 hour and 3 mcg/mL at 8 hours following a 500-mg dose, and 64 mcg/mL at 1 hour and 7 mcg/mL at 8 hours following a 1 -gram dose.~~
~~IV administration:~~
~~Studies have shown that following intravenous administration of cefazolin to normal volunteers, mean serum concentrations peaked at approximately 185 mcg/mL and were approximately 4 mcg/mL at 8 hours for a 1-gram dose.~~
~~In a study (using normal volunteers) of constant intravenous infusion with dosages of 3.5 mg/kg for 1 hour (approximately 250 mg) and 1.5 mg/kg the next 2 hours (approximately 100 mg), cefazolin produced a steady serum level at the third hour of approximately 28 mcg/mL.~~
~~Studies in patients hospitalized with infections indicate that cefazolin produces mean peak serum levels approximately equivalent to those seen in normal volunteers.~~
~~The serum half-life for cefazolin is approximately 1.8 hours following IV administration and approximately 2.0 hours following IM administration~~
~~Bile levels in patients without obstructive biliary disease can reach or exceed serum levels by up to 5 times; however, in patients with obstructive biliary disease, bile levels of cefazolin are considerably lower than serum levels (< 1.0 mcg/mL).~~
~~After administration of therapeutic doses in patients with inflamed meninges, concentrations ranges of Cefazolin measured in cerebrospinal fluid vary from 0 to 0.4 micrograms/ml.~~
~~In synovial fluid, the level of cefazolin becomes comparable to that reached in serum at about 4 hours after drug administration.~~
~~Studies of cord blood show prompt transfer of cefazolin across the placenta, cefazolin is present in very low concentrations in the milk of nursing mothers.~~
~~Cefazolin binds to plasma proteins at about 70%- 86%.~~
~~The volume of distribution is approximately 11 L/1.73 m2~~
~~Biotransformation:~~
~~Cefazolin is not metabolized in the body.~~
~~Elimination:~~
~~Cefazolin is excreted unchanged in the urine. In the first 6 hours approximately 60% of the drug is excreted in the urine and this increases to 70% to 80% within 24 hours. Cefazolin achieves peak urine concentrations of approximately 2,400 mcg/mL and~~
~~4,000 mcg/mL respectively following 500-mg and 1-gram intramuscular doses.~~
~~Cefazolin is mainly removed from the serum by glomerular filtration, the renal clearance is 65 mll min/1.73 m2.~~
~~In patients undergoing peritoneal dialysis (2 L/hr.), cefazolin produced mean serum levels of approxi¬mately 10 and 30 mcg/mL after 24 hours instil¬lation of a dialyzing solution containing 50 mg/L and 150 mg/L, respectively. Mean peak levels were 29 mcg/mL (range 13 to 44 mcg/mL) with 50 mg/L (3 patients), and 72 mcg/mL (range 26 to 142 mcg/mL) with 150 mg/L (6 patients). Intraperitoneal adminis¬tration of cefazolin is usually well tolerated.~~

~~Controlled studies on adult normal volunteers, re¬ceiving 1 gram 4 times a day for 10 days, monitoring CBC, SGOT, SGPT, bilirubin, alkaline phosphatase, BUN, creatinine, and urinalysis, indicated no clinically significant changes attributed to cefazolin.~~

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.

קיימים עדכונים נוספים . למידע נוסף יש לעיין בעלון לרופא המעודכן.

העלון לרופא נשלח לפרסום במאגר התרופות שבאתר משרד הבריאות , וניתן לקבלו מודפס על ידי פניה לבעל הרישום
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בברכה,

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רוקחת ממונה