מרץ 2021

רופא/ה נכבד/ה,

רוקח/ת נכבד/ה,

חברת נוברטיס ישראל בע"מ מבקשת להודיעכם על עדכון העלון של התכשיר:

CEFAZOL 1G

Powder for solution for injection

מרכיב פעיל: cefazolin (as sodium) 1g/vial

ההתוויות העדכניות המאושרות לתכשיר הינן:

Treatment of serious infections caused by susceptible organisms and also perioperatively for prophylaxis.
Treatment Respiratory tract:
Respiratory tract infections due to streptococcus pneumoniae (formerly diplococcus pneumoniae) klebsiella species haemophilus influenzae staphylococcus aureus (penicillin-sensitive and penicillin-resistant) and group A B - hemolytic streptococci.
Cefazolin is effective in the eradication of streptococci from the nasopharynx. However data establishing the efficacy of cefazolin in the subsequent prevention of rheumatic fever are not available at present.
Urinary tract:
Infections due to escherichia coli klebsiella species proteus mirabilis and some strains of Enterobacter and enterococci.
Skin and skin structure:
-hemolytic beta Infections due to Staphylococcus aureus (penicillin-sensitive and penicillin-resistant) group A streptococci and other strains of streptococci.
Biliary tract:
Infections due to escherichia coli various strains of streptococci proteus mirabilis klebsiella species and staphylococcus aureus.
Bone and joint :
Infections due to staphylococcus aureus.
Genital infections (i.e. prostatitis epididymitis) due to escherichia coli proteus mirabilis klebsiella species and some strains of enterococci.
Septicemia due to streptococcus pneumoniae (formerly diplococcus pneumoniae) staphylococcus aureus (penicillin-sensitive and penicillin-resistant) proteus mirabilis escherichia coli and klebsiella species.
Endocarditis caused by staphylococcus aureus (penicillin-sensitive and penicillin-resistant) and group A betahemolytic streptococci.
Appropriate culture and susceptibility studies should be performed to determine the susceptibility of the causative organism to cefazolin.
Perioperative prophylaxis:
The prophylactic administraton of cefazolin perioperatively (preoperatively intraoperatively and postoperatively) may reduce the incidence of certain postoperative infectons in patients undergoing surgical procedures (e.g. hysterectomy gastrointestinal surgery and transurethral prostatectomy) that are classified as contaminated or potentially contaminated.
The perioperative use of cefazolin may also be effective in surgical patients in whom infection at the operative site would present a serious risk (e.g. open-heart surgery and prosthetic arthroplasty).

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נוברטיס ישראל בע"מ.
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העלון לרופא אומץ כלשונו מהאסמכתא המאושרת (בוצע מעבר אסמכתא בהתאם לאישור משרד הבריאות), והותאם לפורמט החדש. בשל מעבר האסמכתא, והעדכונים הנרחבים שבוצעו במסגרתו, העלון המעודכן מצורף בשלמותו להודעה זו.

ניתן לראות מטה את השינויים המהותיים בלבד.

מקרא לעדכונים המסומנים מטה:

תוספת החמרה – כתב כחול

תוספת – כתב כחול

מידע שהוסר – קו אדום חוצה ~~XXX~~

4.3 Contraindications

~~This medicinal product must not be used in cases of known~~ ~~h~~Hypersensitivity to ~~cefazolin~~ the active substance, ~~or~~ other cephalosporins or to any of the excipients listed in section 6.1.
~~and in patients who have previously shown~~ History of previous immediate and/or severe hypersensitivity reaction~~s~~ to a penicillin or to any other type of beta-lactam drug ~~antibiotic~~.
~~For use in children of less than 30 months of age, Cefazol must not be dissolved in lidocaine solutions.~~
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

- In patients ~~exhibiting~~ developing allergic reactions~~,~~ the drug ~~product must~~ should be discontinued and appropriate symptomatic ~~therapy~~ treatment should be instituted. ~~Serious acute hypersensitivity reactions may require adrenaline (epinephrine) and other emergency measures, including oxygen, IV fluids, IV antihistamines, corticosteroids, pressor amines and airway management, as clinically indicated.~~ Cross allergies~~y~~ with other cephalosporins and occasionally occuring cross allergies with penicillins ~~must~~ should be considered ~~borne in mind~~. In cases of known hypersensitivity to penicillins, a cross-allergy ~~with~~ to other beta-lactams, ~~e.g.~~such as cephalosporins~~, must~~ should be taken into account. ~~Cross hypersensitivity among beta-lactam antibiotics has been clearly documented and may occur in up to 10% of patients with a history of penicillin allergy.~~

~~In patients with impaired renal function, the dosage and/or dosing frequency must be adjusted to the degree of renal dysfunction~~ - 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). ~~As with other beta-lactam antibiotics, seizures may occur if inappropriately high doses are administered to patients with impaired renal function~~.

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

- *Antibiotic-related pseudomembranous colitis*
  Cases of antibiotic-associated colitis have been reported in almost all antibiotics, the severity of which can range from mild to life threatening (see section 4.8). Therefore it is important to be mindful of this diagnosis in patients who experience diarrhoea during or after using an antibiotic. In the event of antibiotic-associated colitis, cefazolin should be discontinued immediately, a doctor consulted, and appropriate treatment initiated. Anti-peristaltic medicinal products are contraindicated in this situation.

- With long-term use of cefazolin, non-sensitive pathogens can get out of control. Close monitoring of the patient is therefore essential. If a superinfection occurs during treatment, appropriate measures must be taken.

Long-term or high-dose therapy
- Regular check of organ system functions, including renal, hepatic and hematopoietic function, is advisable during long-term or high-dose treatment. Elevated liver enzymes and changes in blood cells have been reported (see section 4.8).

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

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

Athletes should bear in mind that positive results may be obtained in anti-doping tests when cefazolin is dissolved in lidocaine.

Not for intrathecal use.

Prescribing cefazolin 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.

Intrathecal administration

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

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

4.7 Effects on ability to drive and use machines

Cefazol has no influence or negligible influence on the ability to drive and use machines. No studies on the effects on the ability to drive and use machines have been performed. However, some adverse reactions (e.g. vertigo, headache, paresthesia, agitation, seizures; see section 4.8) there may be side effects (e.g allergic reactions, dizziness) which may affect the ability to concentrate and on reaction times and may therefore impair the ability to drive or and use machines (see section 4.8).

4.8 Undesirable effects

System organ class	Common	Uncommon	Rare	Very rare	Not known
Infections and infestations			Rhinitis		Long-term treatment or repeated use may lead to superinfections or colonisation with resistant bacteria or yeasts-like fungi (oral thrush, vaginal candidiasis monoliasis vaginalis)
Blood and lymphatic system disorders		Thrombocytopenia, neutropenia, leucopenia, eosinophilia, agranulocytosis, haemolytic anaemia,	Coagulation disorders, haemorrhages *		Leukocytosis granulocytosis, monocytosis, lymphocytopenia, basophilia, reduced haemoglobin

		granulocytosis, leukocytosis, monocytosis, lymphocytopenia, basophilia			~~and/or haematocrit, aplastic anaemia, pancytopenia~~
Immune system disorders	Allergic skin reactions such as erythema, ~~generalized exanthema,~~ urticaria and pruritus	~~Serious~~ Severe hypersensitivity reactions such as angioedema and drug-induced fever		Life threatening anaphylactic shock **	~~Erythema exsudativum multiforme. Interstitial pneumonia or pneumonitis, Lyell's syndrome, Stevens-Johnsons syndrome~~
Metabolism and nutrition disorders			Hyperglycaemia, hypoglycaemia		
Nervous system disorders			dizziness		~~Headache, dizziness, malaise, tiredness, vertigo, paraesthesia, excitation of the central nervous system, hyperactivity, nervousness or anxiety, sleeplessness, sleepiness, weakness, hot flushes, colour perception changes and confused states, myoclonus, seizures§, convulsive fits~~ convulsions§ ~~aseptic meningitis~~

Respiratory, thoracic and mediastinal disorders			Pleural effusion, dyspnoea or respiratory distress, cough		
Gastrointestinal disorders	Diarrhoea, nausea, vomiting, loss of appetite~~, flatulence, abdominal pain#~~				Pseudomembranous colitis +
Skin and subcutaneous tissue disorders	Rash	Erythema multiforme, angioedema	Toxic epidermal necrolysis, Stevens-Johnson syndrome		
Hepatobiliary disorders		Slight ~~Mild~~, transient elevation of AST, ALT and alkaline phosphatase	Temporary increase in GGT, bilirubin and/or LDH	Reversible hepatitis and cholestatic jaundice	~~Raised GGT, bilirubin and/or LDH~~
Renal and urinary disorders			Interstitial nephritis and other kidney diseases $		~~Transient rise in BUN levels (blood, urea, nitrogen) and serum creatinine concentrations, nephrotoxicity $~~
General disorders and administration site conditions		Phlebitis, thrombophlebitis	Malaise, fatigue, chest pain		~~Chest pains, pleural effusion, dyspnea or respiratory distress, cough, rhinitis, raised or lowered serum glucose concentration, genital and anal pruritus, genital moniliasis, vaginitis, pain from IM~~

					~~administration .~~ ~~Photosensitive phenomena have been described~~

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 peristaltic 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 haematocrit, anaemia, aplastic anaemia,pancytopenia and haemolytic anaemia.

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

Nightmares, vertigo, hyperactivity, nervousness or anxiety, insomnia, drowsiness, weakness, hot flushes, disturbed colour vision, confusion and epileptogenic activity.

מלבד השינויים המפורטים מעלה, קיימים עדכונים נוספים.

למידע נוסף, ניתן לעיין בעלון לרופא המצורף להודעה זו.

העלון לרופא נשלח לפרסום במאגר התרופות באתר משרד הבריאות:

https://data.health.gov.il/drugs/index.html#!/byDrug

כמו כן ניתן לקבלו מודפס על ידי פניה לחברת נוברטיס ישראל בע"מ.

לעדכונכם בברכה,

דפנה סנדובסקי

רוקחת ממונה חטיבת סנדוז

נוברטיס ישראל בע"מ