

**DBL™ PIPERACILLIN AND TAZOBACTAM FOR INJECTION 2 g/0.25g  
and  
DBL™ PIPERACILLIN AND TAZOBACTAM FOR INJECTION 4 g/0.5 g**

**Name of medicine**

DBL™ Piperacillin and Tazobactam for Injection 2 g/0.25 g and  
DBL™ Piperacillin and Tazobactam for Injection 4 g/0.5 g

**Presentation**

DBL™ Piperacillin and Tazobactam for Injection is available as a lyophilised powder for administration following reconstitution.

Each 2 g/0.25 g single dose vial contains piperacillin sodium equivalent to 2 grams of piperacillin and tazobactam sodium equivalent to 250 mg of tazobactam.

Each 4 g/0.5 g single dose vial contains piperacillin sodium equivalent to 4 grams of piperacillin and tazobactam sodium equivalent to 500 mg of tazobactam.

DBL™ Piperacillin and Tazobactam for Injection is a monosodium salt of piperacillin and a monosodium salt of tazobactam containing a total of 2.36 mEq (54.28 mg) of Na<sup>+</sup> per gram of piperacillin in the combination product.

**Uses**

**Actions**

Piperacillin, a broad spectrum, semisynthetic penicillin active against many Gram positive and Gram negative aerobic and anaerobic bacteria, exerts bactericidal activity by inhibition of both septum and cell wall synthesis. Tazobactam, a triazolylmethyl penicillanic acid sulfone, is a potent inhibitor of many beta-lactamases, including the plasmid and chromosomally mediated enzymes that commonly cause resistance to penicillins. The presence of tazobactam in the piperacillin/tazobactam formulation enhances and extends the antibiotic spectrum of piperacillin to include many beta-lactamase producing bacteria normally resistant to it. Thus piperacillin/tazobactam combines the properties of a broad spectrum antibiotic and a beta-lactamase inhibitor.

**Pharmacokinetics**

*Distribution and plasma levels*

Mean plasma concentrations of piperacillin and tazobactam at steady state of the combination appear in Table 1. Peak piperacillin and tazobactam plasma concentrations are attained immediately after completion of an intravenous infusion. When given with tazobactam, piperacillin plasma levels are similar to those attained when equivalent doses of piperacillin are administered alone.

**Table 1**

Plasma levels in adults after a 30 minute intravenous infusion of piperacillin/tazobactam (steady state)

Piperacillin/ tazobactam dose	Piperacillin plasma levels (microgram/mL)					
	30* minutes	1 hour	1.5 hours	2 hours	3 hours	4 hours
2 g/ 250 mg	134	57	29	17	5	2
4 g/500 mg	298	141	87	47	16	7
Piperacillin/ tazobactam dose	Tazobactam plasma levels (microgram/mL)					
	30* minutes	1 hour	1.5 hours	2 hours	3 hours	4 hours
2 g/ 250 mg	14.8	7.2	4.2	2.6	1.1	0.7
4 g/500 mg	33.8	17.3	11.7	6.8	2.8	1.3

\* Completion of 30 minute infusion

In healthy subjects, piperacillin/ tazobactam plasma elimination half-lives range from 0.7 to 1.2 hours following single or multiple doses. These half-lives are unaffected by dose or duration of infusion. Piperacillin and tazobactam are 21 and 23%, respectively, bound to plasma proteins. The protein binding of either piperacillin or tazobactam is unaffected by the presence of either compound. Piperacillin and tazobactam are widely distributed in tissues and body fluids including intestinal mucosa, gall bladder, lung and bile.

#### *Biotransformation*

Piperacillin does not undergo biotransformation in humans. Approximately 20% of a dose of tazobactam is metabolised to a single metabolite that has been found to be microbiologically inactive.

#### *Excretion*

Piperacillin and tazobactam are eliminated by the kidney via glomerular filtration and tubular secretion. Piperacillin is excreted rapidly as unchanged drug, with 69% of the dose appearing in the urine. Piperacillin is also secreted into bile. Tazobactam and its metabolite are eliminated primarily by renal excretion, with 80% of the dose appearing as unchanged drug and the remainder of the dose appearing as the metabolite.

#### *Impaired renal function*

The half-life of piperacillin and tazobactam increases with decreasing creatinine clearance. The increase is two-fold and four-fold for piperacillin and tazobactam, respectively, at creatinine clearance below 20 mL/minute, compared to patients with normal renal function. Dosage adjustments are recommended when creatinine clearance is below 40 mL/minute (see Dosage and Administration).

Piperacillin and tazobactam are removed from the body during haemodialysis with 31 and 39% of the doses of piperacillin and tazobactam, respectively, recovered in the dialysis fluid. Piperacillin and tazobactam are removed from the body by peritoneal dialysis with 5 and 12% of the dose, respectively, appearing in the dialysate. For dosage recommendations in patients undergoing haemodialysis, see Dosage and Administration.

#### *Impaired hepatic function*

Piperacillin half-life and AUC (area under the curve) were increased by 25 and 40% respectively and tazobactam half-life and AUC by 18 and 23% respectively in patients with hepatic impairment. However, dosage adjustments in patients with hepatic impairment are not necessary.

#### *Children*

The pharmacokinetics of piperacillin and tazobactam have been examined in 24 paediatric patients aged two months to 12 years receiving piperacillin 100 mg/kg plus tazobactam 12.5 mg/kg (see Table 2). The maximum concentration ( $C_{max}$ ) for both piperacillin and tazobactam is increased relative to the maximum adult dose but the predicted time above the minimum inhibitory concentration is slightly decreased. The dosage of piperacillin 100 mg/kg plus tazobactam 12.5 mg/kg administered every eight hours is predicted to provide coverage 31 to 61% of the time for the range of MIC values of 2 to 16 microgram/mL commonly found in intra-abdominal infections in children.

**Table 2**

Piperacillin and tazobactam pharmacokinetics in children (CV%) following single doses

Dose	Patient age	$C_{max}$ (mg/L)	AUC (mg.h/L)	CL (mL/min/kg)	V <sub>ss</sub> (L/kg)	T <sub>1/2</sub> (h)
Piperacillin 100 mg/kg	2-5 months	382 (15)	539 (29)	3.3 (24)	0.28 (32)	1.3 (16)
	6-23 months	344 (15)	373 (27)	4.8 (29)	0.25 (27)	1.0 (24)
	2-5 years	408 (80)	331 (21)	5.2 (19)	0.23 (36)	0.9 (26)
	6-12 years	394 (24)	404 (17)	4.2 (21)	0.24 (42)	0.8 (27)
Tazobactam 12.5 mg/kg	2-5 months	43 (49)	63 (32)	3.6 (28)	0.32 (31)	1.3 (15)
	6-23 months	35 (22)	42 (23)	5.2 (24)	0.33 (29)	1.1 (23)
	2-5 years	45 (42)	37 (24)	5.8 (19)	0.27 (33)	0.9 (29)
	6-12 years	45 (25)	57 (27)	3.9 (36)	0.28 (36)	1.3 (57)

## Microbiology

Piperacillin/tazobactam is active against most strains of the following beta-lactamase producing and non-beta-lactamase producing microorganisms.

Gram negative bacteria: *Escherichia coli*, *Citrobacter* sp., *Klebsiella* sp. (including *K. pneumoniae*), *Enterobacter* sp. (including *E. cloacae*), *Proteus vulgaris*, *Proteus mirabilis*, *Serratia* sp. (including *S. marcescens*), *Pseudomonas aeruginosa* and other *Pseudomonas* sp., *Neisseria gonorrhoeae*, *Neisseria meningitidis*, *Moraxella catarrhalis*, *Acinetobacter* sp., *Haemophilus influenzae*.

Gram positive bacteria: Streptococci (*S. pneumoniae*, *S. pyogenes*, *S. agalactiae*, *S. viridans*), Enterococci (*E. faecalis*, *E. faecium*), *Staphylococcus aureus* (not methicillin resistant *Staph. aureus*), *Staph. epidermidis* (coagulase negative *Staphylococci*).

Anaerobic bacteria: *Bacteroides* sp. including *Bacteroides fragilis* group, *Peptostreptococcus* sp., *Fusobacterium* sp., *Eubacterium* group, *Clostridia* sp., *Veillonella* sp.

Susceptibility. Local information of resistance is desirable, particularly when treating severe infections. This information provides guidance on microorganisms susceptible to piperacillin/ tazobactam. The following MIC<sub>90</sub> values were reported in 1996 for clinical isolates collected in three Australian states (see Table 3).

**Table 3**

MIC<sub>90</sub> for 1,952 clinically significant isolates

Organism number	MIC <sub>90</sub> (mg/L)
<i>E.coli</i> (528)	2.0
<i>Klebsiella</i> sp. (180)	4.0
<i>Klebsiella</i> sp. (ESBL 44)	64.0
<i>Enterobacter</i> sp. (142)	16.0
<i>Citrobacter/Serratia</i> sp. (84)	8.0
<i>Morganella/Proteus/Providencia</i> sp. (45)	2.0
<i>Proteus mirabilis</i> (104)	2.0
<i>Pseudomonas aeruginosa</i> (88)	32.0
<i>Acinetobacter calcoaceticus</i> (40)	32.0
<i>Staphylococcus aureus</i> (433)	4.0
Coagulase-negative <i>Staphylococci</i> (28)	16.0
<i>Streptococcus pneumoniae</i> (45)	0.015
Enterococci (109)	4.0
<i>Haemophilus influenzae</i> (59)	0.094
<i>Bacteroides fragilis</i> gp (23)	4.0

### Disc Susceptibility test

Dilution or diffusion techniques – either quantitative (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 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.

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

The latest NCCL references are:

Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard, Fifth Edition, NCCLS document M7-A5, Vol. 20, No. 2. 2000. NCCLS, Wayne, PA.

For anaerobes:

Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria; Approved Standard, Fourth Edition. NCCLS document M11-A4, Vol. 17, No. 22. 1997. NCCLS, Wayne, PA.

### **Indications**

Treatment of serious bacterial infections caused by susceptible strains of beta-lactamase producing organisms in the following conditions: lower respiratory tract infections; urinary tract infections (complicated and uncomplicated); intra-abdominal infections; skin and skin structure infections; bacterial septicaemia; gynaecological infections.

#### *Children under the age of 12 years*

In hospitalised children aged 2 to 12 years, Piperacillin/tazobactam is indicated for the treatment of serious intra-abdominal infections. It has not been evaluated in this indication for paediatric patients below the age of two years.

While Piperacillin/tazobactam is indicated only for the conditions listed above, it may be used as a single agent in the treatment of mixed infections caused by piperacillin susceptible and beta-lactamase producing, piperacillin resistant organisms. Appropriate culture and susceptibility tests should be performed before treatment in order to identify organisms causing infection and to determine their susceptibilities to Piperacillin/tazobactam. Therapy with Piperacillin/tazobactam, however, may be initiated before results of such tests are known when there is reason to believe the infection may involve any of the beta-lactamase producing organisms listed above; however, once these results become available, appropriate therapy should be continued.

In serious infections, presumptive therapy with Piperacillin/tazobactam may be initiated before susceptibility test results are available.

Combination therapy with Piperacillin/tazobactam and aminoglycosides may be used in the treatment of serious infections caused by *Pseudomonas aeruginosa*. Both drugs should be used in full therapeutic doses. As soon as results of culture and susceptibility tests become available, antimicrobial therapy should be adjusted.

### **Dosage and administration**

Piperacillin/tazobactam may be given by slow intravenous infusion (20 to 30 minutes).

#### *Adults, children 12 years and older*

The usual intravenous dosage for adults and children with normal renal function is piperacillin 4 g/tazobactam 0.5 g (piperacillin/tazobactam) given every eight hours.

The total daily dose depends on the severity and localisation of the infection and can vary from piperacillin 2 g/tazobactam 0.25 g to piperacillin 4 g/tazobactam 0.5 g (piperacillin/tazobactam) administered every six or eight hours.

#### *Children under the age of 12 years*

Recommended intravenous dosage for hospitalised children with intra-abdominal infection. For children aged 2 to 12 years, weighing up to 40 kg, and with normal renal function, the recommended dosage is piperacillin 100 mg/tazobactam 12.5 mg per kg every eight hours.

For children aged 2 to 12 years, weighing over 40 kg, and with normal renal function, follow the adult dose guidance, i.e. piperacillin 4 g/tazobactam 0.5 g every eight hours.

The duration of therapy should be guided by the severity of the infection and the patient's clinical and bacteriological progress. Therapy is recommended to be a minimum of five days and a maximum of 14 days, considering that dose administration should continue at least 48 hours after the resolution of clinical signs and symptoms.

### Dose modifications

#### *Renal impairment*

In patients with renal insufficiency, the intravenous dose should be adjusted to the degree of actual renal function impairment. The suggested daily doses are shown in Table 4.

**Table 4**  
Intravenous dosage schedule for adults with impaired renal function

<b>Creatinine Clearance</b>	<b>Recommended piperacillin/tazobactam dosage</b>
> 40 mL/minute	No dosage adjustment necessary
20-40 mL/minute	12 g/1.5 g/day in divided doses (piperacillin 4 g/tazobactam 0.5 g every 8 hours)
< 20 mL/minute	8 g/1 g/day in divided doses (piperacillin 4 g/tazobactam 0.5 g every 12 hours)

For patients on haemodialysis, the maximum daily dose of piperacillin/tazobactam is piperacillin 8 g/tazobactam 1 g. In addition, because haemodialysis removes 30 to 50% of piperacillin in four hours, one additional dose of piperacillin 2 g/tazobactam 0.25 g should be administered following each dialysis period. For patients with renal failure and hepatic insufficiency, measurement of serum levels of piperacillin/tazobactam will provide additional guidance for adjusting dosage.

#### *Children aged 2 to 12 years*

The pharmacokinetics of piperacillin/ tazobactam have not been studied in paediatric patients with renal impairment. Each patient must be monitored closely for signs of drug toxicity. Drug dose and interval should be adjusted accordingly.

### Duration of therapy

In acute infections, treatment with piperacillin/tazobactam should be for a minimum of five days and continued for 48 hours beyond resolution of clinical symptoms or the fever.

### Preparation of solution

DBL™ Piperacillin and Tazobactam for Injection is available as a lyophilised powder for administration following reconstitution.

Prior to use, DBL™ Piperacillin and Tazobactam for Injection 2.25 g and 4.5 g must be reconstituted with sterile water for injections or sodium chloride injection as per Table 5 below.

**Table 5**  
Piperacillin/tazobactam injection

<b>Vial size (piperacillin / tazobactam)</b>	<b>Minimum volume of diluent to be added to vial</b>
2.25 g (2 g/ 0.25 g)	10 mL
4.50 g (4 g/ 0.5 g)	20 mL

The reconstituted solution may be further diluted to 50 mL with saline, glucose 5% or dextran 6% in saline.

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

### Administration:

#### *Intravenous administration*

Reconstitute each vial with the volume of diluent shown in Table 5 above, using sterile water for injections or sodium chloride injection as a diluent. Shake until dissolved.

**Compatibility:**

Piperacillin/tazobactam should not be mixed with other drugs in a syringe or infusion bottle since compatibility has not been established. Whenever piperacillin/tazobactam is used concurrently with another antibiotic, the drugs must be administered separately.

Because of chemical instability, piperacillin/tazobactam should not be used with lactated Ringer's solution, solutions containing only sodium bicarbonate or having a pH in the basic range. piperacillin/tazobactam should not be added to blood products or albumin hydrolysates.

**Contraindications**

History of allergic reactions to any of the penicillins and/or cephalosporins or beta-lactamase inhibitors.

**Warnings and precautions**

Serious and occasionally fatal hypersensitivity (anaphylactic/ anaphylactoid (including shock)) reactions have been reported in patients on penicillin/ cephalosporin therapy. Although anaphylaxis is more frequent following parenteral therapy, it has occurred in patients on oral penicillins/ cephalosporins. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity and/or a history of sensitivity to multiple allergens. There have been reports of individuals with a history of penicillin/ cephalosporin hypersensitivity who have experienced severe reactions when treated with either a penicillin or cephalosporin. Past history of a severe allergic reaction to penicillin/ cephalosporin is a contraindication to the use of Piperacillin/tazobactam. Before initiating therapy with any penicillin/ cephalosporin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins or other allergens. If an allergic reaction occurs, Piperacillin/tazobactam should be discontinued and the appropriate therapy instituted. Serious anaphylactoid reactions require immediate emergency treatment with adrenaline. Oxygen, intravenous steroids and airway management including intubation should also be administered as indicated.

Antibiotic associated pseudomembranous colitis has been reported with many antibiotics including piperacillin. 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 *Cl. difficile* should be considered. Fluids, electrolytes and protein replacement should be provided when indicated.

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

Leucopenia and neutropenia may occur, especially during prolonged therapy. Therefore, periodic assessment of haemopoietic function should be performed.

**Use with caution in the following circumstances:**

Bleeding manifestations have occurred in some patients receiving piperacillin. These reactions have sometimes been associated with abnormalities of coagulation tests, e.g. clotting time, platelet aggregation and prothrombin time, and are more likely to occur in patients with renal failure. If bleeding manifestations occur, the antibiotic should be discontinued and appropriate therapy instituted.

The possibility of the emergence of resistant organisms that might cause superinfections should be kept in mind, particularly during prolonged treatment. If this occurs, appropriate measures should be taken.

As with other penicillins, patients may experience neuromuscular excitability or convulsions if higher than recommended doses are given intravenously.

Repeated use of lignocaine as a solvent 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).

Combined administration of beta-lactamase inhibitors and beta-lactam antibiotics may be associated with a slightly increased risk of hepatic adverse reactions. The incidence of increased liver enzymes in patients treated with Piperacillin/tazobactam was slightly higher than has been reported previously with the use of piperacillin alone. The potential for increased hepatic adverse reactions should be borne in mind when using Piperacillin/tazobactam.

**Check the following before use:**

Periodic assessment of organ system functions, including renal, hepatic and haemopoietic, during prolonged therapy (greater than or equal to 21 days), is advisable.

For patients with renal impairment and/or hepatic insufficiency, measurement of serum levels of piperacillin will provide guidance for adjusting dosage.

In patients with creatinine clearance  $\leq 40$  mL/min and dialysis patients (hemodialysis and CAPD), the intravenous dose should be adjusted to the degree of renal function impairment. (See DOSAGE AND ADMINISTRATION).

Piperacillin/tazobactam contains 54.28 mg (2.36 meq) of sodium per gram of Piperacillin, which may increase a patient's overall sodium intake.

Periodic electrolyte determinations should be made in patients with low potassium reserves and the possibility of hypokalaemia should be kept in mind with patients who have potentially low potassium reserves and who are receiving cytotoxic therapy or diuretics.

Because of its poor penetration into the CSF, piperacillin is not advised in the treatment of meningitis and brain abscess.

Antimicrobials used in high doses for short periods to treat gonorrhoea may mask or delay symptoms of incubating syphilis. Therefore, prior to treatment, patients with gonorrhoea should also be evaluated for syphilis. Specimens for darkfield examination should be obtained from patients with any suspected primary lesion and serological tests should be made for a minimum of four months.

*Impaired renal function*

See Check the following before use, above.

*Impaired hepatic function*

See Check the following before use, above.

Piperacillin therapy has been associated with an increased incidence of fever and rash in cystic fibrosis patients.

***Pregnancy and lactation***

*Category B1*

Adequate human studies on the use of Piperacillin/tazobactam during pregnancy are not available. Limited studies with piperacillin alone in rats and mice revealed no teratogenic effects or harm to the fetus. Studies with tazobactam (doses up to 3,000 mg/kg intravenously) or tazobactam and piperacillin (doses up to 750 mg/kg and 3,000 mg/kg intravenously) in mice showed no evidence of teratogenicity or harm to the fetus. Studies in rats at these dose levels showed no evidence of teratogenicity although maternal toxicity, in the form of decreased weight gain, was noted at the dose levels tested. Piperacillin has been found to cross the placenta in rats. Pregnant women should be treated only if the expected benefit outweighs the possible risks to the pregnant woman and fetus.

**Use in lactation**

Adequate clinical studies on the use of Piperacillin/tazobactam during pregnancy are not available. Piperacillin is excreted in low concentrations in milk. In animal studies, both piperacillin and

tazobactam were excreted in the milk of lactating rats. Women who are breastfeeding should be treated only if the expected benefit outweighs the possible risks to the woman and child.

### **Effects on ability to drive and use machines**

Presumed to be safe or unlikely to produce an effect on the ability to drive or use machinery

### **Other**

#### **Carcinogenicity, mutagenicity, impairment of fertility**

Long-term carcinogenicity studies of Piperacillin/tazobactam in animals have not been performed. Mutagenicity studies with piperacillin and tazobactam showed no evidence of genotoxicity in assays for chromosomal and DNA damage. One assay for gene mutations (mouse lymphoma assay) was weakly positive at tazobactam and piperacillin concentrations greater than or equal to 3,200 microgram/mL and 2,500 microgram/mL, respectively. Piperacillin and tazobactam did not affect the fertility of male or female rats.

#### **Use in children**

Safety and efficacy of the use of Piperacillin/tazobactam in children under the age of two years have not yet been established.

#### **Adverse effects**

Piperacillin/tazobactam is generally well tolerated. The overall incidence of adverse events was 15.7% although a cause/ effect relationship was not established in all cases. This incidence was comparable to that observed with other agents used in the clinical studies. Treatment had to be discontinued in only 2.9% of cases due to adverse reactions.

#### **More common reactions (>5%)**

The most frequently reported adverse clinical reactions were diarrhoea, rash, erythema, pruritus, vomiting, allergic reactions, nausea, urticaria, superinfection, phlebitis, thrombophlebitis, dyspepsia and insomnia.

#### **Less common reactions (<5%)**

Additional adverse clinical reactions reported as possibly, probably or definitely drug related occurring in less than 0.1% of patients are listed within each body system in order of decreasing severity.

##### *Skin and appendages*

Skin reactions, eruptions (including bullous dermatitis), increased sweating, erythema multiforme, eczema, exanthema, maculopapular rash, Stevens-Johnson syndrome, toxic epidermal necrolysis.

##### *Gastrointestinal*

Soft/ loose stools, stomatitis, constipation, bloody diarrhoea, abdominal pain; very rarely, pseudomembranous colitis has been reported with piperacillin.

##### *Central nervous system*

Muscular weakness, hallucination, headache, dizziness, fatigue, insomnia.

##### *Autonomic nervous system*

Dry mouth.

##### *Musculoskeletal system*

Muscle pain, prolonged muscle relaxation, arthralgia.

##### *Vascular system*

Superficial phlebitis, hypotension, thrombophlebitis and flushing.

##### *Body as a whole*

Fever, hot flushes, oedema, tiredness, rigors.

##### *Local reactions*

Injection site inflammation, injection site pain.

##### *Haematological changes*

Transient reduction in the white blood cell count (leucopenia), neutropenia, thrombocytopenia, eosinophilia, disturbed thrombocyte function, positive Coombs' test, rarely haemorrhagic manifestations (including purpura, epistaxis and bleeding time prolonged), anaemia, haemolytic anaemia, agranulocytosis, pancytopenia, prolonged partial thromboplastin time, prothrombin time prolonged, thrombocytosis.

#### *Hepatic*

Transient rise in the serum levels of liver enzymes (ALT, AST, GGT, alkaline phosphatase), bilirubin. The incidence of such rises is higher than with piperacillin alone. Rarely, cholestatic jaundice or hepatitis may occur.

#### *Renal*

Increased levels of renal function parameters in serum (urea, creatinine) may occur infrequently. Rarely, interstitial nephritis or renal failure may occur.

#### *Hypokalaemia*

This was reported rarely in patients with liver disease and those receiving cytotoxic therapy or diuretics when given high doses of piperacillin.

#### *Superinfection*

Superinfection, including candidiasis, may occur, especially with prolonged treatment.

#### *Immune system disorders*

Hypersensitivity reaction, anaphylactic/ anaphylactoid reaction (including shock).

#### *Metabolism and nutrition disorders*

Very rarely decreases in blood albumin, blood glucose and blood total protein have been observed.

Piperacillin therapy has been associated with an increased incidence of fever and rash in cystic fibrosis patients.

## **Interactions**

Concurrent administration of probenecid and Piperacillin/tazobactam produced a longer half-life and lower renal clearance for both piperacillin and tazobactam. However, peak plasma concentrations of neither drug are affected. No kinetic interaction is found between Piperacillin/tazobactam and vancomycin.

Concurrent administration of piperacillin and tobramycin in patients with severe renal dysfunction (i.e. chronic haemodialysis patients) has been reported to reduce the elimination half-life and significantly increase the total body clearance of tobramycin.

The alteration of tobramycin pharmacokinetics in patients with mild to moderate renal dysfunction who are taking piperacillin concomitantly is unknown. However, reports suggest that the aminoglycoside inactivation in patients concomitantly taking an aminoglycoside with broad spectrum beta-lactam penicillin is only clinically significant in patients with severe renal dysfunction.

The inactivation of aminoglycosides in the presence of penicillin class drugs has been recognised. It has been postulated that penicillin/ aminoglycoside complexes form; these complexes are microbiologically inactive and of unknown toxicity.

Piperacillin, when used concomitantly with vecuronium, has been implicated in the prolongation of the neuromuscular blockade of vecuronium. Piperacillin/tazobactam (piperacillin/ tazobactam) could produce the same phenomenon if given along with vecuronium. Due to their similar mechanism of action, it is expected that the neuromuscular blockade produced by any of the non-depolarising muscle relaxants could be prolonged in the presence of piperacillin.

Piperacillin may reduce the excretion of methotrexate; therefore, serum levels of methotrexate should be monitored in patients to avoid drug toxicity.

If piperacillin/tazobactam is used concurrently with another antibiotic, especially an aminoglycoside, the drugs must not be mixed in intravenous solutions or administered concurrently, due to physical incompatibility.

During simultaneous administration of piperacillin/tazobactam and high doses of heparin, oral anticoagulants and other drugs that may affect the blood coagulation system and/or the thrombocyte function, the coagulation parameters should be tested more frequently and monitored regularly.

### Effects on laboratory tests

As with other penicillins, the administration of piperacillin/ tazobactam may result in a false positive reaction for glucose in the urine using a copper reduction method. It is recommended that glucose tests based on enzymatic glucose oxidase reactions be used.

There have been reports of positive test results using Bio-Rad Laboratories Platelia Aspergillus EIA test in patients receiving piperacillin/tazobactam, who were subsequently found to be free of Aspergillus infection. Cross reactions with non-Aspergillus polysaccharides and polyfuranoses with Bio-Rad Laboratories Platelia Aspergillus EIA test have been reported. Therefore, positive test results in patients receiving piperacillin/tazobactam should be interpreted cautiously and confirmed by other diagnostic methods.

## Overdosage

### Symptoms

There have been postmarketing reports of overdose with piperacillin/ tazobactam. The majority of those events experienced, including nausea, vomiting and diarrhoea, have also been reported with the usual recommended dosages. Patients may experience neuromuscular excitability or convulsions if higher than recommended doses are given intravenously (particularly in the presence of renal failure).

### Treatment

No specific antidote is known. In the event of an emergency, all required intensive medical measures are indicated as in the case of piperacillin. In cases of motor excitability or convulsions, anticonvulsive agents (e.g. diazepam or barbiturates) may be indicated. In cases of anaphylactic reactions, the usual countermeasures are to be initiated (adrenaline, antihistamines, corticosteroids and, if required, oxygen and airway management).

Excessive serum concentrations of either piperacillin or tazobactam may be reduced by haemodialysis.

For further detailed information, advice may be sought from the Poisons Information Centre (In New Zealand call 0800 764 766).

## Pharmaceutical precautions

### Special precautions for storage

DBL™ Piperacillin and Tazobactam for Injection should be stored below 25°C.

## Medicine classification

Prescription Medicine

## Package quantities

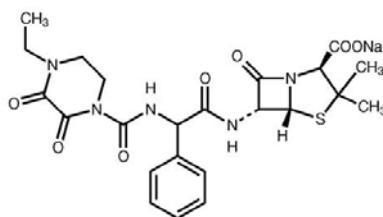
DBL™ Piperacillin and Tazobactam for Injection is supplied in vials as shown below.

Product	Pack Size
2g / 0.25g	1 vial
4g / 0.5g	1 vial

## Further Information

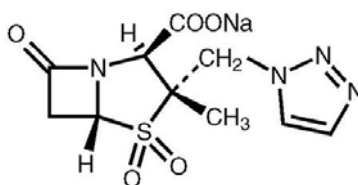
Piperacillin sodium is derived from D(-)-(alpha)-aminobenzyl-penicillin. The chemical name of piperacillin sodium is sodium (2 S ,5 R ,6 R )-6-[( R )-2-(4-ethyl-2,3-dioxo-1-piperazine- carboxamido)-

2-phenylacetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate. The chemical structure of piperacillin sodium is:



Molecular formula:  $C_{23}H_{26}N_5NaO_7S$   
 Relative Molecular mass: 539.5  
 CAS Number: 59703-84-3

Tazobactam sodium, a derivative of the penicillin nucleus, is a penicillanic acid sulfone. Its chemical name is sodium (2*S*,3*S*,5*R*)-3-methyl-7-oxo-3-(1*H*-1,2,3-triazol-1-ylmethyl)-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate-4,4-dioxide. The chemical structure of tazobactam sodium is:



Molecular formula:  $C_{10}H_{11}N_4NaO_5S$   
 Relative Molecular mass: 322.3  
 CAS Number: 89785-84-2

### Clinical Trials

#### Paediatric

A study was performed to compare the safety, tolerance and efficacy of piperacillin 100 mg/kg plus tazobactam 12.5 mg/kg with those of cefotaxime 50 mg/kg plus metronidazole 7.5 mg/kg administered intravenously (IV) every eight hours for the treatment of hospitalised paediatric patients (aged 2 to 12 years of age) with clinically or bacteriologically diagnosed intra-abdominal infection (IAI). The cure rates in the efficacy evaluable (EE) population at the follow-up visit were 90 and 91% for piperacillin/tazobactam and cefotaxime plus metronidazole, respectively. The results of the clinical and microbiological analyses in 521 patients showed that piperacillin/ tazobactam (Piperacillin/tazobactam) administered intravenously was at least as effective as cefotaxime plus metronidazole in the treatment of children aged 2 to 12 years with severe IAIs.

### Name and address

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### Date of Preparation

18 January 2011