

DBL[®] CEFOTAXIME SODIUM FOR INJECTION

Cefotaxime (as sodium salt) 500 mg, 1g, 2g injections

Presentation

Vials containing 500 mg, 1g or 2g of cefotaxime as cefotaxime sodium.

DBL[®] Cefotaxime Sodium for Injection is a white to pale yellow crystalline sterile powder, which, when dissolved in water for injections B.P., forms a pale yellow solution suitable for intravenous or intramuscular administration.

Variations in the intensity of colour of the freshly prepared solution do not indicate change in potency or safety.

Uses

Actions

DBL[®] Cefotaxime Sodium for Injection is a broad spectrum bactericidal cephalosporin antibiotic. DBL[®] Cefotaxime Sodium for Injection is exceptionally active *in vitro* against Gram-negative organisms sensitive or resistant to first or second generation cephalosporins. It is similar to other cephalosporins in activity against Gram-positive bacteria.

The following organisms have shown *in vitro* sensitivity to DBL[®] Cefotaxime Sodium for Injection.

Gram-positive:

Staphylococci spp, including coagulase-positive, coagulase-negative and penicillinase-producing strains.
Streptococci spp, including β -haemolytic and other streptococci such as *Streptococcus mitis* (*viridans*), *Streptococcus pneumoniae*. (Many strains of enterococci, e.g. *Streptococcus faecalis*, are relatively resistant).
Clostridium perfringens.

Gram-negative:

Escherichia coli,
Haemophilus influenzae including ampicillin-resistant strains,
Klebsiella spp.,
Proteus spp. both indole-positive and indole-negative,
Enterobacter spp.,
Providencia spp.,
Serratia spp.,
Citrobacter spp.,
Neisseria spp. including β -lactamase producing strains of *Neisseria gonorrhoeae*
Salmonella spp. including *Salmonella typhi*,
Shigella spp.

DBL[®] Cefotaxime Sodium for Injection has frequently exhibited useful *in vitro* activity against *Pseudomonas* and *Bacteroides* species although some strains of *Bacteroides fragilis* are resistant.

There is *in vitro* evidence of synergy between DBL[®] Cefotaxime Sodium for Injection and aminoglycoside antibiotics such as gentamicin against some species of Gram-negative bacteria including some strains of *Pseudomonas*. No *in vitro* antagonism has been noted. In severe infections caused by *Pseudomonas* spp. the concurrent use of an aminoglycoside antibiotic may be indicated.

Pharmacokinetics

DBL[®] Cefotaxime Sodium for Injection is administered by intramuscular and intravenous injection. After administration of a 1 gram dose, the mean plasma concentration is approximately 20 mg/L (intramuscular, t_{max} = 30 minutes), 102 mg/L (intravenous over 2-5 minutes), 27.9 mg/L (30 minute IV infusion). There is no significant evidence of accumulation after repetitive dosing in subjects with normal

renal function. Mean elimination half life is 1.45 hour (IM), 1.06 hour (rapid IV) and 1.13 hour (30 minute IV infusion).

The desacetyl metabolite of DBL[®] Cefotaxime Sodium for Injection is detectable in blood and urine and is microbiologically active against a similar spectrum of bacteria, but is less active by a factor of 2 to 3. Approximately 20-36% of drug is excreted unchanged in the urine.

DBL[®] Cefotaxime Sodium for Injection is 32-44% bound to plasma protein and has a high renal clearance. 85-90% of the administered dose is recovered in the urine while the faeces accounted for 7-9.5% of the recovery total. 70-80% of the administered dose is recovered in the first 4 hours after administration.

The elimination half-life of DBL[®] Cefotaxime Sodium for Injection is 0.7-1.3 hours, whilst that of the metabolites is approximately 2 hours in patients with normal renal function. Mean peak urinary concentrations obtained after 1 gram administration of Cefotaxime Sodium for Injection, IM, IV and IV infusion at 4 hours were 903 mg/L, 1309 mg/L and 599 mg/L, respectively.

Concentrations of DBL[®] Cefotaxime Sodium for Injection in the CSF are considerably lower than plasma.

Indications

DBL[®] Cefotaxime Sodium for Injection is indicated in the treatment of the following infections either before the infecting organism has been identified or when caused by bacteria of established sensitivity.

Septicaemia.

Respiratory tract infections: acute and chronic bronchitis, bacterial pneumonia, infected bronchiectasis, lung abscess and post-operative chest infections.

Urinary tract infections: acute and chronic pyelonephritis, cystitis and asymptomatic bacteriuria.

Soft tissue infections: cellulitis, peritonitis and wound infections.

Bone and joint infections: osteomyelitis, septic arthritis.

Obstetric and gynaecological infections: pelvic inflammatory disease.

Gonorrhoea: particularly if penicillin-resistant.

Other bacterial infections: meningitis and other sensitive infections suitable for parenteral antibiotic therapy.

The administration of DBL[®] Cefotaxime Sodium for Injection prophylactically may reduce the incidence of certain post-operative infections in patients undergoing surgical procedures that are classified as contaminated or potentially contaminated or in clean operations where infections would have serious effects. Protection is best ensured by achieving adequate local tissue concentrations at the time contamination is likely to occur. DBL[®] Cefotaxime Sodium for Injection should therefore be administered immediately prior to surgery and if necessary continued in the immediate post-operative period.

Administration should usually be stopped within 24 hours since continuing use of any antibiotic in the majority of surgical procedures does not reduce the incidence of subsequent infections.

Dosage and Administration

DBL[®] Cefotaxime Sodium for Injection should be administered only by the intramuscular or intravenous routes.

The dosage, route of administration and dosage interval will depend on the site and severity of the infection, sensitivity of the pathogens and condition of the patient.

Adults

For urinary tract infections:

The recommended dose is 2g daily in two divided doses.

Other Infections:

For other infections the minimum recommended dosage is 2g daily in divided doses. This dosage may be increased to 3, 4 or 6g daily according to the severity of the infection, sensitivity of causative organisms and condition of the patient.

For prevention of post-operative infection:

DBL[®] Cefotaxime Sodium for Injection should be administered immediately prior to surgery. A single dose of 1g is suitable for most procedures. For procedures longer than 4 hours a dose of 2g is recommended. A single 1g dose in combination with 500 mg metronidazole is effective in colorectal surgery.

For the treatment of gonorrhoea:

Uncomplicated gonorrhoea due to non beta-lactamase producing organisms: One single intramuscular dose of 1g.

Uncomplicated gonorrhoea due to beta-lactamase producing organisms: One single intramuscular dose of 0.5g of DBL[®] Cefotaxime Sodium for Injection plus probenecid, 1g orally, given 1 hour earlier.

Paediatrics

Neonatal meningitis: The following dosage schedule is recommended:

0-1 week of age 50 mg/kg IV every 12 hours

1-4 weeks of age 50 mg/kg IV every 8 hours

Children

The usual dosage range is 100-150 mg/kg/day in 3 to 4 divided doses. However, in very severe infections doses of up to 200 mg/kg/day may be required.

Impaired Renal Function

Because of extra-renal elimination, it is only necessary to reduce the dosage of DBL[®] Cefotaxime Sodium for Injection in severe renal failure (creatinine clearance <10 ml/min). After an initial loading dose of 1g, the daily dose should be halved without change in the frequency of dosing, eg. 1g 12 hourly becomes 0.5g 12 hourly, 1g 8 hourly becomes 0.5g 8 hourly, 2g 8 hourly becomes 1g 8 hourly.

Intravenous and Intramuscular Administration

Dissolve DBL[®] Cefotaxime Sodium for Injection in Water for Injections B.P. as shown below. Shake well until dissolved and then withdraw the entire contents of the vial into the syringe and use immediately.

Vial size	Volume of water for injections to be added
500 mg	2 ml
1g	4 ml
2g	10 ml

Intravenous Infusion

DBL[®] Cefotaxime Sodium for Injection may be administered by intravenous infusion. 1-2g are dissolved in 40-100ml of Water for Injections B.P. or in the infusion fluids listed under "Pharmaceutical Precautions". The prepared infusion should be administered over 20-60 minutes.

Elderly

No specific recommendations for the elderly.

Contraindications

Known allergy to cephalosporins

Lignocaine hydrochloride should not be administered by the intravenous route nor be used as a diluent for:

- patients with a known history of hypersensitivity to lignocaine or other local anaesthetics of the amide type;
- patients with non-paced heart block;
- patients with severe heart failure;
- infants aged less than 30 months.

Warnings & Precautions

This product should not ordinarily be given to those known to be allergic to penicillin or to cephalosporins especially if they have experienced an allergic or urticarial reaction.

Hypersensitivity Reactions

- Patients should be asked about allergies and particularly hypersensitivity to beta-lactam antibiotics.
- Occurrence of a hypersensitivity reaction requires treatment being stopped.
- The use of cefotaxime is strictly contraindicated in subjects with a previous history of immediate type hypersensitivity to cephalosporins. In any doubt, it is essential that a physician be present at the time of the first administration, in order to treat any possible anaphylactic reaction.
- As there is cross allergy between penicillin's and cephalosporins in 5 to 10% of cases, use of the latter should be undertaken with extreme care in penicillin sensitive subjects; careful monitoring is necessary from the first administration.
- Hypersensitivity reactions (anaphylaxis) occurring with these two antibiotic families may be serious or even fatal.

Pseudomembranous Colitis

Severe or persistent diarrhoea has been observed during treatment, or in the initial weeks following treatment, with various antibiotics. It may be indicative of pseudomembranous colitis, the diagnosis of which is confirmed by colonoscopy. This event, rare with cephalosporins, but possibly fatal, requires that cefotaxime be stopped immediately and appropriate specific antibiotic therapy started without delay (eg. oral vancomycin or metronidazole). The administration of drugs favouring faecal stasis is strictly forbidden during cefotaxime therapy, particularly in bed patients.

Clostridium difficile-associated disease

Diarrhoea, particularly if severe and /or persistent, occurring during treatment or in the initial weeks following treatment with particularly broad spectrum antibiotics, may be symptomatic of *Clostridium difficile* -associated disease. The most severe form of this disease is pseudo-membranous colitis. The diagnosis of this rare but possibly fatal condition is confirmed by endoscopy and /or histology. Screening of faeces for this pathogen and its cytotoxin is the best way to diagnose *Clostridium difficile* -associated disease.

If a diagnosis of pseudomembranous colitis is suspected, cefotaxime should be stopped immediately and appropriate specific antibiotic therapy should be started without delay (e.g. oral vancomycin or metronidazole). *Clostridium difficile* -associated disease can be favoured by faecal stasis.

Hepatic and Renal Disease

Transient rises in hepatic enzymes, urea and creatinine have been seen in some patients given DBL[®] Cefotaxime Sodium for Injection, so careful monitoring of hepatic and renal function is advised where any

dysfunction exists. For dosage adjustment in moderate and severe renal impairment see Dosage and Administration.

Repeated use of lignocaine hydrochloride should be avoided in patients with severe liver disease or decreased hepatic blood flow due to the possibility of lignocaine toxicity (resulting from decreased metabolism and accumulation).

Renal Function

Caution should be exercised if cefotaxime is administered together with aminoglycosides. Renal function must be monitored in all such cases.

Neutropenia

For treatment courses lasting longer than 10 days, the white blood cell count should be monitored and treatment stopped in the event of neutropenia.

Renal Insufficiency

The dosage should be modified according to the creatinine clearance or the serum creatinine where measurement of the former is not possible (see Dosage and Administration)

Sodium Intake

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

Joint Prescription with Other Medicaments

Care should be taken to monitor renal function during treatment with other antibiotics that are potentially nephrotoxic (notably aminoglycosides) or potent diuretics.

Pregnancy

Cefotaxime crosses the placental barrier.

Studies in several animal species have not revealed any teratogenic or foetotoxic effect. However, the safety of cefotaxime has not been established in human pregnancy and it should not be used during pregnancy.

Lactation

As DBL[®] Cefotaxime Sodium for Injection passes into breast milk either breast feeding or treatment of the mother should be stopped.

Adverse Reactions

Hypersensitivity

Rash, pruritis, fever, and less frequently: urticaria anaphylactic reactions (eg. angioedema, bronchospasm, malaise possibly culminating in shock).

As with other cephalosporins, isolated cases of bullous eruptions (erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis) have been reported.

Gastrointestinal

Nausea, vomiting, abdominal pain, diarrhoea, rarely pseudomembranous colitis (see Warnings and Precautions). During treatment with cefotaxime nausea, vomiting, abdominal pain or diarrhoea may occur. As with all broad spectrum antibiotics diarrhoea may sometimes be a symptom of enterocolitis, which may, in some cases, be accompanied by blood stools. A particular form of enterocolitis that can occur with antibiotics is pseudomembranous colitis [in most cases due to *Clostridium difficile*](see Warnings).

Hepatic

Moderate regressive increase in transaminases (ALAT, ASAT, gamma-GT and or alkaline phosphatase) and /or bilirubin). These laboratory abnormalities, which may also be explained by the infection, may

rarely exceed twice the upper limit of the normal range and elicit a pattern of liver injury, usually cholestatic and most often asymptomatic.

Haematological

As with all beta-lactam antibiotics, neutropenia and more rarely agranulocytosis may occur, particularly during prolonged treatment. The white cell count should be monitored where treatment lasts more than 10 days and treatment stopped in the event of neutropenia.

Some cases of eosinophilia and thrombocytopenia, rapidly reversible on stopping treatment, have been reported. Rare cases of haemolytic anaemia have also been reported.

Renal Toxicity

Decrease in renal function (increase of creatinine) have been observed with cephalosporins including cefotaxime, particularly when co-prescribed with aminoglycosides and/or potent diuretics.

As with some other cephalosporins, rare cases of interstitial nephritis have been reported in patients treated with cefotaxime.

Neurological

Administration of 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).

Cardiovascular

In single cases, arrhythmia following rapid bolus infusion through central venous catheter.

Other

Superinfection:

As with other antibiotics, the use of DBL[®] Cefotaxime Sodium for Injection, 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.

Inflammatory reactions at the IV or IM injection site.

Fever.

As reported with other antibiotics 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 in breathing, joint discomfort. To some extent, these manifestations are consistent with the symptoms of the underlying disease for which the patient is being treated.

For IM formulations: since the solvent contains lidocaine, systemic reactions to lidocaine may occur, especially in the event of inadvertent intravenous injection or injection into highly vascularized tissue or in the event of an overdose.

Interactions

Medicine Interactions

DBL[®] Cefotaxime Sodium for Injection exhibits an additive microbiological effect with gentamicin. However, because of physical incompatibility DBL[®] Cefotaxime Sodium for Injection should not be mixed with an aminoglycoside antibiotic into a single preparation.

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

As with other cephalosporins, cefotaxime may potentiate the nephrotoxic effects of nephrotoxic drugs.

Interactions with Laboratory Tests

Appearance of a positive Coombs test may be seen during treatment with DBL[®] Cefotaxime Sodium for Injection.

In urine glucose testing with non-specific reducing agents, a false positive reaction may occur in patients treated with DBL[®] Cefotaxime Sodium for Injection. This phenomenon is not seen when a glucose-oxidase specific method is used.

Overdosage

Animal evidence suggests that DBL[®] Cefotaxime Sodium for Injection has a very low toxic potential. LD50 studies in mice and rats administered DBL[®] Cefotaxime Sodium for Injection intravenously have shown no mortality or signs of intoxication up to doses of 716 mg/kg and 2000 mg/kg respectively.

As with all cephalosporins, there is a risk of reversible encephalopathy. No specific antidote exists. Serum levels of DBL[®] Cefotaxime Sodium for Injection may be reduced by haemodialysis.

In case of overdose, immediately contact the Poisons Information Centre for advice on management (New Zealand call 0800 764 766.)

Pharmaceutical Precautions

The dry sterile powder in vials should be stored away from heat and protected from light. The pH of the formulated material is 4.5 to 6.5. Raising the pH (as by addition of strong base) will result in an intense yellow colour and possible degradation.

Whilst it is preferable to use only freshly prepared solutions for both intravenous and intramuscular injection, DBL[®] Cefotaxime Sodium for Injection is compatible with several commonly used intravenous fluids and will retain satisfactory potency for up to 24 hours refrigerated, or up to 8 hours at room temperature, in the following:

Water for Injections BP

0.9% Sodium Chloride Injection BP

5% Dextrose Injection BP

Compound Sodium Lactate Injection BP
(Ringer-Lactate Injection)

After 24 hours any unused solution should be discarded. DBL[®] Cefotaxime Sodium for Injection is also compatible with 1% lignocaine. Freshly prepared solutions should be used. 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.

Medicine Classification

Prescription Medicine.

Package Quantities

Single vials and packs of 10 vials containing 500 mg or 1g cefotaxime as cefotaxime sodium. Single vials containing 2g cefotaxime as cefotaxime sodium.

Further Information

Each gram of DBL[®] Cefotaxime Sodium for Injection contains approximately 48 mg (2.09 mmol) of sodium. Cefotaxime Sodium for Injection has been used with other beta-lactam antibiotics such as carbenicillin in the treatment of neutropenic patients.

DBL[®] Cefotaxime Sodium for Injection may also be administered separately with metronidazole in the treatment of mixed infections caused by anaerobic and aerobic organisms. DBL[®] Cefotaxime Sodium for Injection usually passes the blood-brain barrier in levels above the MIC of common sensitive pathogens when the meninges are inflamed. The laboratory abbreviation for cefotaxime is CTX.

Displacement information

Strength of DBL[®] Cefotaxime Sodium for Injection	Displacement volume
500mg	0.2 ml
1g	0.4 ml
2g	1 ml

Name and Address

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