

DBL[®] CEFTAZIDIME FOR INJECTION

Name of medicine

Ceftazidime pentahydrate

Presentation

DBL[®] Ceftazidime for Injection is a cephalosporin antibiotic for use by injection only. It is supplied as a white to faintly yellow powder in vials containing 1 g and 2 g ceftazidime (as pentahydrate) with sodium carbonate anhydrous (115 mg per gram of ceftazidime). On the addition of Water for Injections, DBL[®] Ceftazidime for Injection dissolves with effervescence to produce a clear, colourless solution for injection.

DBL[®] Ceftazidime for Injection contains approximately 50 mg (2.17 mEq) of sodium per gram of ceftazidime. 116 mg ceftazidime pentahydrate is equivalent to 100 mg ceftazidime anhydrous. For laboratory tests associated with ceftazidime administration, ceftazidime pentahydrate should be used.

Uses

Actions

Microbiology

Ceftazidime is bactericidal in action, exerting its effect on target cell wall proteins and causing inhibition of cell wall synthesis. It is stable to most beta-lactamases produced by Gram-positive and Gram-negative organisms and consequently is active against many ampicillin- and cephalothin-resistant strains (but not methicillin-resistant strains). Ceftazidime has been shown to have *in vitro* activity against the following organisms:

Gram-negative:

Pseudomonas aeruginosa
Pseudomonas species (other)
Klebsiella pneumoniae
Klebsiella species (other)
Proteus mirabilis
Proteus vulgaris
Morganella morganii (formerly *Proteus morganii*)
Proteus rettgeri
Providencia species
Escherichia coli
Enterobacter species
Citrobacter species
Serratia species
Acinetobacter species
Neisseria gonorrhoeae
Neisseria meningitidis
Haemophilus influenzae (including ampicillin-resistant strains)

Gram-positive:

Staphylococcus aureus (methicillin-sensitive strains)
Staphylococcus epidermidis (methicillin-sensitive strains)
Micrococcus species
Streptococcus pyogenes
Streptococcus Group B
Streptococcus pneumoniae
Streptococcus species (excluding *Streptococcus faecalis*)

Ceftazidime is not active *in vitro* against methicillin-resistant staphylococci, *Streptococcus faecalis* and many other Enterococci, *Listeria monocytogenes*, Campylobacter species or *Clostridium difficile*.

In vitro the activities of ceftazidime and aminoglycoside antibiotics in combination have been shown to be at least additive; there is evidence of synergy in some strains tested. This property may be important in the treatment of febrile neutropenic patients.

Susceptibility Tests: Disc Susceptibility Test

Dilution or diffusion techniques – Either quantitative (minimum inhibitory concentration (MIC)) or breakpoint should be used following a regularly updated, recognised and standardised method (eg NCCLS). Standardised susceptibility test procedures require the use of laboratory control microorganisms 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 microorganism 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.

Note: The prevalence of resistance may vary geographically for selected species and local information on resistance is desirable, particularly when treating severe infections.

Pharmacokinetics

Absorption of ceftazidime after oral administration is negligible, therefore Ceftazidime for Injection is intended for parenteral use only.

The mean peak serum concentrations of ceftazidime in man following a single intramuscular (IM) administration of ceftazidime are shown in the table below.

Mean peak serum concentrations of ceftazidime following IM administrations

	Serum concentrations (mg/L)		
Ceftazidime IM dose	1 hour	4 hour	8 hour
500 mg	18	8	2
1 g	37	20	5

The mean serum levels of ceftazidime after an intravenous (IV) bolus injection are shown in the table below.

Mean serum concentrations of ceftazidime after an IV bolus injection

	Serum concentrations (mg/L)		
Ceftazidime IM dose	5 minute	1 hour	4 hour
500 mg	46	17	6
1 g	87	32	10
2 g	170	85	15

The serum half life in adults with normal renal function is about 1.8 hours (1.2 to 2.9 hours). This may be prolonged to 20 to 35 hours in anuric patients. In neonates, the serum half life of ceftazidime can be 3 to 4 times greater than that measured in adults. The serum protein binding of ceftazidime is low at about 10%.

Ceftazidime is not metabolised in the body and is excreted unchanged in the active form into the urine by glomerular filtration. In the presence of normal renal function approximately 80 to 90% of the dose is recovered in the urine within 24 hours. Less than 1% is excreted via the bile.

The mean maximum concentrations of ceftazidime in bone, heart, bile, sputum, aqueous humour, synovial and pleural and peritoneal fluids were in excess of the *in vitro* minimum inhibitory levels for susceptible organisms (See **Susceptibility Tests**). Transplacental transfer of the antibiotic readily

occurs. Ceftazidime penetrates the intact blood brain barrier poorly and low levels are achieved in the CSF.

The pharmacokinetics of ceftazidime are similar whether it is administered by a single or by repeat dosage.

Concurrent oral administration of probenecid did not affect the serum levels or urinary recoveries of ceftazidime. The pharmacokinetics of ceftazidime were not affected when administered intramuscularly with 0.5% lignocaine.

Indications

DBL[®] Ceftazidime for Injection is indicated for the treatment of single and mixed infections caused by susceptible aerobic organisms with suspected or documented resistance to other antimicrobials, but not to ceftazidime, and as an alternative to aminoglycosides in pseudomonal infection in patients in whom aminoglycoside toxicity is a cause for concern and other pseudomonal antibiotics cannot be used.

Indications include:

- Severe infections in general: for example septicaemia, including neonatal sepsis, bacteraemia, and in patients in intensive care units with specific problems, e.g., infected burns.
- Respiratory tract infections: for example, pneumonia, broncho-pneumonia, infected pleurisy, infected bronchiectasis and bronchitis.
- Severe ear, nose and throat infections: for example, otitis media, mastoiditis.
- Urinary tract infections: for example, acute and chronic pyelonephritis, pyelitis, cystitis, urethritis (bacterial only), and infections associated with bladder and renal stones.
- Skin and soft tissue infections: for example, erysipelas, abscesses, cellulitis, infected burns and wounds, mastitis.
- Gastrointestinal and abdominal infections: for example, intra-abdominal abscesses, enterocolitis.
- Bone and joint infections: for example, osteitis, osteomyelitis, septic arthritis, infected bursitis.

Dosage and administration

General dosage recommendations

Ceftazidime is to be used by the parenteral route, the dosage depending upon the severity, sensitivity and type of infection and the age, weight and renal function of the patient.

Adults

The adult dosage range for ceftazidime is 1 to 6 g per day: for instance, 500 mg, 1 g or 2 g given 12 or 8 hourly by IV or IM injection. In urinary tract infections and in many less serious infections, 500 mg or 1 g 12 hourly is usually adequate. In the majority of infections, 1 g 8 hourly or 2 g 12 hourly should be given. In very severe infections, 2 g 8 or 12 hourly should be administered. Individual doses in excess of 1 g should be administered intravenously.

Infants and children

The usual dosage range for children aged over 12 months is 25 to 100 mg/kg/day (up to a maximum of 6 g/day) given as two or three divided doses. The maximum daily dosage (6 g) may be given to children with very serious infections e.g. those who are immuno-compromised or who suffer from cystic fibrosis.

Neonates and infants up to 12 months

25 to 100 mg/kg/day in two divided doses. In neonates the serum half life of ceftazidime can be 3 to 4 times greater than that measured in adults.

Use In The Elderly

In view of the reduced clearance of ceftazidime in elderly patients, the daily dosage should be adjusted according to renal function.

Dosage in Impaired Renal Function

Ceftazidime is excreted by the kidneys almost exclusively by glomerular filtration. Therefore, in patients with impaired renal function it is recommended that the dosage of ceftazidime should be reduced to compensate for its slower excretion, except in mild impairment, i.e. glomerular filtration rate (GFR) greater

than 50 mL/min. In patients with suspected renal insufficiency, an initial loading dose of 1 g of ceftazidime may be given. An estimate of GFR should be made to determine the appropriate maintenance dose.

Recommended maintenance doses are shown below: Recommended maintenance doses of ceftazidime in renal insufficiency

Creatinine clearance mL/min	Approx. Serum creatinine # micromol/L	Recommended Unit dose of ceftazidime g	Frequency of dosing Hourly
50-31	150-200	1.0	12
30-16	200-350	1.0	24
15-6	350-500	0.5	24
5	500	0.5	48

These values are guidelines and may not accurately predict renal function in all patients especially in the elderly in whom the serum creatinine concentration may overestimate renal function.

In patients with severe infections who would normally receive 6 g of ceftazidime daily were it not for renal insufficiency, the unit dose given in the table above may be increased by 50% or the dosing frequency increased appropriately. In such patients it is recommended that ceftazidime serum levels should be monitored and trough levels should not exceed 40 mg/L.

When only serum creatinine is available, the following formula (Cockcroft's equation) may be used to estimate creatinine clearance. The serum creatinine should represent a steady state of renal function:

Males:

$$\text{Creatinine clearance (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{age in years})}{72 \times \text{serum creatinine (micromol/L)}} \times 88.4$$

Females: 0.85 x above value.

In children the creatinine clearance should be adjusted for body surface area or lean body mass and the dosing frequency reduced in cases of renal insufficiency as for adults.

The serum half life of ceftazidime during haemodialysis is approximately 3 hours. The appropriate maintenance dose of ceftazidime should be repeated following each haemo-dialysis period. Continuous ambulatory peritoneal dialysis (CAPD) removed approximately 10% of the antibiotic when the dwell time was 4-6 hours.

Administration

DBL[®] Ceftazidime for Injection may be given intravenously or by deep intramuscular injection into a large muscle mass such as the upper outer quadrant of the gluteus maximus or lateral part of the thigh.

Instructions for reconstitution:

DBL[®] Ceftazidime for Injection may be reconstituted with Water for Injections or, for intramuscular injection, with 1.0% or 0.5% Lignocaine. See *table for addition volumes and solution concentrations*.

To reduce microbiological hazard, use as soon as practicable after reconstitution. If storage is necessary, hold at 2 to 8°C for not more than 24 hours. Protect from light.

Following reconstitution, use in one patient on one occasion only and discard any residue.

Preparation of Solution		
Vial Size	Amount of Diluent to be added	Approximate Concentration (mg/mL)
1 g	intramuscular 3.0 mL	260

	intravenous 10 mL	90
2 g	intravenous bolus 10 mL	170
	intravenous infusion 50 mL#	40
# Note: Addition should be in two stages (see text).		

For ease of use, it is recommended that the following techniques of reconstitution are adopted.

1 g IM/IV and 2 g IV bolus vials:

1. Insert the syringe needle through the vial closure and inject the recommended volume of diluent. The vacuum may assist entry of the diluent. Remove the syringe needle.
2. *Shake to dissolve:* carbon dioxide is released and a clear solution obtained in about 1 to 2 minutes.
3. Invert the vial. With the syringe plunger fully depressed, insert the needle through the vial closure and withdraw the total volume of solution into the syringe (the pressure in the vial may aid withdrawal). Ensure that the needle remains within the solution and does not enter the headspace. The withdrawn solution may contain small bubbles of carbon dioxide; they may be disregarded.

2 g IV infusion vial:

This vial may be reconstituted for short intravenous infusion (e.g., up to 30 minutes) as follows:

1. Insert the syringe needle through the vial closure and inject 10 mL of diluent. The vacuum may assist entry of the diluent. Remove the syringe needle.
2. Shake to dissolve; carbon dioxide is released and a clear solution obtained in about 1 to 2 minutes.
3. Insert a gas relief needle through the vial closure to relieve the internal pressure and, with the gas relief in position, add a further 40 mL of diluent. Remove the gas relief needle and syringe needle; shake the vial and set up for infusion use in the normal way.

Note: To preserve product sterility, it is important that a gas relief needle is not inserted through the vial closure before the product has dissolved.

These solutions may be given directly into the vein or introduced into the tubing of a giving set if the patient is receiving parenteral fluids.

Solutions of DBL[®] Ceftazidime for Injection reconstituted in Water for Injections retain satisfactory potency for up to 24 hours if kept refrigerated (2 to 8°C).

Ceftazidime is also compatible with the intravenous fluids, 0.9% Sodium Chloride Injection BP and/or 5% Glucose Injection BP. Solutions in these infusion fluids may be stored for up to 24 hours if refrigerated (2 to 8°C).

DBL[®] Ceftazidime for Injection may be reconstituted for intramuscular administration using 0.5% and 1.0% Lignocaine Hydrochloride Injection BP; the resultant solutions may be stored for up to 24 hours under refrigeration (2 to 8°C).

Some increase in the colour of prepared solutions of DBL[®] Ceftazidime for Injection may occur on storage. It is, however, advisable to use the reconstituted product as soon as possible.

Sodium Bicarbonate Injection is not recommended as a diluent.

Ceftazidime and aminoglycosides should not be mixed in the same giving set or syringe.

Precipitation has been reported when vancomycin has been added to ceftazidime in solution. Therefore, it would be prudent to flush giving sets and intravenous lines between the administration of these two agents

Contraindications

DBL[®] Ceftazidime for Injection is contraindicated in persons who have shown hypersensitivity to cephalosporins or who have experienced a major allergy to penicillin (anaphylaxis, angioneurotic oedema, urticaria).

Lignocaine should not be used as a diluent for intramuscular injection in patients who are hypersensitive to lignocaine.

Warnings and precautions

As with other beta-lactam antibiotics, before therapy with ceftazidime is instituted, careful inquiry should be made for a history of hypersensitivity reactions to ceftazidime, cephalosporins, penicillins, or other drugs. Ceftazidime should be given only with special caution to patients with mild type I or immediate hypersensitivity reactions to penicillin. If an allergic reaction to ceftazidime occurs, discontinue the drug. Serious hypersensitivity reactions may require adrenaline, hydrocortisone, antihistamine or other emergency measures.

Antibiotic associated pseudomembranous colitis has been reported with many antibiotics including ceftazidime. A toxin produced by *Clostridium difficile* appears to be the primary cause. The severity of the colitis may range from mild to life threatening. It is important to consider this diagnosis in patients who develop diarrhoea or colitis in association with antibiotic use (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 with a suitable oral antibacterial agent effective against *Clostridium difficile* should be considered. Fluids, electrolytes and protein replacement should be provided when indicated.

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

Clostridium difficile infection rarely manifests as diarrhoea in neonates.

Peak concentrations of ceftazidime in the CSF are considerably lower than those in the plasma. Its use in the treatment of infections of the CNS, e.g. meningitis, brain abscess, etc. is not advised at present.

Prescribing ceftazidime in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Inducible type I beta-lactamase resistance has been noted with some organisms (e.g. *Enterobacter* spp., *Pseudomonas* spp., and *Serratia* spp.). As with other extended-spectrum beta-lactam antibiotics, resistance can develop during therapy, leading to clinical failure in some cases. When treating infections caused by these organisms, periodic susceptibility testing should be performed when clinically appropriate. If patients fail to respond to monotherapy, an aminoglycoside or similar agent should be considered.

Cephalosporins may be associated with a fall in prothrombin activity. Those at risk include patients with renal and hepatic impairment, or poor nutritional state, as well as patients receiving a protracted course of antimicrobial therapy. Prothrombin time should be monitored in patients at risk and exogenous vitamin K administered as indicated.

Ceftazidime should be prescribed with caution to individuals with a history of gastrointestinal disease, particularly colitis.

Distal necrosis can occur after inadvertent intra-arterial administration of ceftazidime.

Patients with Impaired Renal Function

Ceftazidime has shown some evidence of renal toxicity in animals. Clinical studies have shown only transient elevations in serum urea and serum creatinine. It is excreted almost entirely by glomerular filtration and its half life is prolonged in patients with impaired renal function. In such patients dosage adjustment may be required in order to avoid the clinical consequences of elevated antibiotic levels. Neurological sequelae have occasionally been reported when the dose has not been reduced appropriately (See **DOSAGE AND ADMINISTRATION**).

Use in Patients with Impaired Liver Function

Transient rises in hepatic enzymes have been noted in some patients given ceftazidime, so careful monitoring of hepatic function is advised when any dysfunction exists.

Repeated use of lignocaine hydrochloride as a diluent for IM use 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 consequent accumulation.

As with other broad spectrum antibiotics, prolonged use of ceftazidime may result in the overgrowth of non-susceptible organisms (e.g., *Candida*, *Enterococci*) which may require interruption of treatment or adoption of appropriate measures. Repeated evaluation of the patient's condition is essential.

Paediatric Use

Ceftazidime is effective in the treatment of neonatal infections caused by susceptible organisms.

Effect on Laboratory Tests

The development of a positive Coombs' test associated with the use of ceftazidime in about 5% of patients may interfere with the cross-matching of blood.

The administration of ceftazidime may result in a false-positive reaction for glucose in the urine when using CLINITEST[®] tablets, Benedict's solution, or Fehling's solution. It is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as CLINISTIX[®]) be used.

Ceftazidime does not interfere in the alkaline picrate assay for creatinine.

Pregnancy and Lactation

Use in Pregnancy

Category B1.

The safety of ceftazidime in pregnancy has not been established, although animal studies have not produced evidence of embryopathic or teratogenic effects attributable to ceftazidime. Therefore it may be administered during known or suspected pregnancy only if in the opinion of the treating physician the expected benefits outweigh the possible risks.

Use in Lactation:

Ceftazidime is excreted in human breast milk in low concentrations therefore it is not recommended for nursing mothers unless the expected benefits to the mother greatly outweigh any potential risk to the infant.

Adverse effects

Clinical trial experience has shown that ceftazidime is generally well tolerated.

Adverse reactions are infrequent and include:

Local

Phlebitis or thrombophlebitis with IV administration; pain and/or inflammation after IM injection.

Hypersensitivity

Maculopapular or urticarial rash, fever, pruritus, and very rarely angioedema and anaphylaxis (including bronchospasm and hypotension), erythema multiforme, Stevens Johnson Syndrome and toxic epidermal necrolysis.

Gastrointestinal

Diarrhoea, nausea, vomiting, abdominal pain, and very rarely oral thrush or colitis.

Pseudomembranous colitis has been reported.

Central Nervous System

Headache, dizziness, paraesthesia and bad taste. There have been reports of neurological sequelae including tremor, myoclonia, convulsions and encephalopathy and coma occurring in patients with renal impairment in whom the dose of ceftazidime has not been appropriately reduced.

Genito-urinary

Candidiasis, vaginitis.

Renal

Transient elevations of blood urea, serum urea and/or serum creatinine have been observed occasionally.

Hepatic

Elevations in one or more of the hepatic enzymes, SGOT, SGPT, LDH, GGT and alkaline phosphatase may occur.

Haematological

Eosinophilia, positive Coombs' test, thrombocytosis; very rarely, transient leucopenia, haemolytic anaemia, neutropenia, thrombocytopenia and lymphocytosis have been seen.

Miscellaneous

Hot flushes, superficial desquamation around injection site.

Interactions

Aminoglycoside antibiotics and/or diuretics:

Nephrotoxicity has been reported following concomitant administration of cephalosporins with aminoglycoside antibiotics or potent diuretics such as furosemide. Renal function should be carefully monitored, especially if higher dosages of the aminoglycosides are to be administered or if therapy is prolonged, because of the potential nephrotoxicity and ototoxicity of aminoglycosidic antibiotics. Nephrotoxicity and ototoxicity were not noted when ceftazidime was given alone in clinical trials.

Chloramphenicol:

Chloramphenicol has been shown to be antagonistic to beta-lactam antibiotics, including ceftazidime, based on in vitro studies and time kill curves with enteric gram-negative bacilli. Due to the possibility of antagonism in vivo, particularly when bactericidal activity is desired, this drug combination should be avoided.

Overdosage

Overdosage can lead to neurological sequelae including encephalopathy, convulsions and coma. Ceftazidime can be removed by haemodialysis.

In case of overdose, immediately contact the Poisons Information Centre for advice on management. (in Australia, call 13 11 26; in New Zealand call 0800 764 766)

Pharmaceutical precautions***Special Precautions for Storage***

Vials of unreconstituted DBL[®] Ceftazidime for Injection should be stored at a temperature below 25°C and protected from light.

Vials of the reconstituted DBL[®] Ceftazidime for Injection can be stored for up to 24 hours at 2 to 8°C and protected from light with:

- WFI
- 0.5% Lignocaine Injection
- 1.0% Lignocaine Injection
- 0.9% Sodium Chloride Injection
- 0.5% Glucose Injection.

Medicine classification

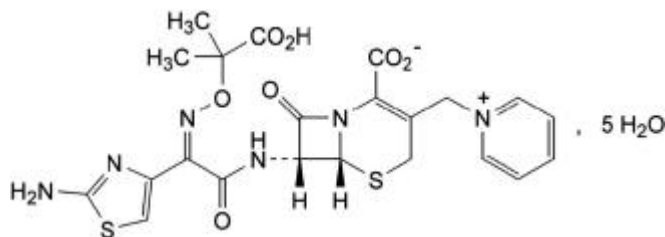
Prescription Medicine

Package quantities

DBL[®] Ceftazidime for Injection 1 g/vial is available in:

- 1 vial per pack, or
- 5 vials per pack (not marketed).

DBL[®] Ceftazidime for Injection 2 g/vial is available in 1 vial per pack.

Further information

CAS No. 72558-82-8

Molecular Weight: 636.6

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