SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Cefazolin <TRADE NAME> <STRENGTH> Powders for solutions for injections or infusions

<REGARDING THE APPROVAL>

1. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains <STRENGTH> cefazolin (as cefazolin sodium).

For the full list of excipients, see section 6.1.

<REGARDING THE APPROVAL>

1. PHARMACEUTICAL FORM

Powders for solutions for injections or infusions

1. CLINICAL PARTICULARS
   1. Therapeutic indications

Cefazolin 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.

* 1. 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**

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**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 Powder for solution for injection/infusion in these patients is not recommended. See also section 4.4.

**Guidelines for paediatric dosage**

<REGARDING THE APPROVAL>

**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**

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

**Method of administration**

Cefazolin Powder for solution for injection/infusion may be administered by slow intravenous injection or by intravenous infusion after dilution. Single doses exceeding 1 g should be given as intravenous infusion.

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). Τhe 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.

* 1. Contraindications

Hypersensitivity to cefazolin sodium.

Patients with known hypersensitivity to cephalosporin antibiotics.

History of severe hypersensitivity (e.g. anaphylactic reaction) to any other type of beta-lactam antibacterial agent (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:

* known history of hypersensitivity to lidocaine or other local anesthetics of the amide type
* non-paced heart block
* severe heart failure
* administration by the intravenous route
* infants aged less than 30 months of age

Cefazolin solutions containing lidocaine should never be administered intravenously.

* 1. Special warnings and precautions for use

**Warnings**

In case of any known hypersensitivity to penicillins or other beta-lactam antibiotics, attention is to be paid to a possible cross-sensitivity (see section 4.3).

As with all beta-lactam antibacterial agents, serious and occasionally fatal hypersensitivity reactions have been reported. In case of severe hypersensitivity reactions, treatment with cefazolin must be discontinued immediately and adequate emergency measures must be initiated.

Before beginning treatment, it should be established whether the patient has a history of severe hypersensitivity reactions to cefazolin, to other cephalosporins or to any other type of beta-lactam agent. Caution should be used if cefazolin is given to patients with a history of non-severe hypersensitivity to other beta-lactam agents.

Cefazolin should be administered only with special caution to patients with allergic reactivity (e. g. allergic rhinitis or bronchial asthma) as the risk for a serious hypersensitivity reaction is increased.

Antibacterial agent-associated pseudomembranous colitis has been reported with use of cefazolin and may range in severity from mild to life threatening. This diagnosis should be considered in patients with diarrhoea during or subsequent to the administration of cefazolin (see section 4.8). Discontinuation of therapy with cefazolin and the administration of specific treatment for Clostridium difficile should be considered. Medicinal products that inhibit peristalsis should not be given.

Paediatric use: As there are no sufficient experiences available so far, Cefazolin Powder for solution for injection/infusion must not be applied to new-borns and babies in the first month of life.

Use of lidocaine:

In case a lidocaine solution is used as a solvent, cefazolin solutions must only be used for intramuscular injection. Contraidications 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.

**Precautions**

In case of a renal insufficiency with a glomerular filtration rate under 55 mL / min, an accumulation of cefazolin must be taken into consideration. Therefore, the dosage has to be reduced accordingly or the dosage interval has to be prolonged (see section 4.2).

In patients with renal impairment the use of cefazolin may be associated with seizures.

Prolonged prothrombin time may occur in patients with renal or hepatic impairment or poor nutritional state, as well as in patients receiving a protracted course of antimicrobial therapy, and patients previously stabilised on anticoagulant therapy. In these patients the prolongation of prothrombin time has to be monitored under treatment with cefazolin since it can very rarely cause plasmatic blood coagulation diseases (see sections 4.5 and 4.8). Therefore, INR (International Normalised Ratio) has to be measured regularly in patients with diseases which can cause haemorrhages (e.g. gastro-intestinal ulcers) as well as in patients with coagulation defects (inherited: e.g. haemophilia; acquired: e.g. by parenteral feeding, malnutrition, disordered liver or renal function or thrombocytopenia; caused by drugs: e.g. by heparin or other oral anticoagulants). Vitamin K can be substituted (10 mg per week) if necessary.

Long-term and repeated administration can lead to overgrowth of resistant organisms.

If superinfection occurs during therapy, appropriate measures should be taken.

Effects on laboratory tests

In rare cases, the non-enzymatic urine sugar test and the Coombs test can show false positive results.

**Excipient information**

<REGARDING THE APPROVAL>

* 1. Interaction with other medicinal products and other forms of interaction

**Anticoagulants**

Cephalosporins may very rarely cause bleeding disorders (see 4.4). During concomitant use with oral anticoagulants (for e.g. warfarin or heparin) in high doses, the coagulation parameters should be monitored.

**Vitamin K1**

Some cefalosporins such as cefamandol, cefazolin and cefotetan can cause interference in the metabolism of vitamin K1, especially in cases of vitamin K1 deficiency. This may require vitamin K1 supplementation.

**Probenecid**

Due to its inhibitory effect on the renal diuresis, the administration of probenicid induces a higher concentration and a longer retention time of cefazolin in the blood.

**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 antivirals (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.

* 1. Fertility, pregnancy and lactation

**Pregnancy**

Cefazolin reaches the embryo/foetus via the placenta. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. There is not sufficient experience in the human use of cefazolin. As a precautionary measure, it is preferable to avoid the use of Cefazolin Powder for solution for injection/infusion during pregnancy, if the use is not necessary.

**Breast-feeding**

Cefazolin passes into breast milk in very low concentrations, and therefore at therapeutic doses, no effects on the infant are expected. If diarrhoea or candidosis occurs in the infant during breastfeeding, the mother should stop breastfeeding or cefazolin should be withdrawn.

**Fertility**

Animal studies have shown no effects on fertility.

* 1. Effects on ability to drive and use machines

Cefazolin has no or negligible influence on the ability to drive and use machines.

* 1. Undesirable effects

Undesirable effects are ranked according to body system and frequency according to the following classification:

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 (MedDRA)** | **Common** | **Uncommon** | **Rare** | **Very rare** | **Not known** |
| **Infections and infestations** |  | Oral candidiasis (prolonged use). | Genital candidiasis (monoliasis), vaginitis |  |  |
| **Blood and lymphatic system disorder** |  |  | Increase or decrease in blood glucose concentration (hyperglycaem ia or hypoglycaemia ). Leukopenia, Granulocytopenia, neutropenia, thrombocytopenia, Coagulation (blood clotting) disorders and bleeding as a consequence. At risk for these side effects are patients with a deficiency of vitamin K or other blood clotting leukocytosis, granulocytosis, monocytosis, lymphocytopenia, basophilia and eosinophilia were observed in blood counts. These effects are rare and reversible. | Coagulation (blood clotting) disorders and bleeding as a consequence. At risk for these side effects are patients with a deficiency of vitamin K or other blood clotting factors, or patients on artificial nutrition, inadequate diet, impaired liver and renal function, thrombocytopenia and patients with disorders or diseases that cause bleeding (e.g., haemophilia, stomach and duodenal ulcers). Also see sections 4.4 and 4.5. Decreased haemoglobin and/or hematocrit, anaemia, agranulocytosi s, aplastic anaemia, pancytopenia and hemolytic anaemia |  |
| **Immune system disorders** |  | Erythema, erythema multiforme, exanthema, urticaria, reversible local permeability of the blood vessels, joints, or mucous membranes (angioedema) , drug-induced fever and interstitial pneumonia or pneumonitis | Toxic epidermal necrolysis (Lyell's syndrome), Stevens-Johnson syndrome. | Anaphylactic shock, swelling of the larynx with narrowing of the airways , increased heart rate, shortness of breath, falling blood pressure, swollen tongue, anal pruritus, genital pruritus, face edema. |  |
| **Nervous system disorders** |  | Seizures (in patients with renal dysfunction, with inappropriate high treated doses) | Dizziness, malaise, fatigue. Nightmares, vertigo, hyperactivity, nervousness or anxiety, insomnia, drowsiness, weakness, hot flushes, disturbed colour vision, confusion and epileptogenic activity. |  |  |
| **Respiratory, thoracic and mediastinal disorders** |  |  | Pleural effusion, chest pain, dyspnoea or respiratory distress, cough,rhinitis. |  |  |
| **Gastrointestin al disorders** | Loss of appetite, diarrhoea, nausea and vomiting. These symptoms are usually moderate and often disappear during or after treatment |  |  | Pseudo-membranous colitis (see section 4.4) |  |
| **Hepatobiliary disorders** |  |  | Temporary increase in serum concentrations of AST, ALT, gamma GT, bilirubin and / or LDH and alkaline phosphatase, transient hepatitis, transient cholestatic jaundice. |  |  |
| **Renal and urinary disorders** |  |  | Nephrotoxicity , interstitial nephritis, undefined nephropathy, proteinuria, temporary increase in blood urea nitrogen (BUN) usually in patients treated concomitantly with other potential nephrotoxic medicines. |  |  |
| **General disorders and administration site conditions** | Pain at the site of intramuscular injection, sometimes with induration | Intravenous administratio n may cause thrombophlebitis |  |  | For IM formulation s (since the solvent contains lidocaine): Systemic reactions to lidocaine |

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 Health Product Vigilance Center; HPVC.

* 1. Overdose

Symptoms of an overdose are headache, vertigo, paraesthesia, central nervous system disorders such as agitation, myoclonia and convulsions.

In case of poisoning, elimination accelerating measures are indicated. A specific antidote does not exist. Cefazolin can be haemodialysed.

1. PHARMACOLOGICAL PROPERTIES
   1. Pharmacodynamic properties

Pharmacotherapeutic group: Other beta-lactam antibacterials, first generation cephalosporins.

ATC code: J01DB04

Cefazolin is a bactericidal cephalosporin antibiotic of the first generation for parenteral administration.

Cephalosporins inhibit cell wall synthesis (in the growth stage) through blocking the penicillin-binding proteins (PBPs) like transpeptidases. The outcome is a bactericidal action.

**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).

**Resistance mechanisms**

Resistance to cefazolin can rest upon one of the following mechanisms:

− Inactivation by beta-lactamases: cefazolin has a high stability against penicillinases of gram-positive bacteria, but only a low stability against plasmid-coded beta-lactamases, e.g. extended-spectrum beta-lactamases or chromosomal-coded beta-lactamases of AmpC-type.

− Reduced affinity of the PBPs to cefazolin: the acquired resistance of pneumococci and other streptococci is caused by modifications of the PBPs due to mutations. The resistance of methicillin (oxacillin)-resistant Staphylococci is due to the formation of an additional PBP with a lower affinity to cefazolin.

− Insufficient penetration of cefazolin through the outer cell wall of gram-negative bacteria can lead to an insufficient inhibition of the PBPs.

− Cefazolin can be transported outside the cell through efflux pumps.

There is a partial or total cross-resistance of cefazolin with other cephalosporins and penicillins.

**Breakpoints**

The following breakpoints have been established by the European Committee for Antimicrobial Susceptibility Testing (EUCAST) Clinical MIC Breakpoints (Version 8.1, valid from 2018-05-15).

|  |  |  |
| --- | --- | --- |
| **PATHOGEN** | **SUSCEPTIBLE** (≤) | **RESISTANT** (>) |
| **Staphylococcus spp.** | Note A | Note A |
| **Streptococcus*spp.***  ***(Groups A, B, C, G)*** | Note B | Note B |
| **Viridans group streptococci** | 0.5 mg / L | 0.5 mg / L |
| **PK/PD (Non-species related) breakpoints** | 1 mg / L | 2 mg / L |

ASusceptibility of staphylococci to cephalosporins is inferred from the cefoxitin susceptibility except for cefixime, ceftazidime, ceftazidime-avibactam, ceftibuten and ceftolozane-tazobactam, which do not have breakpoints and should not be used for staphylococcal infections. Some methicillin-resistant S. aureus are susceptible to ceftaroline and ceftobiprole.

BThe susceptibility of streptococcus groups A, B, C and G to cephalosporins is inferred from the benzylpenicillin susceptibility.

**Microbiological susceptibility**

The following table shows clinically relevant pathogens classified as sensitive or resistant on the basis of in vitro and in vivo data. Cefazolin is effective against some species in vitro, but not clinically, thus these species are classified here as resistant.

The prevalence of acquired resistance may vary geographically and with time for selected species and local information is desirable, particularly when treating severe infections. If necessary, expert advice should be sought when the local prevalence of resistance is such that the efficacy of cefazolin is questionable. Especially in case of severe infections or failure of therapy, a microbiological diagnosis including identification of the microorganism and its susceptibility to cefazolin should be conducted.

**Commonly susceptible species**

Aerobe Gram-positive

Staphylococcus aureus (methicillin-sensitive)

**Species for which acquired resistance may be a problem**

Aerobe Gram-positive

Group A, B, C and G beta-haemolytic streptococci

Staphylococcus epidermidis (methicillin-sensitive)

Streptococcus pneumoniae

Aerobe Gram-negative

Haemophilus influenzae

**Inherently resistant organisms**

Aerobe Gram-positive

Staphylococcus aureus, methicillin-resistant

Aerobe Gram-negative

Citrobacter spp.

Enterobacter spp.

Klebsiella pneumoniae

Morganella morganii

Proteus mirabilis

Proteus stuartii

Proteus vulgaris

Pseudomonas aeruginosa

Serratia spp.

* 1. Pharmacokinetic properties

**Absorption**

Cefazolin is administered parenterally. After administration of 500 mg intramuscular injection, maximum serum levels obtained after approximately an hour were 20-40 micrograms / mL. After administration of 1 g maximum serum levels of 37 – 63 micrograms / mL were obtained. In one continuous intravenous infusion of cefazolin study in healthy adults at doses of 3.5 mg / kg for one hour (approx 250 mg) followed by 1.5 mg / kg for the next two hours (approx. 100 mg) a stable serum concentration of approx. 28 micrograms / mL was demonstrated in the third hour. The following table shows the mean serum concentration of cefazolin after intravenous injection of a single dose of 1 g.

**Distribution**

Cefazolin for 70% - 86% bound to plasma proteins. The volume of distribution is approximately 11 L / 1.73 m2. When cefazolin is administered to patients without obstruction of the bile ducts the antibiotic levels 90 – 120 minutes after administration were generally higher than antibiotic levels in the serum.

Conversely, where obstruction exists the concentrations of antibiotic in the bile were much lower than serum levels. After administration of therapeutic doses in patients with inflamed meninges, varying concentrations of cefazolin from 0 to 0.4 micrograms / mL were measured in cerebrospinal fluid. Cefazolin can easily pass through inflamed synovial membranes and the antibiotic concentration achieved in joints is similar to serum levels.

**Biotransformation and elimination**

Cefazolin is not metabolised.

**Elimination**

The serum half-life is about 1 hour 35 minutes. Cefazolin is excreted in a microbiologically active form in the urine. Approximately 56-89% of an intramuscular dose of 500 mg is excreted in the first six hours, 80% to almost 100% is excreted within 24 hours. After intramuscular administration of 500 mg and 1 g urine levels can reach 500-4000 μg / mL. Cefazolin is mainly removed from the serum by glomerular filtration, the renal clearance is 65 mL / min / 1.73 m2.

* 1. Preclinical safety data

The acute toxicity of cefazolin is low.

Repeated administration of cefazolin in dogs and rats for 1-6 months by different routes of administration did not show any significant effect on hematological and biochemical parameters. Renal toxicity was observed after repeated doses in rabbits, but not in dogs or rats. Cefazolin showed no teratogenic or embryotoxic activity.

No studies are available on the mutagenicity and carcinogenicity of cefazolin.

1. PHARMACEUTICAL PARTICULARS
   1. List of excipients

<REGARDING THE APPROVAL>

* 1. 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.

* 1. Shelf life

<REGARDING THE APPROVAL>

* 1. Special precautions for storage

<REGARDING THE APPROVAL>

* 1. Nature and contents of container

<REGARDING THE APPROVAL>

* 1. Special precautions for disposal

**Preparation of the solution** <REGARDING THE APPROVAL>

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**

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**Intravenous injection**

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Reconstitute Cefazolin 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

**Intravenous infusion**

<REGARDING THE APPROVAL>

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

1. MARKETING AUTHORISATION HOLDER

<REGARDING THE APPROVAL>

1. MARKETING AUTHORISATION NUMBER(S)

<REGARDING THE APPROVAL>

1. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

<REGARDING THE APPROVAL>

1. DATE OF REVISION OF THE TEXT1

<REGARDING THE APPROVAL>