

# NEW ZEALAND DATA SHEET

## 1. PRODUCT NAME

DBL™ Cefotaxime Sodium for Injection 1 g Powder for Injection.

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of DBL Cefotaxime Sodium for Injection contains 1 g of cefotaxime sodium.

Each gram of DBL Cefotaxime Sodium for Injection contains approximately 48 mg (2.09 mmol) of sodium.

For the full list of excipients, see section 6.1 List of excipients.

## 3. PHARMACEUTICAL FORM

Powder for Injection.

DBL Cefotaxime Sodium for Injection is a white to pale yellow crystalline powder f

The reconstituted product is a pale yellow solution. Variations in the intensity of colour of the freshly prepared solution do not indicate change in potency or safety.

The pH of the formulated material is 4.5 to 6.5.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic 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.

## **4.2 Dose and method of administration**

### **Dose**

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**

#### ***Urinary tract infections***

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

#### ***Other infections***

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

#### ***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 2 g is recommended. A single 1 g dose in combination with 500 mg metronidazole is effective in colorectal surgery.

#### ***Gonorrhoea***

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

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

### **Dosage adjustment**

#### ***Patients with renal impairment***

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, e.g., 1 g 12 hourly becomes 0.5 g 12 hourly, 1 g 8 hourly becomes 0.5 g 8 hourly, 2 g 8 hourly becomes 1 g 8 hourly.

#### ***Elderly***

No specific recommendations for the elderly.

### ***Paediatric population***

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.

### ***Meningitis – neonatal patients***

The following dosage schedule is recommended:

<b>Age</b>	<b>Dose and duration</b>
0-1 week of age	50 mg/kg IV every 12 hours
1-4 weeks of age	50 mg/kg IV every 8 hours

### **Method of administration**

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

### ***Intravenous (IV) and intramuscular (IM) administration***

Dissolve DBL Cefotaxime Sodium for Injection in water for injections as shown below. Shake well until dissolved and then withdraw the entire contents of the vial into the syringe and use immediately.

<b>Vial size</b>	<b>Volume of water for injections to be added</b>
1 g	4 mL

### ***Intravenous infusion (IV infusion)***

DBL Cefotaxime Sodium for Injection may be administered by intravenous infusion. 1-2 g are dissolved in 40-100 mL of water for injections, isotonic saline, dextrose solution or Ringers-Lactated solution (see listed under section 6.2 Incompatibilities). The prepared infusion should be administered over 20-60 minutes.

It is recommended not to mix cefotaxime with sodium bicarbonate solutions or with aminoglycosides.

When using the intravenous route, it is advisable to initiate therapy by administering cefotaxime directly into the vein.

Particularly sensitive patients may complain of pain after an intramuscular injection; the use of a solvent containing lidocaine hydrochloride 1% solution, twice daily, is recommended for the treatment in these subjects (except in the case of subjects who are hypersensitive to lidocaine). This solution is only for use by intramuscular route and therefore, endovascular administration must be avoided.

The solvent containing lidocaine hydrochloride is not used in children under the age of 12, as intramuscular administration is performed with the solution in water for injection only.

## Displacement information

Strength of DBL Cefotaxime Sodium for Injection	Displacement volume
1g	0.4 mL

## 4.3 Contraindications

Cefotaxime is contraindicated in patients:

- with a history of hypersensitivity to cefotaxime.
- who have had previous experience of a major allergy or anaphylaxis to a cephalosporin or penicillin due to the possibility of cross sensitivity (see Section 4.4 Special warnings and precautions for use).
- in pregnancy and during lactation (See Section 4.6 Fertility, pregnancy and lactation).

Lignocaine hydrochloride should not be used as a diluent for DBL Cefotaxime Sodium :

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

## 4.4 Special warnings and precautions for use

### Superinfection

As with other antibiotics, the use of cefotaxime, especially prolonged use, may lead to increased growth of non-susceptible microorganisms including fungi.

A close examination of the patient's condition is essential. If super-infections arise during therapy, appropriate measures must be taken.

Third-generation cephalosporin, as with other beta-lactams, may induce microbial resistance; this occurrence is more significant with opportunistic organisms, especially *Enterobacteriaceae* and *Pseudomonas*, in immuno-compromised subjects and probably when combining additional beta-lactams.

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.

### Anaphylactic reactions

Before starting treatment with cefotaxime, patients should be asked about allergies and particularly hypersensitivity to beta-lactam antibiotics.

The use of cefotaxime is strictly contraindicated in subjects with a previous history of immediate type hypersensitivity to cephalosporins. If in doubt, it is essential that a physician

is 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 patients with known hypersensitivity to penicillin or other beta-lactam antibiotics; careful monitoring is necessary from the first administration. See Sections 4.3 Contraindications and 4.8 Undesirable effects.

Hypersensitivity reactions (anaphylaxis) occurring with these two antibiotic families may be serious or even fatal.

Some patients receiving treatment with cefotaxime have presented with severe reactions including hypersensitivity reactions with a fatal outcome (see Sections 4.3 Contraindications and 4.8 Undesirable effects. available. Occurrence of a hypersensitivity reaction requires treatment being stopped and suitable treatment must be started (vasopressor amines, antihistamines, corticosteroids) or, in the case of anaphylaxis, immediate treatment with adrenaline or other appropriate emergency measure.

### **Pathologies associated with *Clostridium difficile* (CDAD)**

A particularly severe or persistent diarrhoea that occurs during treatment or in the initial weeks following treatment with particularly broad spectrum antibiotics may be symptomatic of *Clostridium difficile*-associated disease (CDAD). CDAD may vary in intensity from mild to life threatening. The most severe form of this disease is pseudomembranous colitis. It is important to take such diagnosis into consideration in patients who present with diarrhoea during therapy with cefotaxime.

Cases of pseudomembranous colitis have been described with the simultaneous use of cephalosporin (and other broad spectrum antibiotics). It is important to take such diagnosis into consideration in patients who present with diarrhoea during therapy with cefotaxime.

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). Mild cases of colitis may regress after stopping the treatment. The administration of electrolyte and protein solutions is advised for mild or severe cases of colitis. The administration of drugs favouring faecal stasis is strictly forbidden during cefotaxime therapy, particularly in bed patients.

Cefotaxime must be prescribed with caution in individuals with a history of gastrointestinal diseases, particularly colitis.

### **Neurotoxicity**

High doses of beta-lactam antibiotics, including cefotaxime, especially in patients with kidney failure, may lead to encephalopathies (e.g., loss of consciousness, abnormal movements and convulsions) (see section 4.8 Undesirable effects).

Patients should be warned to contact the doctor immediately before continuing with the treatment if reactions of this type occur.

## **Haematological reactions**

During treatment with cefotaxime, especially when administered for long periods, leucopenia, neutropenia and, more rarely, bone marrow deficiency, pancytopenia and agranulocytosis may develop.

For treatment courses of more than 7-10 days, the white blood cell count should be monitored and, in the case of neutropenia, treatment should be discontinued.

Some cases of eosinophilia and thrombocytopenia were reported, which were rapidly reversible after discontinuation of treatment. Cases of haemolytic anaemia were also reported (see section 4.8 Undesirable effects).

## **Precautions for administration**

During post-marketing monitoring of the drug, potentially life-threatening arrhythmias were reported in very few patients who received the rapid intravenous dose of cefotaxime through a central venous catheter. The recommended time for injection or infusion must be followed (see section 4.2 Dose and method of administration).

See section 4.3 for contraindications related to formulations that contain lidocaine. Tissue irritation at the intravenous injection point is rare; this can be avoided by injecting the drug very slowly (3-5 minutes). To minimise the potential for tissue inflammation, infusion sites should be monitored regularly and changed when appropriate.

## **Neutropenia**

Cefotaxime Sodium for Injection has been used with other beta-lactam antibiotics such as carbenicillin in the treatment of neutropenic patients. For treatment courses lasting longer than 10 days, the white blood cell count should be monitored and treatment stopped in the event of neutropenia.

## **Severe cutaneous adverse reactions**

Case of severe bullous rashes and severe cutaneous adverse reactions (SCAR), such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalised exanthematous pustulosis (AGEP) have been reported in patients taking beta-lactam antibiotics. Cutaneous vasculitis may occur. When SCAR is suspected, DBL Cefotaxime Sodium for Injection should be discontinued immediately and an alternative treatment should be considered. See section 4.8 Undesirable effects.

## **Prothrombin time**

Prolonged prothrombin time may occur in patients receiving protracted antimicrobial therapy.

## **Sodium intake**

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

## **Use in renal impairment**

Transient rises in urea and creatinine have been seen in some patients given DBL Cefotaxime Sodium for Injection, therefore, careful monitoring of renal function is advised where any

dysfunction exists. For dosage adjustment in moderate and severe renal impairment see section 4.2 Dose and method of administration.

The dosage should be modified according to the creatinine clearance or the serum creatinine where measurement of the former is not possible (see section 4.2 Dose and method of administration).

The simultaneous use of aminoglycosides or other nephrotoxic drugs (see Section 4.5 Interactions with medicines and other forms of interactions) must be undertaken with caution. Renal function should be monitored in these patients, the elderly and in the case of pre-existing kidney failure.

### **Use in hepatic impairment**

Transient rises in hepatic enzymes have been seen in some patients given DBL Cefotaxime Sodium for Injection, so careful monitoring of hepatic function is advised where any dysfunction exists.

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).

### **Effects on laboratory tests**

As with other cephalosporins, false positive results on the Coombs test have been reported in some patients receiving treatment with cefotaxime. This phenomenon may interfere with blood compatibility tests.

In urine glucose testing with non-specific reducing agents (such as Benedict, Fehling, "Clinitest" methods), 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.

## **4.5 Interaction with other medicines and other forms of interaction**

### **Other antibiotics**

Cefotaxime should not be mixed in the same syringe with other antibiotics.

Cefotaxime should not be combined with medicines with bacteriostatic action (e.g., tetracycline, erythromycin, chloramphenicol or sulfonamides), as antagonistic effect has been observed regarding the anti-bacterial effect *in vitro*.

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.

### **Uricosuric agents (e.g., probenecid)**

Probenecid interferes with the renal tubular transfer of cephalosporins, delaying their excretion and thereby increasing their plasma concentration. Dosage adjustment may be needed in patients with kidney failure (see sections 4.2 Dose and method of administration and 4.4 Special warnings and precautions for use).

## **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). The simultaneous use of aminoglycosides, a combination that, under *in vitro* conditions, produces a synergistic or at least an additive effect, may be indicated in particularly severe infections: the two antibiotics are nevertheless administered in separate syringes; in these cases, it is recommended to monitor renal function constantly.

The administration of high doses of cefotaxime at the same time as high-efficacy saluretics (furosemide) has not yet demonstrated an effect on renal function. As a matter of precaution, however, it should be noted that renal function may be compromised by the simultaneous administration of high doses of cephalosporins and effective saluretics. Renal function must be monitored in these patients (see section 4.4 Special warnings and precautions for use)

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

### **Fertility**

No data available.

### **Pregnancy**

Cefotaxime crosses the placental barrier.

Studies in several animal species have not revealed any teratogenic or fetotoxic 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 it is, therefore, advisable for either breast feeding, for treatment of the mother should be stopped.

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 continue therapy in light of the benefit of breast-feeding for the child and the benefit of therapy for the mother.

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

During the treatment with cefotaxime, undesirable effects may occur (e.g., dizziness), which may influence the ability to drive and use machines. In the case of unwanted effects such as dizziness, the patient's ability to concentrate and properly react may be impaired. Furthermore, high doses of cefotaxime, especially in patients with kidney failure, may cause encephalopathies (e.g., loss of consciousness, abnormal movements and convulsions) (see section 4.8 Special warnings and precautions for use).

Patients should be warned not to drive or operate machinery if they show any of these symptoms.



## **4.8 Undesirable effects**

### **Infections and infestations**

Super-infection, candida vaginitis.

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. See section 4.4 Special warnings and precautions for use.

### **Blood and the lymphatic system disorders**

As with all beta-lactam antibiotics, neutropenia and more rarely agranulocytosis (see section 4.4 Special warnings and precautions for use) 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. Bone marrow deficiency, granulocytopenia, pancytopenia, neutropenia and leucopenia have also been reported.

### **Metabolism and nutrition disorders**

Anorexia.

### **Immune system disorders**

Hypersensitivity reactions including rash, pruritis, fever, and less frequently urticaria. Anaphylactic reactions, angioedema, bronchospasm, malaise possibly culminating in shock may rarely occur.

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.

### **Nervous system and psychiatric disorders**

Convulsions, headache, dizziness, agitation, confusion and vertigo have been reported. Encephalopathy (loss of consciousness, abnormal movements) (see section 4.4 Special warnings and precautions for use, Neurotoxicity).

### **Cardiac disorders**

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

### **Gastrointestinal disorders**

Nausea, vomiting, abdominal pain, diarrhoea, glossitis, heartburn, candidiasis, rarely pseudomembranous colitis (see section 4.4 Special warnings and precautions for use). 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 section 4.4 Special warnings and precautions for use. If a colonoscopy investigation confirms this diagnosis, the antibiotics in use must be discontinued immediately and treatment with oral vancomycin must be started. Peristalsis inhibitor drugs are contraindicated.

### **Hepatobiliary disorders**

Moderate regressive increase in transaminases (ALAT, ASAT, LDH, gamma-GT and or alkaline phosphatase) and/or bilirubin) have been noted. 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.

Hepatitis (potentially with jaundice) may also occur.

### **Skin and other subcutaneous tissue disorders**

Rash, pruritus, urticaria and nocturnal sweating.

As with other cephalosporins, isolated cases of bullous eruptions (erythema multiforme) and severe cutaneous adverse reactions, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalised exanthematous pustulosis (AGEP) have been reported in beta-lactam antibiotics. See section 4.4 Special warnings and precautions for use.

### **Musculoskeletal and connective tissue disorders**

Arthralgia.

### **Renal and urinary disorders**

Decrease in renal function (increase of serum creatinine and blood urea) 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, increase in azotaemia and acute kidney failure has been reported in patients treated with cefotaxime.

### **General disorders and administration site conditions**

Fever and shivering have been reported. Pain at the injection site (IM administration), inflammatory reactions at the injection site, including phlebitis/thrombophlebitis, feeling of tightness in the chest and asthenia. Phlebitis at the site of injection may occur. Pain, phlebitis and tenderness have been reported in approximately 4.8% of cases. Inflammatory reactions at the IV or IM injection site have also been reported. Other reported reactions were hardening and fragility of the injection site.

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.

### **Post marketing experience**

#### ***Hepatobiliary disorders***

Hepatitis (potentially with jaundice) may also occur.

## Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>.

## 4.9 Overdose

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

As with all cephalosporins, there is a risk of reversible encephalopathy with 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 effects (e.g., convulsions). No specific antidote exists. Serum levels of cefotaxime may be reduced by peritoneal dialysis or haemodialysis.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-infective agents, cephalosporin, ATC code: J01DD01.

#### Mechanism of action

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  $\beta$ -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 b-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.

## 5.2 Pharmacokinetic properties

### Absorption

Cefotaxime is not significantly absorbed by the gastrointestinal tract and must therefore be administered via the parenteral route.

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 (IM,  $t_{max}$  = 30 minutes), 102 mg/L (IV 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).

### Distribution

After IM and IV administration of the usual dose of cefotaxime, it is distributed into the tissues and bodily fluids; aqueous humour, bronchial secretion, saliva, middle ear, bone tissue, bile, and ascitic, pleural, prostatic and cerebrospinal fluid.

DBL Cefotaxime Sodium for Injection usually passes the blood-brain barrier in levels above the Minimum Inhibitory Concentration of common sensitive pathogens when the meninges are inflamed. The laboratory abbreviation for cefotaxime is CTX.

## **Biotransformation**

Cefotaxime is partially metabolised in the liver into desacetyl-cefotaxime, which has an antibacterial activity. 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.

## **Excretion**

Cefotaxime and its metabolites are excreted primarily in the urine. Approximately 20-36% of drug is excreted unchanged in the urine. In adults with normal renal function, about 40-60% of a single IM or IV dose is excreted in the urine unchanged and about 24% is excreted as desacetyl-cefotaxime over 24 hours.

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 cerebrospinal fluid are considerably lower than plasma.

## **5.3 Preclinical safety data**

Animal evidence suggests that DBL Cefotaxime Sodium for Injection has a very low toxic potential. LD<sub>50</sub> 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.

### **Genotoxicity**

Studies performed on rats and rabbits showed that cefotaxime has no teratogenic effects.

### **Carcinogenicity**

No data available.

### **Reproductive and developmental toxicity**

Studies performed on rats and rabbits showed that neither fertility nor peri- and postnatal growth were compromised.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

There are no excipients in DBL Cefotaxime Sodium..

### 6.2 Incompatibilities

#### *Incompatibilities*

Cefotaxime sodium should not be mixed with alkaline solutions such as sodium bicarbonate injection. Raising the pH (by addition of strong base) will result in an intense yellow colour and possible degradation.

Cefotaxime is physically incompatible with aminoglycosides. If an aminoglycoside antibiotic needs to be administered with DBL Cefotaxime Sodium for Injection, they should be administered separately and not mixed together as a single preparation.

Cefotaxime should not be mixed with other medicinal products except those listed in sections 4.2. Dose and Method of administration and under the below subsection heading, Compatibilities).

#### *Compatibilities*

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
- 0.9% Sodium Chloride Solution for Injection
- 5% Dextrose Injection for IV infusion
- Compound Sodium Lactate Injection for IV infusion (Ringer-Lactate).

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.

### 6.3 Shelf life

#### **Unopened**

36 months. Stored at or below 25°C. Protect from light.

#### **Reconstituted solution**

24 hours. Stored at 2-8°C. Refrigerate. Do not freeze. Protect from light.

Chemical and physical in-use stability has been demonstrated for 24 hours, Stored at 2-8°C. From a microbiological point of view, once opened, 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 2-8°C.

#### **6.4 Special precautions for storage**

The dry sterile powder in vials should be stored away from heat and protected from light.

#### **6.5 Nature and contents of container**

Clear, Type III, glass vials with bromobutyl cap in packs of 10 vials.

#### **6.6 Special precautions for disposal and other handling**

For single use only. Discard any unused contents. Any unused medicine or waste material should be disposed of in accordance with local requirements.

### **7. MEDICINE SCHEDULE**

Prescription medicine.

### **8. SPONSOR**

Pfizer New Zealand Limited  
P O Box 3998  
Auckland, New Zealand.

Toll Free Number: 0800 736 363.

### **9. DATE OF FIRST APPROVAL**

1 March 2001.

### **10. DATE OF REVISION OF THE TEXT**

15 October 2020.

#### **Summary table of changes**

<b>Section changed</b>	<b>Summary of new information</b>
4.3	Pregnancy and lactation contraindicated.
4.4	Editorial changes and new safety information added in this section under the subsection headings, Superinfection, Anaphylactic reactions, Pathologies associated with <i>Clostridium difficile</i> (CDAD), Precautions for administration, Severe cutaneous adverse reactions, Use in renal impairment, Effects on laboratory tests.
4.8	New adverse events under the following SOC: Blood and lymphatic system disorders, General disorders and administration site condition,

	Nervous system and psychiatric disorders, Skin and subcutaneous tissue disorders.
4.9	New overdose information added.
All	Minor editorial changes.