

## **Cefotaxime**

### **Core Safety Profile**

#### **4.3 Contraindications**

- Hypersensitivity to cephalosporins
- In patients with a history of hypersensitivity to Cefotaxime and/or to any component of <Productname>

Allergic cross reactions can exist between penicillins and cephalosporins (see section 4.4)

For pharmaceutical forms containing lidocaine:

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

#### **4.4 Special warnings and precautions for use**

As with other antibiotics, the use of cefotaxime, especially if prolonged, may result in overgrowth of non-susceptible organisms. Repeated evaluation of the patient's condition is essential. If superinfection occurs during therapy, appropriate measures should be taken.

- Anaphylactic reactions

Serious, including fatal hypersensitivity reactions have been reported in patients receiving cefotaxime (see sections 4.3 and 4.8).

If a hypersensitivity reaction occurs, treatment must be stopped.

The use of cefotaxime is strictly contra-indicated in subjects with a previous history of immediate-type hypersensitivity to cephalosporins.

Since cross allergy exists between penicillins and cephalosporins, use of the latter should be undertaken with extreme caution in penicillin sensitive subjects.

- Serious bullous reactions

Cases of serious bullous skin reactions like Stevens-Johnson syndrome or toxic epidermal necrolysis have been reported with cefotaxime ( see section 4.8). Patients should be advised to contact their doctor immediately prior to continuing treatment if skin and/or mucosal reactions occur.

- *Clostridium difficile* associated disease (e.g. pseudomembranous colitis)

Diarrhea, particularly if severe and/or persistent, occurring during treatment or in the initial weeks following treatment, may be symptomatic of *Clostridium difficile* associated disease (CDAD). CDAD may range in severity from mild to life threatening, the most severe form of which is pseudo-membranous colitis.

The diagnosis of this rare but possibly fatal condition can be confirmed by endoscopy and/or histology.

It is important to consider this diagnosis in patients who present with diarrhoea during or subsequent to the administration of cefotaxime.

If a diagnosis of pseudomembranous colitis is suspected, cefotaxime should be stopped immediately and appropriate specific antibiotic therapy should be started without delay.

*Clostridium difficile* associated disease can be favoured by faecal stasis.

Medicinal products that inhibit peristalsis should not be given.

- Haematological reactions

Leukopenia, neutropenia and, more rarely, agranulocytosis may develop during treatment with cefotaxime, particularly if given over long periods. For treatment courses lasting longer than 7-10 days, the blood white cell count should be monitored and treatment stopped in the event of neutropenia.

Some cases of eosinophilia and thrombocytopenia, rapidly reversible on stopping treatment, have been reported. Cases of haemolytic anemia have also been reported. (see section 4.8)

- Patients with renal insufficiency

The dosage should be modified according to the creatinine clearance calculated.

Caution should be exercised if cefotaxime is administered together with aminoglycosides or other nephrotoxic drugs (see section 4.5). Renal function must be monitored in these patients, the elderly, and those with pre-existing renal impairment.

- Neurotoxicity

High doses of beta-lactam antibiotics, including cefotaxime, particularly in patients with renal insufficiency, may result in encephalopathy (e.g. impairment of consciousness, abnormal movements and convulsions) (see section 4.8).

Patients should be advised to contact their doctor immediately prior to continuing treatment if such reactions occur.

- Precautions for administration

During post-marketing surveillance, potentially life-threatening arrhythmia has been reported in a very few patients who received rapid intravenous administration of cefotaxime through a central venous catheter. The recommended time for injection or infusion should be followed (see section 4.2).

See section 4.3 for contraindications for formulations containing lidocaine.

- Effects on Laboratory Tests

As with other cephalosporins a positive Coombs' test has been found in some patients treated with cefotaxime. This phenomenon can interfere with the cross-matching of blood.

Urinary glucose testing with non-specific reducing agents may yield false-positive results. This phenomenon is not seen when a glucose-oxydase specific method is used.

- Sodium intake

The sodium content of cefotaxime sodium (48.2 mg/g) should be taken into account.

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

Probenecid interferes with the renal tubular transfer of cephalosporins, thereby delaying their excretion and increasing their plasma concentrations.

As with other cephalosporins, cefotaxime may potentiate the nephrotoxic effects of nephrotoxic drugs such as aminoglycosides or potent diuretics (e.g. furosemide). Renal function must be monitored (see section 4.4).

## **4.6 Fertility, pregnancy and lactation**

### **Pregnancy**

The safety of cefotaxime has not been established in human pregnancy.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. There are, however, no adequate and well controlled studies in pregnant women.

Cefotaxime crosses the placental barrier. Therefore, cefotaxime should not be used during pregnancy unless the anticipated benefit outweighs any potential risks.

### **Lactation**

Cefotaxime passes into human breast milk.

Effects on the physiological intestinal flora of the breast-fed infant leading to diarrhoea, colonisation by yeast-like fungi, and sensitisation of the infant cannot be excluded.

Therefore, a decision must be made whether to discontinue breast-feeding or to discontinue therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

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

There is no evidence that cefotaxime directly impairs the ability to drive or to operate machines.

High doses of cefotaxime, particularly in patients with renal insufficiency, may cause encephalopathy (e.g. impairment of consciousness, abnormal movements and convulsions) (see section 4.8). Patients should be advised not to drive or operate machinery if any such symptoms occur.

## 4.8 Undesirable effects

<b>System organ class</b>	<b>Very Common (<math>\geq 1/10</math>)</b>	<b>Common (<math>\geq 1/100</math> to <math>&lt; 1/10</math>)</b>	<b>Uncommon (<math>\geq 1/1,000</math> to <math>&lt; 1/100</math>)</b>	<b>Rare (<math>\geq 1/10,000</math> to <math>&lt; 1/1,000</math>)</b>	<b>Very rare (<math>&lt; 1/10,000</math>)</b>	<b>Not known (cannot be estimated from available data)*</b>
Infections and infestations						Superinfection (see section 4.4)
Blood and the lymphatic system disorders			Leukopenia Eosinophilia Thrombocytopenia			Neutropenia Agranulocytosis (see section 4.4) Haemolytic anaemia
Immune system disorders			Jarisch-Herxheimer reaction			Anaphylactic reactions Angioedema Bronchospasm Anaphylactic shock
Nervous system disorders			Convulsions (see section 4.4)			Headache Dizziness Encephalopathy (e.g. impairment of consciousness, abnormal movements,) (see section 4.4)

<b>System organ class</b>	<b>Very Common (<math>\geq 1/10</math>)</b>	<b>Common (<math>\geq 1/100</math> to <math>&lt; 1/10</math>)</b>	<b>Uncommon (<math>\geq 1/1,000</math> to <math>&lt; 1/100</math>)</b>	<b>Rare (<math>\geq 1/10,000</math> to <math>&lt; 1/1,000</math>)</b>	<b>Very rare (<math>&lt; 1/10,000</math>)</b>	<b>Not known (cannot be estimated from available data)*</b>
Cardiac disorders						Arrhythmia following rapid bolus infusion through central venous catheter
Gastro-intestinal disorders			Diarrhea			Nausea Vomiting Abdominal pain Pseudomembranous colitis (see section 4.4)
Hepato-biliary disorders			Increase in liver enzymes (ALAT, ASAT, LDH, gamma-GT and/or alkaline phosphatase) and/or bilirubin			Hepatitis* (sometimes with jaundice)
Skin and subcutaneous tissue disorders			Rash Pruritus Urticaria			Erythema multiforme Stevens-Johnson syndrome Toxic epidermal necrolysis (see section 4.4)

System organ class	Very Common ( $\geq 1/10$ )	Common ( $\geq 1/100$ to $< 1/10$ )	Uncommon ( $\geq 1/1,000$ to $< 1/100$ )	Rare ( $\geq 1/10,000$ to $< 1/1,000$ )	Very rare ( $< 1/10,000$ )	Not known (cannot be estimated from available data)*
Renal and Urinary disorders			Decrease in renal function/ increase of creatinine (particularly when co-prescribed with aminoglycosides)			Interstitial nephritis
General disorders and administration site conditions	<i>For IM formulations:</i> Pain at the injection site		Fever  Inflammatory reactions at the injection site, including phlebitis/thrombophlebitis			<i>For IM formulations (since the solvent contains lidocaine):</i> Systemic reactions to lidocaine

\* postmarketing experience

#### Jarisch-Herxheimer reaction

For the treatment of borreliosis, a Jarisch-Herxheimer reaction may develop during the first days of treatment.

The occurrence of one or more of the following symptoms has been reported after several week's treatment of borreliosis: skin rash, itching, fever, leucopenia, increase in liver enzymes, difficulty of breathing, joint discomfort.

#### Hepatobiliary disorders

Increase in liver enzymes (ALAT, ASAT, LDH, gamma-GT and/or alkaline phosphatase) and/or bilirubin have been observed. These laboratory abnormalities may rarely exceed twice the upper limit of the normal range and elicit a pattern of liver injury, usually cholestatic and most often asymptomatic.

## **4.9 Overdose**

Symptoms of overdose may largely correspond to the profile of side effects.

There is a risk of reversible encephalopathy in cases of administration of high doses of  $\beta$ -lactam antibiotics including cefotaxime.

In case of overdose, cefotaxime must be discontinued, and supportive treatment initiated, which includes measures to accelerate elimination, and symptomatic treatment of adverse reactions (e.g. convulsions).

No specific antidote exists. Serum levels of cefotaxime can be reduced by haemodialysis or peritoneal dialysis.