PACKAGE LEAFLET: INFORMATION FOR THE USER
Cefotaxime 1g Powder for Solution for Injection or Infusion
Cefotaxime 2g Powder for Solution for Injection or Infusion
Cefotaxime (as Cefotaxime sodium)

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, or pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours. It may harm them, even if their symptoms are the same as yours.
- If you get any side effects, talk to your doctor, or pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

The name of your medicine is Cefotaxime 1g powder for injection or infusion, or Cefotaxime 2g powder for injection or infusion but will be referred to as Cefotaxime or as Cefotaxime Injection in this leaflet.

1. What Cefotaxime is and what it is used for
Cefotaxime is an antibiotic belonging to the cephalosporin group of antibiotics (i.e. a medicine which is used for the treatment of bacterial infections of:
- Bacterial infections of the chest (respiratory tract)
- Complicated infections of the kidneys and upper urinary tract
- Severe infections of the skin and soft tissue
- Genital infections caused by gonococci (gonorrhoea -a sexually transmitted disease), particularly when penicillin has failed or is unsuitable.
- Intra-abdominal infections such as peritonitis (inflammation of the peritoneum, the thin membrane that lines the abdominal wall and covers the organs within)
- Acute bacterial meningitis
- Infection of the blood (septicaemia)

Furthermore cefotaxime is used to treat the Lyme disease (borreliosis, an infection primarily caused by tick bites, e.g. relapsing fever).
Cefotaxime can also be used before and during surgery in order to prevent possible infections

2. What you need to know before you are given Cefotaxime

You must not be given Cefotaxime if:
- you are allergic (hypersensitive) to Cefotaxime or to any cephalosporin antibiotics or any of the other ingredients of this medicine (listed in section 6).
- you have ever had a severe allergic reaction (hypersensitivity) to any other type of beta-lactam antibiotic (penicillins, monobactams and carbapenems).
- Cefotaxime is sometimes mixed with another medicine called lidocaine. In this case do not have this injection if:You are allergic to lidocaine or other local anaesthetics
- Your child is younger than 30 months
- You have heart disease, problems with your heartbeat of severe heart failure.

- You have ever developed a severe skin rash or skin peeling, blistering and/or mouth sores after taking cefotaxime or other cephalosporins.

Do not have this medicine if any of the above applies to you. If you are not sure, talk to your doctor or nurse before you are given Cefotaxime.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before you are given Cefotaxime:
- if you have allergic reactions. If you have had any allergic reaction to other antibiotics such as penicillin, you may also be allergic to Cefotaxime. If an allergic reaction occurs, tratment must be stopped.
- if you suffer from severe, persistent diarrhoea during or after treatment with Cefotaxime. In this case contact your doctor immediately. Do not take any anti-diarrhoea medicine without consulting your doctor.
- if you have a widespread rash with blisters and peeling skin. (These may be signs of Stevens-Johnson syndrome or toxic epidermal necrolysis).
- if you have kidney problems
- if you experince e.g. impairment of consciousness, abnormal movements and cramps after being given this medicine.
- if you are on a low salt diet. Then the sodium content of this product must be taken into account.
- Serious skin reactions including Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalized exanthematous pustulosis (AGEP) have been reported in association with cefotaxime treatment. Stop using cefotaxime and seek medical attention immediately if you notice any of the symptoms related to these serious skin reactions described in section 4.

If any of these apply to you, your doctor may want to change your treatment or give you special advice.
If you are given this medicine over a longer period, your doctor will take additional care and check your blood for possible changes. Also the overgrowth of bacteria that are unsusceptible to cefotaxime must be examined regularly in this case.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. This is extremely important, as using more than one medicine at the same time can strengthen or weaken the effect of the medicines.
Cefotaxime may interfere with:
- diuretics (used to increase the flow of urine)
- probenecid
- aminoglycoside antibiotics (such as gentamycin and streptomycin used to treat infections), other antibiotics (such as tetracycline, erythromycin and chloramphenicol)

In some cases your doctor will arrange further monitoring, but this is routine and nothing to worry about.
It is important to tell the doctor that you are taking this medicine if you require any blood, urine or diagnostic tests.
The effect of the contraceptive pill may be decreased during therapy with Cefotaxime. Additional non-hormonal contraceptive precautions should therefore be taken during therapy with Cefotaxime.

Pregnancy and breast-feeding
Before starting treatment, you must tell your doctor if you are pregnant or if you intend to become pregnant. Your doctor will then decide whether you should receive Cefotaxime

Mothers who wish to breast-feed should discuss this with their doctor who will then advise you on what to do.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
Cefotaxime should not affect your ability to drive or operate machinery.
You may start to move abnormally, suffer from sudden involuntary muscle contractions, dizziness or feel less alert.
If this happens, do not drive or use any tools or machines.

Important information about some of the ingredients of Cefotaxime
This medicinal product contains 2.09 mmol (or 48 mg) sodium per dose. To be taken into consideration by patients on a controlled sodium diet.

3. How to use Cefotaxime

This medicine will always be administered by a doctor or nurse because it needs to be given either as an injection or by a drip.
Adults and adolescents over 12 years

You usually receive 2 to 6 g cefotaxime daily. The daily dose should be divided in two single doses every 12 hours. The dosage may be varied according to the severity of your infection and your condition.

- Common infections in presence (or suspicion) of sensitive bacteria: 1g every 12 hours (i.e. total daily dose of 2g)
- Infections in presence (or suspicion) of several sensitive or moderately sensitive bacteria: 1-2 g every 12 hours(i.e. total daily dose of 2-4g)
- Severe infections or for injections that cannot be localised: 2-3 g as a single dose every 6 to 8 hours (i.e. a maximum daily dose of 12g).

Newborns (0-28 days), infants and children up to 12 years of age

The dosage is dependent on the severity of the infection.
The usual dosage for newborns, infants and children is 50 to 100 to 150 mg cefotaxime per kg body weight per day, divided into 2 to 4 single doses (i.e. every 12 to 6 hours).
For very severe or life-threatening infections up to 200 mg cefotaxime per kg body weight per day, divided into 2 to 4 single doses, may be required. The doctor will take the differences in maturation of the kidneys and their function into account, especially in newborns from 0-7 days.

Premature infants
The recommended dosage is 50mg per kg body weight per day divided into 2 to 4 doses (every 12 to 6 hours). This maximum dose should not be exceeded due to the not yet fully matured kidneys.

Elderly
Provided that your kidney and liver function is normal, no dosage adjustment is required.

People with kidney and/or liver problems
If you have problems with your kidneys and/or liver, you may be given a lower dose. You may need to have blood tests to check that you are getting the dose you need. Your doctor will decide on the dose.

Other special recommendations
Gonorrhoea
You will receive a single injection of 500 mg – 1 g Cefotaxime as an injection into a muscle or a vein for treatment of gonorrhoea.

Bacterial meningitis
Adults receive a daily dose of 9 to 12 g cefotaxime divided into equal doses every 6 to 8 hours.
Children receive 150 to 200 mg per kg body weight divided into equal doses every 6 to 8 hours.
Newborns 0-7 days old babies receive 50 mg per kg body weight every 12 hours, 7 – 28 days old infants every 8 hours.

Prevention of infections (perioperative prophylaxis)
You may be given between 1 g and 2 g cefotaxime before an operation for the prevention of possible infections. If the operation lasts longer than 90 minutes, you may be given an additional dose preventively.

Infections inside the abdomen
You should be given a combination of cefotaxime and an antibiotic acting against 'anaerobic' bacteria.

Treatment duration
Your treatment duration depends on the severity of your infection as well as on your recovery from your illness.
You will usually continue to be given the medicine for at least 2 to 3 days after you have started to recover from your illness. Treatment over at least 10 days is necessary in infections caused by the bacterium Streptococcus pyogenes.

If you use more Cefotaxime than you should:
It is most unlikely that you will be given too much medicine by the nurse or doctor. Your doctor and nurse will be monitoring your progress, and checking the medicine that you are given. Always ask if you are not sure why you are getting a dose of medicine.

If you forget to use Cefotaxime:
Your doctor or nurse have instructions when to give you your medicine. It is most unlikely that you will not be given the medicine as it has been prescribed. If you think that you may have missed a dose then talk to your nurse or doctor. It is important that the course of treatment your doctor has prescribed is taken. You may start to feel better but it is important not to stop taking this medicine, until the doctor advises, otherwise your condition may get worse again.
If you have any further questions on the use of this product, ask your doctor or pharmacist.

If you stop using Cefotaxime:
Low dosage, irregular administration or stopping treatment too early can compromise the outcome of the treatment or lead to a relapse, whose treatment is more difficult. Please follow the instructions of your doctor.
If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Cefotaxime can cause side effects although not everybody gets them.

Stop taking cefotaxime and tell your doctor immediately if you notice any of the following symptoms:
• Reddish non-elevated, target-like or circular patches on the trunk, often with central blisters, skin peeling, ulcers of mouth, throat, nose, genitals and eyes. These serious skin rashes can be preceded by fever and flu-like symptoms (Stevens-Johnson syndrome, toxic epidermal necrolysis).

• Widespread rash, high body temperature and enlarged lymph nodes (DRESS syndrome or drug hypersensitivity syndrome).

• A red, scaly widespread rash with bumps under the skin and blisters accompanied by fever. The symptoms usually appear at the initiation of treatment (acute generalised exanthematous pustulosis).

You must contact your doctor immediately if you notice any of the following:
Uncommon side effects (may affect up to 1 in 100 people)

- Increased tendency to bleed or bruise more easily caused by a fall in the number of blood platelets (thrombocytopenia), fever, sore throat or mouth ulcers due to infections caused by a low level of white blood cells (leucopenia) or high level of a specific type of white blood cells (eosinophilia)

Not known: frequency cannot be estimated from the available data

- Inflammation of the bowels, called colitis (or antibiotic-associated colitis), causing severe long-lasting watery or blood diarrhoea with stomach cramps and fever
- Serious blood problems, including changes in the numbers of some white blood cells (which may cause frequent infections, fever, severe chills, sore throat, or mouth ulcers)

- Damage to red blood cells (causing tiredness, being short of breath or looking pale)
- Severe allergic reactions with symptoms such as swelling of the lips, tongue, face and neck, sudden difficulty in breathing, speaking and swallowing
- Headache, dizziness, convulsions (fits) (these may be symptoms of a brain disorder called encephalopathy)
- Changes in heart beat (rhythm or rate), after a very quick injection into a vein
- Yellow skin and eyes, loss of appetite, light-coloured urine caused by inflammation of the liver
- Skin rash, which may blister, and looks like small targets (central dark spot surrounded by a paler area, with a dark ring around the edge)
- A widespread rash with blisters and peeling sking. (These may be signs of Stevens-Johnson syndrome or toxic epidermal necrolysis)
- Increased or reduced urinie output, or traces of blood in your urine, sometimes with swollen limbs and/ or flank pain caused by kidney problems
- For intramuscular injections: combination with lidocaine can cause systemic reactions.

Other possible side effects:

Very common: may affect more than 1 in 10 people

- Intramuscular injection may be painful

Uncommon: may affect more than 1 in 100 people

- People being treated for injections with bacteria called spirochetes often show symptoms like fever and shivering which are described as 'Herxheimer reaction' and indicate the effectiveness of the therapy.
- Changes in the results of blood tests that check how the liver and kidneys are working
- Fever
- Allergic reactions such as skin rash (nettle rash), itchy skin
- Painfull swelling and inflammation where the injection is given into a vein
- Soft stools or diarrhoea
- Convulsions

Not known: frequency cannot be estimated from the available data

- Feeling sick (nausea) and being sick (vomiting)
- Pain in your stomach (abdomen)

Your doctor may want to perform tests during your treatment to measure any changes.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.
By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Cefotaxime

Keep this medicine out of the sight and reach of children.

Do not use Cefotaxime after the expiry date which is stated on the label after EXP. The expiry date refers to the last day of that month.

Always keep this medicine in the closed original pack, in order to protect from light.

Do not store above 25˚C.

Once reconstituted, this medicine should be used immediately.
This medicine is for single use only: discard any remaining solution immediately after use.
Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. Contents of the pack and other information

What Cefotaxime contains
The active substance is Cefotaxime Sodium.

Cefotaxime 1g powder for solution for injection or infusion contains Cefotaxime sodium equivalent to 1 g of Cefotaxime.

Cefotaxime 2g powder for solution for injection or infusion contains 2 g of Cefotaxime sodium Ph. Eur., equivalent to 2 g of Cefotaxime base.
There are no other ingredients.

What Cefotaxime looks like and contents of the pack
Cefotaxime is a white or slightly creamy powder which forms a straw-coloured solution on reconstitution.

Cefotaxime 1g powder for injection or infusion is available in packs of 10 or 50 vials.
Cefotaxime 2g powder for injection or infusion is available in packs of 10 vials.
Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:
Reig Jofre UK Limited
Unit 9A Caddsdown Business Support Centre, Caddsdown Industrial Park,
Bideford, Devon, EX39 3DX, UK

Manufacturer:
Laboratorio Reig Jofre, S.A.
Gran Capitán, 10 - 08970 Sant Joan Despí,
Barcelona, Spain

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

This leaflet was last revised April 2024

The following information is intended for medical or healthcare professionals only

Cefotaxime Sodium 1g Powder for Solution for Injection or Infusion
TECHNICAL LEAFLET

Trade name of the medicinal product
Cefotaxime 1g Powder for Solution for Injection or Infusion.

Qualitative and quantitative composition
Each vial contains Cefotaxime sodium equivalent to 1g cefotaxime. Also contains 48mg (2.09mmol) of sodium per vial.
For a full list of excipients, see ‘List of excipients’.

Pharmaceutical form
White or slightly creamy powder.
Powder for solution for injection or infusion.

CLINICAL PARTICULARS

Cefotaxime is indicated for the treatment of the following severe infections when known or thought very likely to be due to bacteria that are susceptible to cefotaxime (see section 4.4 and 5.1):

- Bacterial pneumonia.

- Complicated infections of the urinary tract including pyelonephritis
- Severe skin and soft tissue infections
- Genital infections including gonorrhoea
- Intraabdominal infections (such as peritonitis)
- Bacterial meningitis
- Endocarditis
- Borreliosis

Treatment of patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above.

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

Posology and method of administration

Cefotaxime may be administered by intravenous bolus injection, by intravenous infusion, by intramuscular injection after reconstitution of the solution according to the directions given below. Dosage and mode of administration should be determined by the severity of the infection, susceptibility of the causative organism and the patient's condition. Therapy may be started before the result of microbiological tests are known.

Adults and adolescents over 12 years

The usual dose in adults and adolescents is 2 to 6g cefotaxime daily. The daily dose should be divided in two single doses every 12 hours.

- - Common infections in presence (or suspicion) of a sensitive bacteria: 1g every 12 hours Infections in presence (or suspicion) of several sensitive or moderatively sensitive bacteria: 1-2g every 12 hours.
- Severe infection or for infections that cannot be localized: 2-3g as a single dose every 6 to 8 hours (maximum daily dose 12 g).

A combination of cefotaxime and other antibiotics in indicated in severe infections.

Term newborn (0-28 days), infants and children up to 12 years of age

Depending on the severity of the infection: 50-100-150 mg/kg/day, 12 – 6 hourly.

In life-threatening situations the daily dose may be raised to 200 mg/kg/day under careful attention of the renal function, especially in the newborn period of 0 – 7 days due to not fully matured kidney function.

Premature infants

The recommended dosage is 50 mg/kg/day divided into 2 to 4 doses (every 12 to 6 hours). This maximum dose should not be exceeded due to the not yet fully matured kidneys.

Elderly

No dosage adjustment is required, provided that renal and hepatic function are normal.

Other special recommendations

Gonorrhoea:

For gonorrhoea, a single injection (intramuscularly or intravenously) of 500 mg - 1 g cefotaxime. For complicated infections, consideration should be given to available official guidelines. Syphilis should be excluded before initiating treatment.

*Bacterial meningitis:*Adults: Daily doses of 9 - 12 g cefotaxime divided into equal doses every 6 – 8 hours (3g 3 – 4 times daily).

Children: 150 - 200 mg/kg/day divided in equal doses every 6 to 8 hours.

New-borns: 0 – 7 days 50 mg/kg every 12 hours; 7 – 28 days: 50mg/kg every 8 hours.

Perioperative prophylaxis

1-2 g as single dose as close to start of surgery as possible. In those cases where the operation time exceeds 90 minute an additional dose of prophylactic antibiotic should be given.

Intra-abdominal infections:

Intra-abdominal infection should be treated with Cefotaxime in combination with other antibiotics with coverage for anaerobic bacteria.

Dosage in renal function impairment

In adult patients with a creatinine clearance of ≤ 5 ml/min, the initial dose is similar to the recommended usual dose should be halved without change in the frequency of dosing. Blood tests to determine the required dose may be carried out.

Dosage in dialysis or peritoneal dialysis

In patients on haemodialysis and peritoneal dialysis an intravenous injection of 500mg - 2 g, given at the end of each dialysis session and repeated every 24 hours, is sufficient to treat most infections efficaciously.

Duration of therapy

The duration of therapy with Cefotaxime depends on the clinical condition of the patient and varies accoriding to the course of the disease. Administration of Cefotaxime should be continued until symptoms have subsided or evidence of bacterial eradication has been obtained. Treatment over at least 10 days is necessary in infections caused by *Streptococcus pyogenes* (parenteral therapy may be switched to an adequate oral therapy before the end of the 10 day period).

Method of administration

- Intravenous infusion

In order to avoid any risk of infection, the reconstitution of the solution for infusion should be done in close aseptic conditions. Do not postpone the infusion after the reconstitution of the solution.

For *short intravenous infusion* Following reconstitution, the solution should be administered over 20 minutes.

For *long lasting intravenous infusion* Following reconstitution, the solution should be administered over 50-60 minutes.

- Intravenous injection

For intermittent intravenous injections the solution must be injected over a period of 3-5 minutes. During post-marketing surveilance, potentially life-threatening arrhythmia has been reported in a very few patients who received rapid intravenous administration of cefotaxime through a central venous catheter.

- Intramuscular injection

The intramuscular method of administration is restricted to exceptional clinical situations (e.g. gonorrhoea). It is not indicated in severe infections and should undergo a risk-benefit assessment. It is recommended that no more than 4 ml are injected unilaterally. If the daily dose exceeds 2g cefotaxime or if cefotaxime is injected more frequently than twice per day, the intravenous route is recommended.

Incase of severe infections, intramuscular injection is not recommended.

The solution should be administered by deep intramuscular injection. Solutions with lidocaine must not be administered intravenously. Cefotaxime reconstituted with lidocaine should not be administrated to children in the first year of age. The product information of the chosen lidocain containing medicinal product must be regarded.

For instructions on reconstitution and dilution of the medicinal product before administration, see section 6.6. Cefotaxime and aminoglycosides should not be mixed in the same syringe or perfusion fluid.

Contraindications

-- Hypersensitivity to the active substance, to other cephalosporins.
- Previous, immediate and/or severe hypersensitivity reaction to penicillin or any betalactam antibiotic.

- Cefotaxime constituted with lidocaine must never be used:

by the intravenous route

in infants under 30 months

in subjects with a previous history of hypersensitivity to this product

in patients who have an unpaced heart block

in patients with severe heart failure.

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 contraindicated in subjects with a previous history of immediate-type hypersensitivity to cephalosporins.

Since cross allergy extists 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 diarrhea 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

Leucopenia, neutropenia and, more rarely, bone marrow failure, pancytopenia, or agranulocytosis may develop during treatment with cefotaxime (see Section 4.8.)

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

For patients with impaired renal function, the dosage should be modified according to the creatinine clearance calculated (see section 4.2).
Caution should be exercised if cefotaxime is administered together with aminoglycosides; probenecid or other nephrotoxic drugs (see section 4.5).
Renal function must be monitored in these patients, the elderly, and those with preexisting renal impairment.

- Neurotoxicity

High doses of beta-lactam antibiotics, including cefotaxime, particulary 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.

The use of cefotaxime for treatment of endocarditis should be restricted to patients known to have penicillin allergy (not type 1). Cefotaxime should be used in combination with other appropriate antibacterial agents, considering its limited antibacterial spectrum.

- 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

This medicinal product contains 48.07 mg (2.09 mmol) sodium per vial, equivalent to 4.8% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Interaction with other medicinal products and other forms of interaction

Uricosurics
Probenecid interferes with the renal tubular transfer of cefotaxime, thereby increasing cefotaxime exposure about 2-fold and reducing renal clearance to about half at therapeutic doses. Due to the large therapeutic index of cefotaxime, no dosage adjustment is needed in patients with normal renal function. Dosage adjustment may be needed in patients with renal impairment (see sections 4.4 and 4.2).

Aminoglycoside antibiotics and diuretics
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 in these patients (see section 4.4).

Bacteriostatic antibiotics
Cefotaxime should not be combined with bacteriostatic antibiotics (e.g. tetracyclines, erythromycin and chloramphenicol) since an antagonistic effect is possible.

Interference with 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.
A false-positive reaction to glucose may occur with reducing substances (Fehling's solution) but not with the use of specific enzyme-based tests (glucose oxidase methods).

Fertility, Pregnancy and lactation

Pregnancy
There are no adequate data to assess possible harmfulness of cefotaxime during pregnancy. To date, animal experiments show no indication for adverse effects. Caution should be exercised when prescribing to pregnant women.

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

Breastfeeding
Cefotaxime is excreted in human milk in low concentrations. Use during lactation can have effects on the physiological intestinal flora of the breast-fed infant leading to diarrhoea, to colinisation by yeast-like fungi and sensitization. A decision should be made whether to discontinue nursing or discontinue treatment taking into account the importance of cefotaxime to the nursing woman.

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).
In the case of side effects such as dizziness the patient's ability to concentrate and to react properly may be impaired. In such cases patients should refrain from driving cars and using machines.

Undesirable effects

Very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1000, ≤1/100), rare (≥1/10000, ≤1/1000), very rare (≤1/10000), not known (cannot be estimated from the available data).

System organ class	***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 (</10,000)***	***Not known (cannot be estimated from available data)****
Infections and infestations						Superinfection (see section 4.4)
Blood and the lymphatic system disorders			Leukopenia Eosinophilia Thrombocytopenia			Bone marrow failure Pancytopenia 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)
Cardiac disorders						Arrhythmia following rapid bolus infusion through central venous catheter Palpitations
Gastrointestinal			Diarrhea			Nausea,

disorders						Vomiting Abdominal pain Pseudomembranous colitis (see section 4.4)
Hepato-bilary 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) Acute generalized Exanthematous pustulosis (AGEP) Drug reaction with eosinophilia and system symptoms (DRESS) (see section 4.4)
Renal and urinary disorders			Decrease in renal function/ increase of creatinine (particularly when co-prescribed with aminoglycosides)			Acute renal failure (see section 4.4) Interstititial nephritis
General disorders and administration site conditions	*For IM formulations:* Pain at the injection **site**		Fever Inflammatory reactions at the injection site, including phlebitis/ thrombophlebitis Malaise, Fatigue			*For IM formulations (since the solvent contains lidocaine):* Systemic reactions to lidocaine

*postmarketing experience

Jarisch-Herxheimer reaction

For the treatment of borreliosis (Lyme's Disease), a Jarisch-Herxheimer r eaction 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.

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 the Yellow Card Scheme at: www.mhra.gov.uk/yellowcardor search for MHRA Yellow Card in the Google Play or Apple App Store.

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 ß-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 exist. Serum levels of cefotaxime can be reduced by haemodialysis or peritoneal dialysis.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: Third-generation cephalosporin, ATC code: J01DD01

Mechanism of action

The bactericidal activity of cefotaxime results from the inhibition of bacterial cell wall synthesis (during the period of growth) caused by an inhibition of penicillinbinding proteins (PBPs) like transpeptidases.

Mechanism of resistance

A resistance to cefotaxime may be caused by following mechanisms:

- Inactivation by beta-lactamases. Cefotaxime can be hydrolysed by certain betalactamases, especially by extended-spectrum beta-lactamases (ESBLs) which can be found in strains of *Escherichia coli* or *Klebsiella pneumoniae*, or by chromosomal encoded inducible or constitutive beta-lactamases of the AmpC type which can be detected in *Enterobacter cloacae*. Therefore infections caused by pathogens with inducible, chromosomal encoded AmpC-beta-lactamases should not be treated with cefotaxime even in case of proven *in-vitro*

susceptibility because of the risk of the selection of mutants with constitutive, derepressed AmpC- beta-lactamases-expression.

- Reduced affinity of PBPs to cefotaxime. The acquired resistance of Pneumococci and other Streptococci is caused by modifications of already existing PBPs as a consequence of a mutation process. In contrast to this concerning the methicillin- (oxacillin-) resistant *Staphylococcus*, the creation of an additional PBP with reduced affinity to cefotaxime is responsible for resistance.

- Inadequate penetration of cefotaxime through the outer cell membrane of gramnegative bacteria so that the inhibition of the PBPs is insufficient.

- The presence of transport mechanism (efflux pumps) being able to actively transport cefotaxime out of the cell. A complete cross resistance of cefotaxime occurs with ceftriaxone and partially with other penicillins and cephalosporins.

Breakpoints:
The following minimal inhibitory concentrations were defined for sensitive and resistant germs: EUCAST (European Committee on Antimicrobial Susceptibility Testing) break points (2019-01-01):

	Susceptible	Resistant
Enterobacteriaceae	≤ 1 mg/L	>2 mg/L
Staphylococcus spp^{HE}	Note[1]	Note[1]
Streptococcus (group A, B, C, G)	Note[2]	Note[2]
Streptococcus pneumoniae	≤0.5 mg/L	>2 mg/L
Viridans group streptococci	≤0.5 mg/L	>0.5 mg/L
Haemophilus influenzae	≤0.125 mg/L	>0.125 mg/L
Moraxella Catarrhalis	≤1 mg/L	>2mg/L
Neisseria gonorrhoeae	≤0.125 mg/L	>0.125 mg/L
Neisseria Meningitidis[3]	≤0.125 mg/L	>0.125 mg/L
Pasteurella multocida	≤0.03 mg/L	>0.03 mg/L
Kingella Kingae	≤0.125 mg/L	>0.125 mg/L
PK-PD (Non-species related) breakpoints	≤1mg/L	>2mg/L

HE = high exposition / high dose only for *S. aureus* (high dose of at least 3 x 2 g iv)

[1] Susceptibility 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.

[2] The susceptibility of *streptococcus* groups A, B, C and G to cephalosporins is inferred from the benzylpenicillin susceptibility.

[3] Non-susceptible isolates are rare or not yet reported. The identification and antimicrobial susceptibility test result on any such isolate must be confirmed and the isolate sent to a reference laboratory.

Susceptibility

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable particularly when treating severe infections.
If the efficacy of cefotaxime is questionable due to the local prevalence of resistance, expert opinion should be sought regarding the choice of therapy. In particular in the case of severe infections or failure of therapy, a microbiological diagnosis including a verification of the germ and its susceptibility should be aspired.

COMMONLY SUSCEPTIBLE SPECIES
Gram-positive aerobe
Staphylococcus aureus (Methicillin-susceptible)
Streptococcus agalactiae
Streptococcus pneumoniae(incl. penicillin-resistant strains)
Streptococcus pyogenes
Gram-negative aerobes
Borrellia burgdorferi
Haemophilus influenzae
Moraxella catarrhalis
Neisseria gonorrhoeae
Neisseria meningitides
Proteus mirabilis [%]
SPECIES FOR WHICH ACQUIRED RESISTANCE MAY BE A PROBLEM
Gram-positive aerobes
Staphylococcus aureus
Staphylococcus epidermidis[+]
Staphylococcus haemolyticus[+]
Staphylococcus hominis[+]
Gram-negative aerobes

Citrobacter freundii
Enterobacter aerogenes
Enterobacter cloacae
Escherichia coli[%]
Klebsiella oxytoca[%]
Klebsiella pneumoniae[#%]
Morganella morganii
Proteus vulgaris
Serratia marcescens
Anaerobes
Bacteroides fragilis
INHERENTLY RESISTANT SPECIES
Gram-positive aerobes
Enterococcus spp.
Listeria monocytogenes
Staphylococcus aureus (methicillin-resistant)
Gram-negative aerobes
Acinetobacter spp.
Pseudomonas aeruginosa
Stenotrophomonas maltophilia
Anaerobes
Clostridium difficile
Others *Chlamydia* *sppChlamydophila* spp. *Legionella pneumophila* *Mycoplasma spp.* *Treponema pallidum*
[+] *In at least one region the resistance rate is > 50 %.* [#] *In Intensive Care Units the resistance rate is < 10 %.* [%] *Extended Spectrum Beta-Lactamase (ESBL) producing strains are always resistant*

Pharmacokinetic properties

Absorption

Cefotaxime is for parenteral application. Mean peak concentrations 5 minutes after intravenous injection are about 81-102 mg/l following a 1 g dose cefotaxime and about 167-214 mg/l 8 minutes after a 2 g dose. Intramuscular injection produces mean peak plasma concentrations of 20 mg/l within 30 minutes following a 1 g dose.

Distribution

Cefotaxime gives good penetration into different compartments. Therapeutic drug levels exceeding the minimum inhibitory levels for common pathogens can rapidly be achieved. Cerebrospinal fluid concentrations are low when the meninges are not inflamed but cefotaxime usually passes the blood-brain barrier in levels above the MIC of the sensitive pathogens when the meninges are inflamed (3-30 µg/ml). Cefotaxime concentrations (0.2-5.4 µg/ml), inhibitory for most Gram-negativebacteria, are attained in purulent sputum, bronchial secretions and pleural fluid after doses of 1 or 2 g.

Concentrations likely to be effective against most sensitive organisms are similarly attained in female reproductive organs, otitis media effusions, prostatic tissue, interstitial fluid, peritoneal fluid and gall bladder wall, after therapeutic doses. High concentrations of cefotaxime and O-desacetyl-cefotaxime are attained in bile. Cefotaxime passes the placenta and attains high concentrations in foetal fluid and tisues (up to 6 mg/kg). Small amounts of cefotaxime diffuses into the breast milk.

Protein binding for cefotaxime is approximately 25-40%.

The apparent distribution volume for cefotaxime is 21-37 l after 1g intravenous infusion over 30 minutes.

Biotransformation

Cefotaxime is partly metabolized in human beings. Approximately 15-25% of a parenteral dose is metabolized to the O-desacetylcefotaxime metabolite, which also has antibiotic properties.

Elimination

The main route of excretion of cefotaxime and O-desacetylcefotaxime is the kidney. Only a small amount (2%) of cefotaxime is excreted in the bile. In the urine collected within 6 hours 40-60% of the administered dose of cefotaxime is recovered as unchanged cefotaxime and 20% is found as O-desacetlycefotaxime. After administration of radioactive labeled cefotaxime more than 80% can be recovered in the urine, 50-60% of this fraction is unchanged cefotaxime and the rest contains metabolites.

The total clearance of cefotaxime is 240-390 ml/min and the renal clearance is 130- 150 ml/min.

The serum half-lives of cefotaxime and O-desacetylcafotaxime are normally about 50-80 and 90 minutes respectively. In the elderly, the serum half-life of cefotaxime is 120-150 min.

In patients with impaired renal function (creatinine clearance 3-10ml/min) the serum half-life of cefotaxime can be increased to 2.5-3.6 hours.
There is no accumulation following administration of 1000 mg intravenously or 500 mg intramuscularly for 10 or 14 days.

In neonates, the pharmacokinetics are influenced by gestation and chronological age, the half-life being prolonged in premature and low birth weight neonates of the same age.

Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeat dose toxicity, genotoxicity, and toxicity to reproduction.

Cefotaxime passes through the placenta. After intravenous administration of 1 g cefotaxime during the birth values of 14 μg/ml were measures in the umbilical cord serum in the first 90 minutes after application, which dropped to approximately 2.5
μg/ml by the end of the second hour after application. In the amniotic fluid, the highest concentration of 6.9 μg/ml was measured after 3-4 hours. This value exceeds the MIC for most gram-negative bacteria.

PHARMACEUTICAL PARTICULARS

List of excipients

None.

Incompatibilities

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

Shelf life

Vial before opening: 2 years.

Vial after first opening: The product should be used immediately. After

reconstitution: The product should be used immediately.

From a microbiological point of view, the 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 8ºC, unless reconstitution has taken place in controlled and validated aseptic conditions.
Special precautions for storage

Unopened: Do not store above 25ºC. Keep the vial in the outer carton in order to protect from light.

For storage conditions of the reconstituted medicinal product, see section 6.3.

Nature and contents of container

Type II transparent glass vial, with a bromobutyl stopper and a flip off aluminum and polypropylene cap.

Packs of 10 or 50 vials.

Special precautions for disposalCefotaxime is supplied as a white to slightly creamy powder, which when dissolved in Water for Injections Ph. Eur. forms a straw-coloured solution suitable for IV or IM injection. Variations in the intensity of colour of the freshly prepared solution do not indicate a change in potency or safety.

Whilst it is preferable to use only freshly prepared solutions for both intravenous and intramuscular injection, Cefotaxime is compatible with several commonly used intravenous infusion fluids:

- Water for Injections Ph. Eur.
- Sodium Chloride Injection BP.
- 5% Dextrose Injection BP.
- Dextrose and Sodium Chloride Injection BP.
- Compound Sodium Lactate Injection BP (Ringer-lactate

Injection). Any unused solution should be discarded.

Cefotaxime is also compatible with 1% lidocaine, however freshly prepared solutions should be used.

Cefotaxime is also compatible with metronidazole infusion (500mg/100ml). Some increase in colour of prepared solutions may occur on storage. However, provided the recommended storage conditions are observed, this does not indicate change in potency or safety.

This medicinal product is for single use only; Discard any contents remaining in the vial immediately after use.

The reconstituted solution is to be inspected visually for particulate matter and discoloration prior to administration. The solution should only be used if the solution is clear and free from particles.

MARKETING AUTHORISATION HOLDER

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MARKETING AUTHORISATION NUMBER(S)

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