AUSTRALIAN PRODUCT INFORMATION – DBL™ CEFOTAXIME SODIUM FOR INJECTION (CEFOTAXIME SODIUM)

1. NAME OF THE MEDICINE

Cefotaxime sodium.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Each gram of cefotaxime 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 is a white to pale yellow crystalline powder.

The reconstituted product is a pale yellow solution. Raising the pH (by addition of strong base) will result in an intense yellow colour and possible degradation.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

DBL Cefotaxime Sodium is indicated for the treatment of the following types of infection when caused by susceptible micro-organisms:

- infections of the respiratory tract (upper and lower)
- infections of the urinary tract
- septicaemia - concomitant therapy with an aminoglycoside may be instituted prior to isolation of the causative organism
- intra-abdominal infection
- gonorrhoea (including gonorrhoea caused by beta lactamase producing strains of *N. gonorrhoeae*)
- ear, nose and throat infections
- skin and skin structure infections
- bone and joint infections
- meningitis. Cefotaxime should be combined with an appropriate alternative antibiotic (ampicillin, chloramphenicol or penicillin G) for initial therapy in children (excluding neonates) pending the availability of culture and sensitivity results. In adults, the empirical use of cefotaxime should be restricted to patients suspected of having meningitis caused by

Gram negative enteric bacilli.

Cefotaxime may be used for the prevention of post operative infection in obstetrical surgery, vaginal and abdominal hysterectomy and biliary surgery.

In serious cases, cefotaxime may be used, if considered appropriate, before the results of sensitivity tests become available.

The emergence of resistance to cefotaxime may complicate treatment.

4.2 Dose and method of administration

Dosage

Adults

For urinary tract infections

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

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

For prevention of post operative infections

In vaginal or abdominal hysterectomy, 1 g should be administered intramuscularly 30 to 60 minutes before incision and repeated thereafter on completion of surgery and at 8 hourly intervals for a total duration of 24 hours.

In obstetrical surgery (caesarean section)

1 g should be administered intravenously after the cord has been clamped and thereafter at 6 and 12 hours.

In biliary surgery

1 g IV at induction.

For the treatment of 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 Cefotaxime plus probenecid, 1 g orally, given 1 hour earlier.

Paediatric population

For meningitis – Neonatal patients

- 0 to 1 week of age; 50 milligram/kg IV every 12 hours.
- 1 to 4 weeks of age; 50 milligram/kg IV every 8 hours.

Paediatric patients

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

Method of administration

DBL Cefotaxime Sodium should be administered only by intramuscular injection, intravenous injection or intravenous infusion.

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.

Intravenous injection

For intravenous injection, the contents of one vial of DBL Cefotaxime Sodium 1 g are dissolved in at least 4 mL Water for Injections and then injected over a period of 3 to 5 minutes, either into a vein or into the distal part of a clamped-off infusion tube.

Intravenous infusion

For short infusion, two vials of DBL Cefotaxime Sodium 1 g are dissolved in 40 mL Water for Injections or an infusion solution and then infused over 20 to 30 minutes. For continuous intravenous infusion, two vials of DBL Cefotaxime Sodium 1 g are dissolved in 100 mL of an isotonic saline or glucose solution and infused over 4 hours. Sodium bicarbonate solutions must not be mixed with DBL Cefotaxime Sodium.

Intramuscular injection

Intramuscular injections should be given laterally deep into the gluteus muscle. It is not advisable to inject more than 4 mL in either buttock. The pain of injection can be avoided by dissolving DBL Cefotaxime Sodium in a 0.5% lignocaine solution (see Sections 4.4 Special warnings and precautions for use and 4.3 Contraindications). Intravascular injection of this solution must be strictly avoided.

If the daily dose exceeds 2 g or if DBL Cefotaxime Sodium 1 g is administered more than twice daily, intravenous injection is preferred.

In administering the 500 milligram dose, half the amount of any one of the solutions mentioned above may be used.

The duration of treatment depends on the patient's response. It should be continued for at least three days after normalisation of the body temperature.

Compatibility with other medicines

DBL Cefotaxime Sodium is compatible with the commonly used intravenous infusion fluids listed below:

- Water for injection
- Sodium Chloride Injection
- 5% Glucose Injection
- Compound Sodium Lactate Injection (Ringer-Lactate Injection).

DBL Cefotaxime Sodium is also compatible with 0.5% lignocaine. Freshly prepared solutions should be used. 0.5% lignocaine solutions are to be used for intramuscular injections only.

Product contains no antimicrobial agent. For single use in one patient only. Discard any residue.

To reduce microbiological hazard, the diluted solution should preferably be used immediately and any remaining residue discarded.

Dosage adjustments

Use in renal impairment

The biological half life of the desacetyl metabolite of cefotaxime increases significantly and progressively below creatinine clearance of 20 mL/minute.

Furthermore, when the creatinine clearance is less than 5 mL/minute the half life of the parent compound is also increased. Because of these changes in the pharmacokinetics of the drug it is recommended that dosage adjustments should be made in patients with creatinine clearance of less than 20 mL/minute in order to achieve approximately equal peak serum levels during repeated dosage.

As a guide when creatinine clearance is less than or equal to 20 mL/minute, it is recommended that the current daily dose, for the treatment of the specific infection, be reduced by half and given every 12 hours. When creatinine clearance is less than or equal to 5 mL/minute, the recommended dose is 500 milligram every 12 hours (1 g daily).

4.3 Contraindications

DBL Cefotaxime Sodium is contraindicated in patients:

- with a history of hypersensitivity to cefotaxime.
- with known hypersensitivity to cephalosporins or with a history of a previous major allergic response to a 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 to dilute DBL Cefotaxime Sodium:

- for intravenous use 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

Anaphylactic reactions

Before starting therapy with DBL Cefotaxime Sodium, an accurate history must be determined to highlight previous hypersensitivity reactions to cefotaxime, cephalosporin, penicillin or other drugs.

The use of cefotaxime is contraindicated in patients with a previous history of hypersensitivity to cephalosporins.

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 Adverse effects (undesirable effects)).

Since cross allergy exists between penicillins and cephalosporins, cefotaxime should be used with caution in patients with known hypersensitivity to penicillin or other beta-lactam antibiotics. Serious, including fatal hypersensitivity reactions have been reported in patients receiving cefotaxime (see Sections 4.3 Contraindications and 4.8 Adverse effects (undesirable effects)). If a hypersensitivity reaction occurs, treatment must be stopped.

The possibility of severe or fatal anaphylactic reactions should be borne in mind and appropriate treatment kept available.

Cephalosporin antibiotics in high doses should be given with caution to patients receiving aminoglycoside antibiotics or potent diuretics such as furosemide.

Precautions for administration

Potentially life-threatening arrhythmias have been reported in very few patients who received rapid intravenous administration through a central venous catheter. Therefore, when administered by intermittent intravenous injection, cefotaxime must be given over a period of 3 to 5 minutes (see Section 4.2 Dose and method of administration).

Cefotaxime sodium like other parenteral anti-infective drugs, may be locally irritating to tissues. To minimise the potential for tissue inflammation, infusion sites should be monitored regularly and changed when appropriate.

Superinfection

As with other antibiotics, the use of cefotaxime, especially prolonged use, may lead to increased growth of non-sensitive micro-organisms.

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

Superinfection with non-susceptible organisms, including fungi, may occur and requires appropriate therapy.

Third-generation cephalosporin, as with other beta-lactams, may induce microbial resistance; this occurrence is more significant with opportunistic organisms, especially Enterobacteriales and Pseudomonas, in immunocompromised patients and probably when combining additional beta-lactams.

Pathologies associated with *Clostridium difficile* (CDAD)

Antibiotic associated pseudomembranous colitis has been reported with many antibiotics including cefotaxime. A toxin produced with *C. difficile* appears to be the primary cause. The severity of the colitis may range from mild to life threatening; the most severe form is pseudomembranous colitis.

It is important to take such diagnosis into consideration in patients who present with diarrhoea during therapy with cefotaxime. This may occur up to several weeks after cessation of antibiotic therapy. Mild cases usually respond to drug discontinuation alone. However, in moderate to severe cases appropriate therapy such as antibacterial agents effective against *C. difficile* should be considered. Fluids, electrolytes and protein replacement should be provided when indicated.

If a diagnosis of pseudomembranous colitis is suspected, treatment with cefotaxime must be stopped immediately and an appropriate therapy with a specific antibiotic must be started right away. The pathology associated with *C. difficile* may be exacerbated by faecal stasis. Drugs that inhibit peristalsis should not be administered. Treatment with broad spectrum antibiotics alters the normal flora of the colon and this may promote the growth of clostridia.

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

Drugs which delay peristalsis, e.g., opiates and diphenoxylate with atropine may prolong and/or worsen the condition and should not be used.

Sodium intake

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

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. When SCAR is suspected, DBL Cefotaxime Sodium should be discontinued immediately and an alternative treatment should be considered. See Section 4.8 Adverse effects (undesirable effects).

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.

Cases of haemolytic anaemia were also reported.

Also see Section 4.8 Adverse effects (undesirable effects).

Neurotoxicity

There have been reports of neurotoxicity associated with cephalosporin treatment. Symptoms of neurotoxicity include encephalopathy (e.g., loss of consciousness, abnormal movements and convulsions), seizures and/or myoclonus. Risk factors for developing neurotoxicity with cephalosporin treatment include being elderly, renal impairment, central nervous system disorders and intravenous administration. Withdrawal of the medicine should be considered if there are signs of neurotoxicity (see Section 4.8 Adverse effects (undesirable effects)).

Patients should be warned to contact the doctor immediately before continuing with the treatment if reactions of this type occur. Also see Section 4.4 Special warnings and precaution for use, Use in renal impairment.

Use in hepatic impairment

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).

Transient rises in hepatic enzymes have been seen in some patients given cefotaxime, therefore careful monitoring of hepatic function is advised where any dysfunction exists. See Section 4.8 Adverse effects (undesirable effects).

Use in renal impairment

Transient rises in urea and creatinine have been seen in some patients given cefotaxime, therefore, careful monitoring of renal function is advised where any dysfunction exists.

The dosage should be modified based on creatinine clearance (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 the elderly

No data available.

Paediatric use

For use in paediatric patients, refer to Section 4.2 Dose and method of administration.

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.

The administration of cephalosporins may interfere with some laboratory tests causing false positives for glycosuria in methods performed using non-specific reducing agents (such as Benedict or Fehling methods) but this phenomenon does not occur when enzyme methods are used (such as the specific glucose-oxidase method).

4.5 Interactions with other medicines and other forms of interactions

Other antibiotics

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

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 antibacterial effect *in vitro*.

Cefotaxime exhibits an additive microbiological effect with gentamicin. However, because of physical incompatibility cefotaxime should not be mixed with an aminoglycoside antibiotic into a single preparation.

Nephrotoxic drugs and loop diuretics

As with other cephalosporins, cefotaxime may potentiate the nephrotoxic effects of nephrotoxic drugs (e.g., aminoglycosides) or potent diuretics (e.g., furosemide).

Renal function must be monitored in these patients (see Section 4.4 Special warnings and precautions for use, Neurotoxicity and Use in renal impairment).

Uricosuric agents (e.g., probenecid)

Administration of oral probenecid decreases renal clearance slightly and increases total body concentrations (see Section 5.2 Pharmacokinetic properties).

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).

4.6 Fertility, pregnancy and lactation

Effects on fertility

No data available.

Use in pregnancy – Category B1

The safety of cefotaxime in pregnancy has not been established. However, cefotaxime crosses the placenta and therefore, it should not be used used during pregnancy unless the expected benefit outweighs the potential risks.

Use in lactation

Cefotaxime is excreted in the breast milk, it is therefore, advisable to stop breast-feeding when administering the drug. Peak concentrations measured 2 or 3 hours after intravenous administration of 1 g doses, ranged from 0.25 to 0.52 microgram/mL (mean 0.32 ± 0.09). 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, cefotaxime is not recommended for nursing mothers unless the expected benefits outweigh any potential risk or if alternative arrangements for feeding the infant can be made.

4.7 Effects on 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 Adverse effects (undesirable effects)). Patients must be warned not to drive or use machines if they show any of these symptoms.

4.8 Adverse effects (undesirable effects)

Infections and infestations

Superinfection (see Section 4.4 Special warnings and precautions for use), candida vaginitis.

Immune system disorders

Anaphylactic reactions, Jarisch-Herxheimer reaction. Angioedema, bronchospasm and malaise, possibly culminating in shock may rarely occur.

Blood and lymphatic system disorders

As with some other cephalosporins, leucopenia, granulocytopenia, thrombocytopenia, bone marrow deficiency, pancytopenia, neutropenia and more rarely agranulocytosis (see Section 4.4 Special warnings and precautions for use) may develop during treatment with cefotaxime. Some patients have developed positive direct Coombs test and rarely haemolytic anaemia, during treatment with cefotaxime. Eosinophilia.

Metabolic and nutrition disorders

Anorexia.

Musculoskeletal and connective tissue disorders

Arthralgia.

Hepatobiliary disorders

Increases in serum transaminases (Alanine aminotransferase (ALT), aspartate transaminase (AST)), blood lactate dehydrogenase (LDH), gamma-glutamyltransferase and alkaline phosphatase and/or bilirubin levels have been noted. These laboratory abnormalities, which also may 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.

General disorders and administration site condition

Pain at the injection site, phlebitis and tenderness have been reported in approximately 4.8% of cases. Also inflammatory reactions at the injection site including phlebitis/thrombophlebitis have been reported. Fever, systemic reactions to lidocaine (IM administration, since the solvent contains lidocaine), feeling of tightness in the chest, asthenia.

Other reported reactions were hardening and fragility at the injection site.

Gastrointestinal disorders

Glossitis, heartburn, nausea, vomiting, abdominal pain and diarrhoea. As with other broad spectrum antibiotics, colitis, including rare instances of pseudomembranous colitis has been reported with cefotaxime (see Section 4.4 Special warnings and precautions for use).

Other gastrointestinal pathologies

The occurrence of severe and prolonged diarrhoea has been connected with the use of various classes of antibiotics. In this event, the possibility of enterocolitis must be considered, which is sometimes accompanied by the presence of blood in the stools. Pseudomembranous colitis is a specific form of enterocolitis occurring with the use of antibiotics (most cases are caused by *C. difficile*). 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.

Renal and urinary disorders

Decrease in renal function/elevations in serum creatinine (especially when prescribed with aminoglycosides) and blood urea have been reported infrequently. As with some other cephalosporins, rare cases of interstitial nephritis and acute kidney failure (see Section 4.4 Special warnings and precautions for use) have been reported in patients treated with cefotaxime. Increase in azotaemia.

Nervous system and psychiatric disorders

Headache, dizziness, agitation, confusion and vertigo. 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 (see Section 4.4 Special warnings and precautions for use)).

Cardiac disorders

Potentially life-threatening arrhythmias have been reported in a few patients who received rapid intravenous administration of cefotaxime through a central venous catheter.

Skin and subcutaneous tissue disorders

Rash, pruritus, urticaria, hives 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) (see Section 4.4 Special warnings and precautions for use), drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalised exanthematous pustulosis (AGEP) have been reported in beta-lactam antibiotics.

Post-marketing experience

Hepatobiliary disorders

Hepatitis (potentially with jaundice).

Nervous system disorders

Seizures, encephalopathy, myoclonus.

Immune system disorders

Acute coronary syndrome associated with an allergic reaction (Kounis syndrome) has been observed.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 Overdose

Serum levels of cefotaxime may be reduced by haemodialysis.

There is a risk of reversible encephalopathy in cases of administration of high doses of beta-lactam antibiotics including cefotaxime. No specific antidote exists.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Cefotaxime sodium is a semi-synthetic cephalosporin for use by injection only.

Microbiology

At plasma concentrations achieved with the recommended therapeutic doses, cefotaxime is active *in vitro* against the following micro-organisms:

Gram-positive pathogens: Staphylococci, including penicillinase producing strains, but not methicillin resistant strains, *Streptococcus pyogenes, Streptococcus pneumoniae. Clostridium perfringens* and *Streptococcus faecalis* are resistant.

Gram-negative pathogens: Strains of Enterobacter, Klebsiella and Serratia group, *Haemophilus influenzae*, Neisseria spp. Gonococcus, (including penicillin resistant gonococci), Proteus genera, including *P. mirabilis, P. morganii, P. vulgaris, P. rettgeri, Escherichia coli* including many cephalothin and gentamicin resistant strains. Approximately 25% of *Pseudomonas aeruginosa* strains and 43% of Bacteroides strains have an *in vitro* MIC of < 16 mg/L.

There is *in vitro* evidence of synergy between cefotaxime and aminoglycoside antibiotics, such as gentamicin, against some species of Gram negative bacteria including some strains of *Pseudomonas aeruginosa, Serratia marcescens, E. coli,* Klebsiella species, *P. mirabilis* and *S. aureus.*

Cefotaxime is resistant to many beta lactamases (penicillinases and cephalosporinases).

Cefotaxime's bactericidal effect is due to inhibition of cell wall synthesis.

Susceptibility tests

Dilution or diffusion techniques, either quantitative (MIC) or breakpoint, should be used following a regularly updated, recognised and standardised method (e.g., NCCLS). Standardised susceptibility test procedures require the use of laboratory control micro-organisms to control the technical aspects of the laboratory procedures.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal and if the micro-organism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone, which prevents small uncontrolled technical factors from

causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable: other therapy should be selected.

Clinical trials

No data available.

5.2 Pharmacokinetic properties

Absorption

Cefotaxime is administered by intravenous or intramuscular injection. It is not adequately absorbed by mouth.

Following the intramuscular administration of a single 500 milligram and 1 g dose to normal volunteers, the following mean peak plasma concentrations at 30 minutes and 4 hours post administration were obtained.

	30 mins (milligram/L)	**4 hours (milligram/L)**
500 milligram	11.7	1.4
1 g	20.5	3.36

With a 2 g dose the plasma level is proportionately increased.

Multiple intramuscular doses of 500 milligram every 8 hours for 10 days in 15 healthy volunteers produced plasma levels ranging from 9.2 to 11.9 milligram/L 30 minutes after dosing, and from 0.08 to 0.55 milligram/L measured just before dosing i.e., at 8 hours.

After intravenous bolus (5 minutes administration) of 0.5 g, 1 g and 2 g to normal volunteers, the following concentrations were obtained, at peak, 1 hour and 4 hours.

	Peak (milligram/L)	**1 hour (milligram/L)**	**4 hours (milligram/L)**
500 milligram	38	9.7	1.0
1 g	102	20	1.9
2 g	214	40	3.3

After intravenous infusion (over 30 minutes) of 1 g, the following mean plasma levels were achieved after the end of the infusion.

	0.5 hours (milligram/L)	**1.5 hours (milligram/L)**	**3.5 hours (milligram/L)**
1 g	27.9	8.81	2.62

After multiple infusion of 1 g 6 hourly for 14 days, the mean steady state trough level was 1.33 milligram/L.

Distribution

Cefotaxime diffuses into the cerebrospinal fluid (CSF) to a significant extent in the presence of inflamed meninges. After intravenous doses of 1 or 2 g, CSF levels achieved are above the minimum inhibitory concentrations of susceptible organisms, i.e., those with MIC values of

less than 0.5 microgram/mL.

Following IV administration of 1 g, mean peak concentrations of 35 milligram/L were recorded in the bile after 30 minutes and declined to 3.30 milligram/L after 4 hours.

Following 1 gram intramuscular dosage the mean plasma clearance is 318 mL/min/1.73m^2.

Studies have shown that concomitant use of 0.5% lignocaine solution does not affect the pharmacokinetics or bioavailability of cefotaxime from intramuscular administration.

Metabolism

Cefotaxime is deacetylated in the body rapidly with measurable levels detectable in the plasma within 5 minutes after administration. Following a single intravenous dose of 15 milligram/kg to normal volunteers, the mean peak serum level for cefotaxime was 100 microgram/mL and for desacetylcefotaxime at 10 minutes post administration was 5.0 microgram/mL.

The desacetyl metabolite is generally less active than the parent compound, but has a similar spectrum of antibacterial activity *in vitro*. Its activity may range from twice as active to 32 times less active than the parent drug depending on the species. The desacetyl metabolite is further degraded to an open lactone form which is microbiologically inactive.

Cefotaxime is 32% to 44% bound to plasma protein while the desacetyl derivative is only bound by half of this value. The affinity for plasma proteins is low, as evidenced by the high urinary clearance.

Mean peak urinary concentrations obtained after administration of 1 g cefotaxime intravenously, intramuscularly and by intravenous infusion at 4 hours were 1309 milligram/L, 903 milligram/L, 599 milligram/L, respectively.

Excretion

85% of the administered dose is recovered in the urine while the faeces accounted for 7.5% of the total recovery. 70% of the administered dose is recovered in the first 4 hours after administration. Studies in human volunteers measuring radioactive recovery in the urine have indicated that 20% of administered drug is excreted as unchanged drug, 15% as the desacetyl metabolite and 20% as the open lactone derivative.

There is no evidence of drug accumulation following multi dose intravenous and intramuscular administration in subjects with normal renal function. The mean elimination half life after intramuscular administration was 1.45 hour, 1.06 hour after rapid intravenous injection and 1.13 hour after 30 minute intravenous infusion.

Interaction studies between parenterally administered cefotaxime and orally ingested probenecid, showed that probenecid increased the retention of cefotaxime by 14% to 40% and decreased the renal clearance by 11% to 32%.

Special population

Neonatal patients

In neonates, the pharmacokinetics are influenced by birth weight. In low birth weight neonates, the elimination half life is prolonged. Following an infusion (10 minutes) of 50 milligram/kg, the following mean concentrations were obtained.

Mean Birth Weight	Peak (milligram/L)	2 hours (milligram/L)	6 hours (milligram/L)	Half Life (hours)
1100 g	115.9	69.8	34.4	4.63
2500 g	132.7	78.9	38.1	3.37

Patients with renal impairment

The elimination half life of cefotaxime is 0.7 to 1.3 hours while that of the metabolites is approximately 2 hours in patients with normal renal function.

In the presence of impaired renal function, the terminal half life of the desacetyl derivative is prolonged much more than of the unchanged drug; in patients with creatinine clearance of 5 to 10 mL/min, the terminal half life of cefotaxime is 3.5 hours compared to 13.0 hours for the desacetyl derivative.

5.3 Preclinical safety data

Genotoxicity

No data available.

Carcinogenicity

No data available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

There are no excipients in DBL Cefotaxime Sodium.

6.2 Incompatibilities

DBL Cefotaxime Sodium should not be mixed with sodium bicarbonate solutions, other antibiotics especially aminoglycosides and other drugs. Cefotaxime is physically incompatible with aminoglycosides. Where an aminoglycoside antibiotic is administered at the same time as DBL Cefotaxime Sodium they should be administered separately and not mixed together as a single preparation.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store below 25°C. Protect from light.

6.5 Nature and contents of container

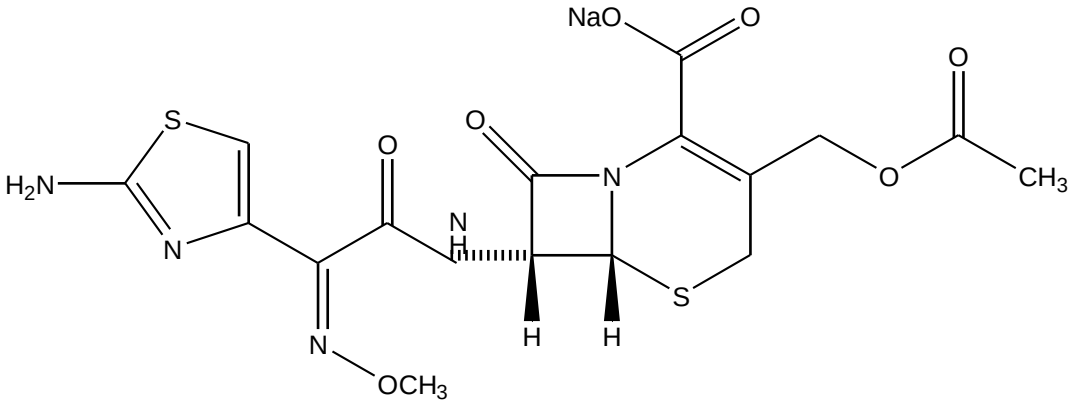
DBL Cefotaxime Sodium is supplied in a 10 mL clear glass vial with rubber stopper in packs of 1 or 10 vials.

6.6 Special precautions for disposal

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 Physicochemical properties

Chemical structure



Molecular Formula: $C_{16}H_{16}N_5NaO_7S_2$.

Molecular Weight: 477.4.

Cefotaxime Sodium is soluble in water (greater than 20%). The pH of the formulated material is 4.5 to 6.5. The pKa value is 3.35.

CAS number

64485-93-4.

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4, Prescription Only Medicine.

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
Sydney NSW 2000.
Toll Free Number: 1800 675 229.
www.pfizermedicalinformation.com.au

9. DATE OF FIRST APPROVAL

22 August 2001.

10. DATE OF REVISION

07 March 2024

Summary table of changes

Section changed	Summary of new information
4.4 and 4.8	Addition of information regarding neurotoxicity associated with cephalosporin treatment.