AUSTRALIAN PRODUCT INFORMATION – PIPERACILLIN/TAZOBACTAM KABI (PIPERACILLIN/TAZOBACTAM) POWDER FOR INJECTION

1 NAME OF THE MEDICINE

Piperacillin sodium/Tazobactam sodium

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Piperacillin/Tazobactam Kabi Injection is an injectable antibacterial combination, consisting of the semisynthetic antibiotic piperacillin sodium and the β-lactamase inhibitor tazobactam sodium, for intravenous administration.

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.

There are no excipients.

3 PHARMACEUTICAL FORM

Piperacillin/Tazobactam is a white to off white powder for solution for infusion.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Piperacillin/Tazobactam Kabi is indicated in the treatment of serious bacterial infections caused by susceptible strains of β-lactamase producing organisms in the conditions listed below:

1. Lower respiratory tract infections

2. Urinary tract infections (complicated and uncomplicated)

3. Intra-abdominal infections

4. Skin and skin structure infections

5. Bacterial septicaemia

6. Gynaecological infections

Children under the age of 12 years

In hospitalised children aged 2 to 12 years, Piperacillin/Tazobactam Kabi Injection 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 2 years.

While Piperacillin/Tazobactam Kabi Injection 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 β-lactamase producing, piperacillin-resistant organisms. Appropriate culture and susceptibility tests should be performed before treatment in order to identify organisms causing infection 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 β-lactamase producing organisms listed above; however, once these results become available, appropriate therapy should be continued.

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

Combination therapy with Piperacillin/Tazobactam Kabi 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.

4.2 DOSE AND METHOD OF ADMINISTRATION

Piperacillin/Tazobactam Kabi Injection may be given by slow intravenous infusion (20 - 30 minutes).

Adults and children 12 years and older

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

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

Children under the age of 12 years

<u>Hospitalised children with intra-abdominal infection</u>

For children aged 2 to 12 years, weighing up to 40 kg, and with normal renal function, the recommended intravenous dosage is 100 mg piperacillin/12.5 mg tazobactam per kilogram every 8 hours.

For children aged 2 to 12 years, weighing over 40 kg, and with normal renal function, follow the adult dose guidance, i.e. 4 g piperacillin/0.5 g tazobactam every 8 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 5 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.

Dosage adjustment

Renal impairment

In patients with renal impairment or in haemodialysis patients, the intravenous dose and administration interval should be adjusted to the degree of actual renal function impairment.

The suggested daily doses are as follows:

Table 1: Intravenous dosage schedule for adults with impaired renal function

Creatinine Clearance (mL/min)	Recommended Piperacillin/Tazobactam Dosage
> 40	No dosage adjustment necessary
20-40	12 g/1.5 g/day Divided Doses 4 g piperacillin/0.5 g tazobactam q 8 hr
< 20	8 g/1 g/day Divided Doses 4 g piperacillin/0.5 g tazobactam q 12 hr

For patients on haemodialysis, the maximum daily dose is 8 g/1 g/day Piperacillin/Tazobactam Injection. In addition, because haemodialysis removes 30%-50% of piperacillin in 4 hours, one additional dose of 2 g piperacillin/0.25 g tazobactam (Piperacillin/Tazobactam Injection) should be administered following each dialysis period. For patients with renal failure and hepatic insufficiency, measurement of serum levels of Piperacillin/Tazobactam Injection 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 Injection should be for a minimum of five days and continued for 48 hours beyond resolution of clinical symptoms or the fever.

Method of administration

Piperacillin/Tazobactam is administered by intravenous use only.

Product is for single use in one patient only. Discard any remaining contents.

Reconstitution directions

Swirl until dissolved. When swirled constantly, reconstitution should occur within 10 minutes.

Diluents for reconstitution: Sterile water for injections

0.9% Sodium chloride injection

Glucose 5% injection

Reconstitute each vial with the volume of diluent shown in the table below, using one of the above diluents.

Table 2: Volume of diluent to reconstitute each vial

Vial Size (piperacillin/tazobactam)	Minimum volume of diluent to be added to vial
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 the desired volume (e.g. 50 mL to 150 mL) with one of the compatible solvents for intravenous use listed below.

- Sterile water for injections‡
- Saline
- 5% Glucose
- Dextran 6% in Saline

‡ Maximum recommended volume of sterile water for injections per dose is 50 mL.

4.3 CONTRAINDICATIONS

The use of Piperacillin/Tazobactam is contraindicated in patients with a history of allergic reactions to any of the penicillins and/or cephalosporins or β-lactamase inhibitors or any of its excipients.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Serious and occasionally fatal hypersensitivity (anaphylactic/anaphylactoid [including shock] reactions have been reported in patients on penicillin/cephalosporin therapy, including piperacillin/tazobactam. 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 anaphylactic/anaphylactoid reactions (including shock) require

immediate emergency treatment with adrenaline. Oxygen, intravenous steroids and airway management, including intubation, should also be administered as indicated.

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, Piperacillin/Tazobactam should be discontinued immediately and an alternative treatment should be considered.

Rare cases of haemophagocytic lymphohistiocytosis (HLH) have been observed following therapy (>10 days) with piperacillin tazobactam, often as a complication of DRESS. HLH is a pathologic immune activation which leads to excessive systemic inflammation and can be life threatening and early diagnosis and rapid initiation of immunosuppressive therapy is essential. Characteristic signs and symptoms include fever, hepatosplenomegaly, cytopenias, hyperferritinaemia, hypertriglyceridaemia, hypofibrinogenaemia, and haemophagocytosis. If piperacillin tazobactam is suspected as possible trigger, treatment should be discontinued.

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 *C. difficile* should be considered. Fluids, electrolytes and protein replacement should be provided when indicated. Drugs that delay peristalsis eg: opiates and diphenoxylate with atropine (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 haematopoietic function should be performed.

As with treatment with other penicillins, neurological complications in the form of convulsions (seizures) may occur when high doses are administered, especially in patients with impaired renal function (see **Section 4.8 ADVERSE EFFECTS (undesirable effects)**).

As with other antibiotic preparations, use of this drug may result in overgrowth of non-susceptible organisms, including fungi. Patients should be carefully monitored during therapy. If superinfection occurs, appropriate measures should be taken.

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 such as 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 diluent 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 β-lactamase inhibitors and β-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.

Combined use of **piperacillin/tazobactam** and **vancomycin** may be associated with an increased risk of acute kidney injury.

Check the following before use

Periodical assessment of organ system functions including renal, hepatic and haematopoietic during prolonged therapy (≥21 days) is advisable.

Each vial of Piperacillin/Tazobactam 2 g /0.25 g contains 4.9 mmol (112 mg) of sodium and each vial of Piperacillin/Tazobactam 4 g/0.5 g contains 9.7 mmol (224 mg) of sodium. This should be taken into consideration for patients who are on a controlled sodium diet.

Periodical 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 4 months.

Use in renal impairment

Due to its potential nephrotoxicity (refer to **Section 4.8 ADVERSE EFFECTS (Undesirable effects)**), piperacillin/tazobactam should be used with care in patients with renal impairment or dialysis patients (haemodialysis and CAPD). The intravenous dose and administration interval should be adjusted to the degree of renal function impairment. Measurement of serum levels of piperacillin will provide guidance for adjusting dosage (refer to **Section 4.2 DOSE AND METHOD OF ADMINISTRATION**).

In a secondary analysis using data from a large multi-center, randomized-controlled trial when glomerular filtration rate (GFR) was examined after administration of frequently used antibiotics in critically ill patients, the use of piperacillin/tazobactam was associated with a lower rate of reversible GFR improvement compared with the other antibiotics. This secondary analysis concluded that piperacillin/tazobactam was a cause of delayed renal recovery in these patients.

Combined use of piperacillin/tazobactam and vancomycin may be associated with an increased incidence of acute kidney injury (see **Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS**).

Use in the elderly

No data available

Paediatric use

Safety and efficacy of the use of Piperacillin/Tazobactam Injection in children under the age of 2 years has not yet been established.

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 injection, 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.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Aminoglycosides

For information related to the administration of piperacillin/tazobactam with aminoglycosides please refer to **Section 6.2 INCOMPATIBILITIES**.

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.

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 a broad-spectrum beta-lactam penicillin is only clinically significant in patients with severe renal dysfunction.

Probenecid

Concurrent administration of probenecid and Piperacillin/Tazobactam produces a longer half-life and lower renal clearance for both piperacillin and tazobactam. However, peak plasma concentrations of neither drug are affected.

Vancomycin

Studies have detected an increased incidence of acute kidney injury in patients concomitantly administered piperacillin/tazobactam and vancomycin as compared to vancomycin alone (see **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**). Some of these studies have reported that the interaction is vancomycin dose-dependent. Expert guidelines recommend intensive vancomycin dosing and maintenance of trough levels between 15 mg/L and 20 mg/L which is an increase from previously published recommendations of target trough concentrations of 5 - 10 mg/L. Attaining these trough concentrations often requires practitioners to prescribe vancomycin doses which exceed manufacturers' recommendations. Therefore, it is possible that in addition to the increased risk of vancomycin-induced nephrotoxicity reported with adherence to these guidelines the risk of nephrotoxicity may also increase due to an interaction with piperacillin/tazobactam.

Non-depolarizing muscle relaxants

Piperacillin when used concomitantly with vecuronium has been implicated in the prolongation of the neuromuscular blockade of vecuronium. 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.

Methotrexate

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

Anticoagulants

During simultaneous administration of heparin, oral anticoagulants and other medicines that may affect the blood coagulation system including the thrombocyte function, appropriate coagulation tests should be performed more frequently and monitored regularly.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

Piperacillin and tazobactam did not affect the fertility of male or female rats.

Use in pregnancy - Pregnancy 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 foetus. Studies with tazobactam (doses up to 3000 mg/kg IV) or tazobactam and piperacillin (doses up to 750 mg/kg and 3000 mg/kg IV) in mice showed no evidence of teratogenicity or harm to the foetus. Studies in rats at these dose levels showed no evidence of teratogenicity though maternal toxicity, in the form of decreased weight gain, was noted at the dose levels tested. Piperacillin and tazobactam cross the placenta in humans. Pregnant women should be treated only if the expected benefit outweighs the possible risks to the pregnant woman and foetus.

Use in lactation

Adequate clinical studies on the use of Piperacillin/Tazobactam Injection during lactation are not available. Piperacillin is excreted in low concentrations in human milk; tazobactam concentrations in human milk have not been studied. In animal studies, both piperacillin and tazobactam were excreted in the milk of lactating rats. Women who are breast-feeding should be treated only if the expected benefit outweighs the possible risks to the woman and child.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE 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.

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

The following adverse reactions have been reported in clinical trials and are listed in CIOMS frequency categories as follows:

Very common:	≥ 10%
Common:	≥ 1%
Uncommon:	≥ 0.1% and <1%
Rare:	≥ 0.01% and <0.1%
Very rare:	< 0.01%
Unknown:	Cannot be estimated from available data

Infections and infestations

Rare: Pseudomembranous colitis

Skin and subcutaneous tissue disorders

Common: Rash

Uncommon: Pruritis, urticaria

Rare: Eruption (including dermatitis bullous), purpura

Unknown: Increased sweating, eczema, exanthema

Gastrointestinal disorders

Common: Diarrhoea (including soft/loose stools), nausea, vomiting

Uncommon: Constipation, dyspepsia, stomatitis

Rare: Abdominal pain

Psychiatric disorders

Uncommon: Insomnia

Nervous system disorders

Uncommon: Headache

Unknown: Hallucination, dizziness, dry mouth

Musculoskeletal and connective tissue disorders

Rare: Arthralgia

Unknown: Muscular weakness, myalgia, prolonged muscle relaxation

Vascular disorders

Uncommon: Phlebitis, hypotension, thrombophlebitis

Rare: Flushing

Unknown: Tachycardia, including supraventricular and ventricular; bradycardia; arrhythmia, including atrial fibrillation, ventricular fibrillation, cardiac arrest, cardiac failure, circulatory failure, myocardial infarction.

Respiratory, thoracic and mediastinal disorders

Rare: Epistaxis

Blood and lymphatic system disorders

Uncommon: Leucopenia, neutropenia, thrombocytopenia

Rare: Anaemia, eosinophilia

Very rare: Disturbed thrombocyte function

Renal and urinary disorders

Rare: Tubulointerstitial nephritis, renal failure

Metabolism and nutrition disorders

Very rare: Hypokalaemia

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

General disorders and administration site conditions

Uncommon: Pyrexia, injection site reaction (pain, inflammation)

Rare: Chills

Unknown: Hot flushes, oedema, tiredness

Investigations

Uncommon: Alanine aminotransferase increased, aspartate aminotransferase increased, blood creatinine increased

Rare: Bleeding time prolonged, blood bilirubin increased†, blood alkaline phosphatase increased†, gamma- glutamyltransferase increased†.

Very rare: Coombs direct test positive, activated partial thromboplastin time prolonged, prothrombin time prolonged, blood albumin decreased, blood glucose decreased, blood total protein decreased, blood urea increased.

† The incidence is higher than with piperacillin alone.

Post-Marketing Experience

Additional adverse events reported from worldwide marketing experience with piperacillin/tazobactam, occurring under circumstances where causal relationship with piperacillin/tazobactam is uncertain.

Blood and lymphatic system disorders

Rare: Haemolytic anaemia

Very rare: Agranulocytosis, pancytopenia, thrombocytosis

Immune system disorders

Uncommon: Hypersensitivity

Rare: Anaphylactoid shock, anaphylactic shock, anaphylactoid reaction, anaphylactic reaction

Psychiatric disorders

Not known: Delirium

Nervous system disorders

Uncommon: Seizure

Infections and infestations

Uncommon: Candida infection (especially with prolonged treatment)

Respiratory, thoracic and mediastinal disorders

Unknown: Eosinophilic pneumonia

Renal and urinary disorders

Rare: Interstitial nephritis, renal failure

Unknown: Acute renal injury

Skin and subcutaneous tissue disorders

Uncommon: Rash maculopapular

Rare: Erythema multiforme

Very rare: Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN)

Unknown: Drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalised exanthematous pustulosis (AGEP), dermatitis exfoliative

Hepatobiliary disorders

Uncommon: Jaundice

Rare: Hepatitis

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

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

There have been post-marketing 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).

No specific antidote is known. Treatment should be supportive and symptomatic according to the patient's clinical presentation. 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 counter measures 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. (refer to **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).

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

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 β-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 β-lactamase producing bacteria normally resistant to it. Thus, Piperacillin/Tazobactam combines the properties of a broad-spectrum antibiotic and a β - lactamase inhibitor.

Microbiology

Piperacillin/ Tazobactam Injection is active against most strains of the following β-lactamase producing and non β-lactamase producing microorganisms:

Gram-negative bacteria

Escherichia coli, Citrobacter spp. Klebsiella spp. (including K. pneumoniae), Enterobacter spp. (including E. cloacae), Proteus vulgaris, Proteus mirabilis, Serratia spp. (including S.

marcescens), Pseudomonas aeruginosa and other Pseudomonas spp., Neisseria gonorrhoeae, Neisseria meningitidis, Moraxella catarrhalis, Acinetobacter spp., Haemophilus influenza.

Gram-positive bacteria

Streptococci (S. pneumoniae, S. pyogenes, S. agalactiae, S. viridans), Enterococci (E. faecalis, E. faecium), Staphylococcus aureus (not methicillin-resistant S. aureus), S. epidermidis (coagulase-negative Staphylococci).

Anaerobic bacteria

Bacteroides spp. including *Bacteroides fragilis* group, *Peptostreptococcus* spp., *Fusobacterium* spp., *Eubacterium* group, *Clostridia* spp., *Veillonella* spp.

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 medicines, the test should be repeated. This category implies possible clinical applicability in body sites where the medicine is physiologically concentrated or in situations where high dosage of the medicine 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. This information provides guidance on micro-organisms susceptible to piperacillin/tazobactam. The following MIC 90 values were reported in 1996 for clinical isolates collected in 3 Australian states[1].

Table 3: MIC 90 for 1,952 clinically significant isolates

Organism (number)	**MIC90 (mg/L)**
E.coli (528)	2.0
Klebsiella spp*. (180)*	4.0
Klebsiella spp*. (ESBL 44)*	64.0
Enterobacter spp*. (142)*	16.0
Citrobacter/Serratia spp*. (84)*	8.0
Morganella/Proteus/Providencia spp*. (45)*	2.0
Proteus mirabilis spp*. (104)*	2.0
Pseudomonas aeruginosa (88)	32.0
Acinetobacter calcoaceticus (40)	32.0
Staphylococcus aureus (433)	4.0
Coagulase-negative Staphylococcal *(28)*	16.0
Streptococcus pneumoniae (45)	0.015
Enterococci (109)	4.0
Haemophilus influenzae (59)	0.094
Bacteroides fragilis gp *(23)*	4.0

The latest NCCL references are:

Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard-Seventh Edition, NCCLS document M7-A5, 2006. NCCLS, Wayne, PA

For anaerobes:

Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria; Approved Standard-Sixth Edition. NCCLS document M1l-A, 2006. NCCLS, Wayne, PA

Clinical trials

Paediatric

A study was performed to compare the safety, tolerance, and efficacy of 100 mg/kg piperacillin/12.5 mg/kg tazobactam with those of 50 mg/kg cefotaxime plus 7.5 mg/kg metronidazole administered intravenously (IV) every 8 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 administered intravenously was at least as effective as cefotaxime plus metronidazole in the treatment of children aged 2 to 12 years with severe IAIs.

5.2 PHARMACOKINETIC PROPERTIES

Distribution

Mean plasma concentrations of piperacillin and tazobactam at steady state of the combination appear in Tables 4 and 5. 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 4: Plasma levels in adults after a thirty-minute intravenous infusion of piperacillin/tazobactam (steady state)

PIPERACILLIN PLASMA LEVELS (µg/mL)						
Piperacillin/Tazobactam Dose 2 g/250 mg 4 g/500 mg	30*min 134 298	1 hr 57 141	1.5 hr 29 87	2 hr 17 47	3 hr 5 16	4 hr 2 7
TAZOBACTAM PLASMA LEVELS (µg /mL)						
Piperacillin/Tazobactam Dose 2 g/250 mg 4 g/500 mg	30*min 14.8 33.8	1 hr 7.2 17.3	1.5 hr 4.2 11.7	2 hr 2.6 6.8	3 hr 1.1 2.8	4 hr 0.7 1.3

*Completion of 30-minute infusion

Table 5: Plasma levels in adults after an intramuscular injection of piperacillin/tazobactam (steady state)

PIPERACILLIN PLASMA LEVELS (µg/mL)						
Piperacillin/Tazobactam Dose 2 g/250 mg	30 min 55	1 hr 45	1.5 hr 31	2 hr 19	3 hr 8	4 hr 4
TAZOBACTAM PLASMA LEVELS (µg/mL)						
Piperacillin/Tazobactam Dose 2 g/250 mg	30 min 10.5	1 hr 7.4	1.5 hr 4.9	2 hr 3.2	3 hr 1.4	4 hr 0.9

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.

Metabolism

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/min compared to patients with normal renal function. Dosage adjustments are recommended when creatinine clearance is below 40 mL/min, refer to **Section 4.2 DOSE AND METHOD OF 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, refer to **Section 4.2 DOSE AND METHOD OF ADMINISTRATION.**

Impaired liver function

Piperacillin half-life and AUC 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 2 months to 12 years receiving 100 mg/kg piperacillin/12.5 mg/kg tazobactam (Table 6). 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 100 mg/kg piperacillin/12.5 mg/kg tazobactam administered every 8 hours is predicted to provide coverage 31% to 61% of the time for the range of MIC values of 2 µg/mL to 16 µg/mL commonly found in intra-abdominal infections in children.

Table 6: 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_{ss} (L/kg)	$T_{1/2}$ (h)
Piperacillin 100 mg/kg	2-5 mo 6-23 mo 2-5 y 6-12 y	382(15) 344(15) 408(80) 394(24)	539(29) 373(27) 331(21) 404(17)	3.3(24) 4.8(29) 5.2(19) 4.2(21)	0.28(32) 0.25(27) 0.23(36) 0.24(42)	1.3(16) 1.0(24) 0.9(26) 0.8(27)
Tazobactam 12.5 mg/kg	2-5 mo 6-23 mo 2-5 y 6-12 y	43(49) 35(22) 45(42) 45(25)	63(32) 42(23) 37(24) 57(27)	3.6(28) 5.2(24) 5.8(19) 3.9(36)	0.32(31) 0.33(29) 0.27(33) 0.28(36)	1.3(15) 1.1(23) 0.9(29) 1.3(57)

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

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 ≥ 3200 µg/mL and 2500 µg/mL, respectively.

Carcinogenicity

Long-term carcinogenicity studies of Piperacillin/Tazobactam Injection in animals have not been performed.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

None

6.2 INCOMPATIBILITIES

Piperacillin/Tazobactam Injection must not be mixed with other medicinal products except those mentioned in **Section 4.2 Dose and Method of Administration**.

Whenever Piperacillin/Tazobactam Injection is used concurrently with another antibiotic (e.g. aminoglycosides), the drugs must be administered separately. The mixing of Piperacillin/Tazobactam Injection with an aminoglycoside *in vitro* can result in substantial inactivation of the aminoglycoside.

Piperacillin/Tazobactam Injection should not be mixed with other drugs in a syringe or infusion bottle since compatibility has not been established.

Piperacillin/tazobactam Injection should be administered through an infusion set separately from any other drugs unless compatibility is proven.

Because of chemical instability, Piperacillin/Tazobactam Injection should not be used with solutions containing only sodium bicarbonate or having a pH in the basic range.

Lactated Ringer's (Hartmann's) solution is not compatible with Piperacillin/Tazobactam Injection.

Piperacillin/Tazobactam Injection should not be added to blood products or albumin hydrolysates.

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. Keep the vials in the outer carton.

To reduce microbiological hazard, use as soon as practicable after reconstitution or not longer than 4 hours at room temperature. If storage is necessary, hold at 2° - 8°C for not more than 24 hours.

Reconstitute before use and use as soon as possible after reconstitution

6.5 NATURE AND CONTENTS OF CONTAINER

Piperacillin/Tazobactam Kabi 2g/0.25g Injection

Colourless glass vial (Type II) of 50mL closed with a chlorobutyl rubber stopper

Pack sizes: 1,5 and 10 vials.

Piperacillin/Tazobactam Kabi 4g/0.5g Injection

Colourless glass vials (Type II) of 50mL closed with a chlorobutyl rubber stopper

Pack sizes: 1, 5 and 10 vials.

*Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

See **Section 6.2 INCOMPATIBILITIES**.

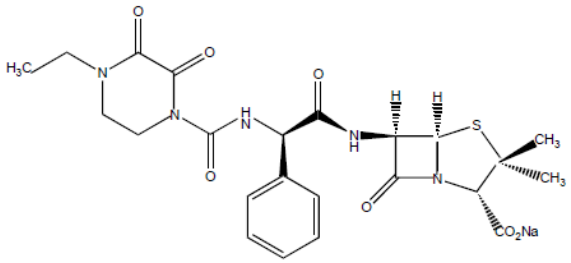
6.7 PHYSICOCHEMICAL PROPERTIES

Piperacillin

Piperacillin sodium is derived from D (-) α-aminobenzylpenicillin.

The chemical name of piperacillin sodium is sodium (2S,5R,6R)-6-[(R)-2-(4-ethyl-2,3-dioxo-1-piperazine-carboxamido)-2-phenylacetamido]-3,3-dimethyl-7-oxo-4-thia-1azabicyclo[3.2.0] heptane-2- carboxylic acid. The empirical formula is $C_{23}H_{26}N_5NaO_7S$ and the molecular weight is 539.54.

Chemical structure



Piperacillin sodium

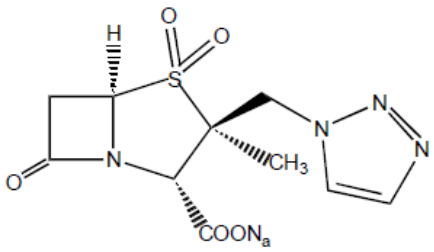
CAS number

Piperacillin Sodium: CAS Registry Number: 59703-84-3

Tazobactam

Tazobactam sodium is a derivative of the penicillin nucleus. Chemically, tazobactam is a penicillanic acid sulfone. Its chemical name is sodium (2S-(2α,3β,5α)-3-methyl-7-oxo-3-(1H-1,2,3-triazol-1-ylmethyl)-4-thia-1-azabicyclo[3.2.0] heptane-2-carboxylic acid 4,4-dioxide. The empirical formula is $C_{10}H_{11}N_4NaO_5S$ and the molecular weight is 322.28.

Chemical structure



Tazobactam sodium

CAS number

Tazobactam Sodium: CAS Registry Number: 89785-84-2

7 MEDICINE SCHEDULE (POISONS STANDARD)

Australia: Schedule 4 - Prescription Only Medicine

8 SPONSOR

Fresenius Kabi Australia Pty Limited
Level 2, 2 Woodland Way
Mt Kuring-gai, NSW 2080
Australia
Telephone: 1300 732 001

9 DATE OF FIRST APPROVAL

10/12/2019

10 DATE OF REVISION

06/02/2023

Reference

1. Daley, D., Mulgrave, L., Munro, S., Smith, H. and Dimech, W. An evaluation of the *in vitro* activity of piperacillin/tazobactam. Pathology 28: 167-172, 1996.

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.2, 4.5 & 6.2	Updated information to remove reference to co-administration with aminoglycosides and co-administration with Hartmann's solution in line with the SmPC. Removed references to EDTA.
All	Minor editorial changes