**PACKAGE LEAFLET**

## 1. NAME OF THE MEDICINAL PRODUCT

CEFAZOLIN ALVOGEN 1 g powder for solution for injection or infusion

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains cefazolin sodium equivalent to 1 g cefazolin.

## 3. PHARMACEUTICAL FORM

Powder for solution for injection or infusion

White to almost white powder

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

CEFAZOLIN ALVOGEN is indicated in adults and children for the treatment of the following infections due to bacteria which are susceptible to cefazolin:
- Respiratory tract infections.
- Sepsis.
- Skin and soft tissue infections.
- Endocarditis.
- Urinary tract and genital infections.
- Bile duct infections.
- Bone and joint infections.

Other indications that require only intravenous administration:

CEFAZOLIN ALVOGEN is indicated for pre-operative prophylaxis of post-operative infections in:
- Neurosurgery (craniotomy, liquor derivation).
- Cardiac surgery.
- Thoracic surgery.
- Vascular surgery.
- Gastro-intestinal surgery.
- Hepatobiliary surgery.
- Caesarean section.
- Abdominal or vaginal hysterectomy.
- Surgery of the head and neck with oropharynx opening.
- Orthopaedic surgery.

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

### 4.2 Posology and method of administration

Posology

*Recommended dosage for intravenous administration*

The following doses can be adjusted depending on the severity of the infection:

| | ***Dose*** | ***Frequency of dosing*** |
|---|---|---|
| Adult patients | 500 mg-1 g | Every 8-12 hours |
| Children and infants (over 1 month) | 25-50 mg/kg | every 24 hours |
| Pre-term newborns and neonates | Not recommended. | |

The safety of cefazolin in pre-term newborns and neonates has not been established. Therefore, the use of cefazolin is not recommended.

*Recommended dosage for intramuscular administration*

The following doses can be adjusted depending on the severity of the infection:

| | ***Dose*** | ***Frequency of dosing*** |
|---|---|---|
| Adult patients | 500 mg-1 g | Every 8-12 hours |
| Children (over 30 months) | 25-50 mg/kg | every 24 hours |
| Pre-term newborns and neonates | Not recommended if diluted with lidocaine. | |

*Recommended dosage in patients with renal impairment*

Severe infections:

| ***Creatinine clearance (ml/min)*** | ***Starting dose*** | ***Maintenance dose*** |
|---|---|---|
| 50-20 | 500 mg | 250 mg daily every 6 hours or<br>500 mg daily every 12 hours |
| 20-10 | 500 mg | 250 mg daily every 12 hours or<br>500 mg daily every 24 hours |
| 10-5 | 500 mg | 250 mg daily every 24-36 hours or<br>500 mg daily every 48-72 hours |
| < 5 in patients on haemodialysis | 500 mg IV | 500 mg daily every 72 hours |

Mild infections:

| ***Creatinine clearance (ml/min)*** | ***Starting dose*** | ***Maintenance dose*** |
|---|---|---|
| 50-20 | 500 mg | 125-250 mg daily every 12 hours |
| 20-10 | 500 mg | 125-250 mg daily every 24 hours |
| 10-5 | 500 mg | 75-125 mg daily every 24 hours |
| < 5 in patients on haemodialysis | 500 mg IV | 50-75 mg daily every 72 hours |

*Prophylaxis of post-operative infections*
Generally, the prophylactic administration of the medicinal product should be short term- within 24 to 48 hours.

- The usual dose is 1 g intravenously administered during the induction of anaesthesia, followed by a dose of 0.5-1 g administered intravenously every 6-8 hours for 24 hours postoperatively.
- For operative procedures lasting longer than 2 hours, 0.5-1 g is administered intravenously during surgery.

Method of administration
CEFAZOLIN ALVOGEN is administered by deep intramuscular injection or by intravenous bolus injection or infusion.
The powder for solution for injection or infusion should be initially diluted with 2-3 ml of diluent. The solution should be further reconstituted as follows:

*Intramuscular injection:*
The solution is further reconstituted with water for injection (concentration of the solution 250 mg/ml).

*Intravenous injection:*
The solution is further reconstituted with water for injection (concentration of the solution 100 mg/ml).

CEFAZOLIN ALVOGEN may be administered either by slow intravenous injection over a period of 3 to 5 min directly into a vein or *via* a drip tube.

*Intravenous infusion:*
The solution is further reconstituted with one of the following compatible diluents (concentration of the solution 20 mg/ml):
- 0.9% NaCl Injection,
- 5% Glucose Injection,
- 10% Glucose Injection,
- 5% Glucose and 0.9% NaCl Injection,
- 5% Glucose and 0.45% NaCl Injection,
- 5% Glucose and 0.225% NaCl Injection,
- 4% Glucose and 0.18% NaCl Injection,
- Compound sodium chloride injection,
- Lactated Ringer's injection.

For instructions on reconstitution and dilution of the medicinal product before administration, see section 6.6.

## 4.3 Contraindications

Hypersensitivity to the active substance or any other cephalosporins.

Pre-term newborns and neonates
The safety of cefazolin in pre-term newborns and neonates has not been established. Therefore, the use of cefazolin is not recommended.

## 4.4 Special warnings and precautions for use

Special warnings
If a hypersensitivity reaction occurs, the treatment should be discontinued.

An inquiry concerning previous hypersensitivity reactions to cephalosporins, penicillins or other medicinal products should be made before starting any new course of therapy with cephalosporins.

There is a cross hypersensitivity between penicillins and cephalosporins in 5-10% of the patients. Therefore:
- Extreme caution and medical supervision during the first administration are required in patients who are hypersensitive to penicillin.
- Cephalosporins should not be used in patients who are known to exhibit immediate hypersensitivity reactions to cephalosporins.
- If there is any doubt, a physician should be present during the first administration to treat any anaphylactic reactions that may occur.

- Hypersensitivity reactions to penicillins and cephalosporins may be severe and sometimes fatal.

Rare cases of pseudomembranous colitis have been reported with use of broad-spectrum antibiotics. It is therefore important to consider this diagnosis in patients who develop diarrhoea during or after treatment with antibacterial medicinal products. The diarrhoea is reversible after treatment discontinuation; however, the severe cases require special treatment.

Cefazolin mixed with lidocaine should not be used:
- Intravenously.
- In children below 30 months.
- In patients with known hypersensitivity to lidocaine or any other local anaesthetics from the amides group.
- In patients with AV block without a pacemaker.

As with other antibacterial agents, prolonged use of cefazolin may result in overgrowth of non-susceptible microorganisms, including candida. It is therefore very important to monitor the patient continuously. Appropriate measures should be taken in the event of a super-infection during treatment.

Precautions
Intramuscular administration of cephalosporin which is mixed with lidocaine may produce a positive reaction in anti-doping tests. Therefore, athletes should be treated with caution.

In patients treated concomitantly with potentially nephrotoxic medicinal products, such as aminoglycosides or diuretics (e.g. furosemide or ethacrynic acid), careful and constant monitoring of the renal function is recommended (see section 4.5).

In patients with renal insufficiency, the dose should be adjusted to the creatinine clearance and the blood creatinine levels (see section 4.2).

Cefazolin is not recommended for use in patients with meningitis (even if it is caused by susceptible microorganisms), because of the poor penetration into the cerebrospinal fluid.

## 4.5 Interaction with other medicinal products and other forms of interaction

Probenecid
Probenecid may decrease renal excretion of cefazolin, therefore their concomitant use may result in increased and more prolonged serum levels of cefazolin.

Anticoagulants
Some cephalosporins, including cefazolin may potentiate the effect of anticoagulants. Coagulation parameters should be therefore monitored regularly during concurrent administration.

Aminoglycosides/diuretics
Concomitant use of cefazolin with potentially nephrotoxic medicinal products such as aminoglycosides and loop diuretics may result in an increased risk of renal impairment.

Laboratory tests
Cases of positive direct and indirect Coombs' tests have been reported during treatment with cephalosporins, including cefazolin.

A false positive reaction for glucose in the urine (with the use of reduction methods) may also occur.

## 4.6 Fertility, pregnancy and lactation

Pregnancy

Animal studies did not demostrate teratogenic effects. Therefore, malformations in humans are not expected.
Studies in pregnant women did not indicate any harmful effects on the pregnancy or any foetotoxic effects.

Nevertheless, this product should be administered only after careful evaluation of the potential effects on the pregnancy.

As a precaution, the use of cefazolin is not recommended during pregnancy, unless clearly necessary.

Breastfeeding
Cefazolin is excreted in breast milk in small amounts (< 5%), which is below the therapeutic dose range. Therefore, cefazolin can be used during breastfeeding.

However, if diarrhoea, fungal infection or skin rash occur, breastfeeding (or treatment with cefazolin) should be discontinued.

### 4.7 Effects on ability to drive and use machines

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

### 4.8 Undesirable effects

The undesirable effects are listed in the table below in accordance with the MedDRA SOC convention.

Frequencies are defined as:
Very common (≥ 1/10),
Common (≥ 1/100 to < 1/10),
Uncommon (≥ 1/1,000 to < 1/100),
Rare (≥ 1/10,000 to < 1/1,000),
Very rare (< 1/10,000),
Not known (cannot be estimated from the available data).

| ***MedDRA SOC*** | ***Frequency*** | ***Undesirable effect*** |
|---|---|---|
| Infections and infestations | Rare | Oral candidiasis, vaginal candidiasis |
| Blood and lymphatic system disorders | Rare | Eosinophilia, leukopenia, thrombocytopenia (reversible) |
| Immune system disorders | Common | Exanthema, urticaria, pruritus |
| | Rare | Angioedema, anaphylactic shock |
| Nervous system disorders | - | Headache, dizziness, paraesthesia, seizures (in patients treated with high doses and especially with renal impairment) |
| Gastrointestinal disorders | Common | Diarrhoea, nausea, anorexia, vomiting, meteorism, abdominal pain |
| | Rare | Pseudomembranous colitis |
| Hepatobiliary disorders | - | Transient increase in hepatic aminotransferases (AST and ALT) and alkaline phosphatase |
| | Very rare | Reversible hepatitis and |

| | | |
|---|---|---|
| | | cholestatic jaundice |
| Renal and urinary disorders | Very rare | Interstitial nephritis (see section 4.5) |
| General disorders and administration site conditions | Rare | Fever, pain at the injection site, phlebitis |

### 4.9 Overdose

Symptoms
Symptoms of overdose include dizziness, paraesthesia and headache. Metabolic encephalopathy (disorders of consciousness, unstable movements, seizures) can occur following overdose with some cephalosporins, particularly in patients with impaired renal function.

Treatment
The administration of cefazolin should be discontinued if symptoms of overdose occur. The vital functions should be monitored closely and anti-convulsant therapy must be provided if seizures occur. Combined haemodialysis and haemoperfusion can be considered in the event of a severe overdose, in particular in patients with renal insufficiency, if the patient does not respond to more conservative therapy. However, there are no data to support this therapy.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other beta-lactam antibacterials; first generation cephalosporins, ATC code: J01DB04

Serum concentrations differentiate the susceptible species from species with intermediate susceptibility and resistant species: S < 8 mg/l and R > 32 mg/l

The prevalence of resistance may vary geographically and with time for selected species, and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

### 5.2 Pharmacokinetic properties

Cefazolin may be administered intramuscularly or intravenously.

A study (of healthy adults) with regards to the continuous intravenous infusion of cefazolin in doses of 3.5 mg/kg for an hour (approximately 250 mg) followed by 1.5 mg/kg for the next two hours (approximatley 100 mg), a stable serum concentration of 28 μg/ml was measured for the third hour.

*Serum concentrations after 1 g intravenous (μg/ml)*

| ***5 min*** | ***15 min*** | ***30 min*** | ***1 hour*** | ***2 hours*** | ***4 hours*** |
|---|---|---|---|---|---|
| 188.4 | 135.8 | 106.8 | 73.7 | 45.6 | 16.5 |

*Serum concentrations after 500 mg anf 1 g intramuscular (μg/ml)*

| | ***½ h*** | ***1 h*** | ***2 h*** | ***4 h*** | ***6 h*** | ***8 h*** |
|---|---|---|---|---|---|---|
| 500 mg IM | 36.2 | 36.8 | 37.9 | 15.5 | 6.3 | 3.0 |
| 1 g IM | 60.1 | 63.8 | 54.3 | 29.3 | 13.2 | 7.1 |

The serum half-life is 1 hour and 40 minutes in patients with normal renal function.

Therapeutic levels are achieved in pleural fluid, synovial fluid and peritoneal fluid. Bile levels in patients without gall bladder obstruction can exceed serum levels. If there is an obstruction, the concentrations of the antibiotic in the bile is much lower than the serum levels.

Cefazolin crosses the placental barrier and reaches the foetal circulation and amniotic fluid. Cefazolin is excreted in breast milk in very small amounts.

Cefazolin is 85-90%% bound to plasma proteins.
Penetration of cefazolin into the cerebrospinal fluid is poor.

Biotransformation
Cefazolin is not metabolised.

Elimination
Cephazolin is excreted in the urine in a biologically active form and in negligible amounts via the bile. For an intramuscular dose of 500 mg, 56-89% is excreted in the first six hours and 80 to nearly 100% is excreted within 24 hours. Urine levels of 1000/2000 μg/ml and 2000/4000 μg/ml on 0-6 h can be achieved following intramuscular administration of 500 mg and 1 g.

### 5.3 Preclinical safety data

Reproductive toxicity studies in rats performed with doses of 500 mg and 1 g revealed no reduction of fertility and foetotoxic effects.

No mutagenicity and carcinogenicity studies have been performed.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

None.

### 6.2 Incompatibilities

Incompatibility has been observed *in vitro* with the mixing of cefazolin with aminoglycosides. If cefazolin should be used concurrently with aminoglycosides, they should not be mixed in the same syringe or infusion fluid due to a risk of inactivation. They should be administered in separate sites at 1 hour interval.

Cefazolin may be precipitated when mixed with solutions with pH < 4.5 or may be hydrolyzed when mixed with solutions with pH > 8.5.

Due to possible physico-chemical interactions of cefazolin *in vitro*, it should not be mixed with other medicinal products in the same syringe.

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

### 6.3 Shelf life

Prior to reconstitution:
As indicated on the outer packaging.

After reconstitution:
Following reconstitution chemical and physical in-use stability has been demonstrated for 48 hours at 25°C and 3 days at 2-8°C.

Following reconstitution chemical and physical in-use stability has been demonstrated for 24 hours when stored at 25°C in a PP bottle and diluted with 0.9% NaCl Injection or 5% Glucose and 0.225% NaCl Injection.

From a microbiological point of view, the reconstituted product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

## 6.4 Special precautions for storage

As indicated on the outer packaging.
Keep the vial in the outer carton in order to protect from light.

For storage conditions after reconstitution and dilution of the medicinal product, see section 6.3.

## 6.5 Nature and contents of container

CEFAZOLIN ALVOGEN is packed into a 15 ml type I glass vial. The vial is closed by chlorobutyl rubber stopper (locally covered by e-PTFE) and sealed by aluminum flip-off cap.

*Pack size:* 50 vials per carton box

## 6.6 Special precautions for disposal and other handling

| ***Route of administration*** | ***Diluents*** | ***Concentration*** | ***Storage container*** | ***At room temperature (25°C)*** | ***In refrigerator (5±3°C)*** |
|---|---|---|---|---|---|
| Intramuscular injection | Water for injection | 250 mg/ml | Both glass bottle and PP bottle | 48 hours | 72 hours |
| Intravenous injection | Water for injection | 100 mg/ml | Both glass bottle and PP bottle | 48 hours | 72 hours |
| Intravenous infusion | 0.9% NaCl Injection | 20 mg/ml | Glass bottle | 48 hours | 72 hours |
| | | | PP bottle | 24 hours | |
| | 5% Glucose Injection | 20 mg/ml | Both glass bottle and PP bottle | 48 hours | 72 hours |
| | 10% Glucose Injection | 20 mg/ml | Both glass bottle and PP bottle | 48 hours | 72 hours |
| | 5% Glucose and 0.9% NaCl Injection | 20 mg/ml | Both glass bottle and PP bottle | 48 hours | 72 hours |
| | 5% Glucose and 0.45% NaCl Injection | 20 mg/ml | Both glass bottle and PP bottle | 48 hours | 72 hours |
| | 5% Glucose and 0.225% NaCl Injection | 20 mg/ml | Glass bottle | 48 hours | 72 hours |
| | | | PP bottle | 24 hours | |

| | | | | | |
|---|---|---|---|---|---|
| | 4% Glucose and 0.18% NaCl Injection | 20 mg/ml | Both glass bottle and PP bottle | 48 hours | 72 hours |
| | Compound sodium chloride injection | 20 mg/ml | Both glass bottle and PP bottle | 48 hours | 72 hours |
| | Lactated Ringer's injection | 20 mg/ml | Both glass bottle and PP bottle | 48 hours | 72 hours |

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

## 7. PRODUCT OWNER

LOTUS INTERNATIONAL PTE. LTD.
80 Robinson Road
#02-00
Singapore 068898

## 8. DATE OF REVISION OF THE TEXT

06/2020