AUSTRALIAN PRODUCT INFORMATION

TAZOPIP

(piperacillin (as sodium) and tazobactam (as sodium)) powder for injection

1 NAME OF THE MEDICINE

Piperacillin (as sodium) and tazobactam (as sodium)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

TAZOPIP is an injectable antibacterial combination, consisting of the semisynthetic antibiotic piperacillin sodium and the beta-lactamase inhibitor tazobactam sodium, for intravenous administration.

Each vial of TAZOPIP contains piperacillin and tazobactam 2 g/0.25 g or 4 g/0.5 g (as the sodium salts). The product contains no excipients or preservatives.

3 PHARMACEUTICAL FORM

Powder for injection.

TAZOPIP is available as a white to off-white sterile, cryodesiccated powder of piperacillin and tazobactam as the sodium salts packaged in glass vials.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

TAZOPIP for injection is indicated in the treatment of serious bacterial infections caused by susceptible strains of beta-lactamase producing organisms in the conditions listed below:

- 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, TAZOPIP for 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 TAZOPIP for 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 beta-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 TAZOPIP. Therapy with TAZOPIP for injection 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 TAZOPIP for injection may be initiated before susceptibility test results are available.

Note: For associated bacteraemia due to extended-beta-lactamase (ESBL) producing organisms, see Section 5.1 PHARMACODYNAMIC PROPERTIES.

Combination therapy with TAZOPIP for injection 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

Dosage

TAZOPIP for 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 (TAZOPIP) 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 4 g piperacillin /0.5 g tazobactam (TAZOPIP) administered every six or eight hours.

Children aged 2 to 12 years:

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 100 mg piperacillin/12.5 mg tazobactam per kilogram every 8 hours.

Hospitalised children with intra-abdominal infection: 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 in Renal Insufficiency

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 1.

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

Creatinine Clearance	**Recommended Piperacillin/Tazobactam Dosage**
> 40 mL/minute	No dosage adjustment necessary
20-40 mL/minute	12 g/1.5 g per day in divided doses (4 g piperacillin/0.5 g tazobactam q 8 hr)
< 20 mL/minute	8 g/1 g per day in 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 per day TAZOPIP for injection. In addition, because haemodialysis removes 30-50% of piperacillin in 4 hours, one additional dose of 2 g piperacillin/ 0.25 g tazobactam 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 TAZOPIP for injection should be for a minimum of five days and continued for 48 hours beyond resolution of clinical symptoms or the fever.

Co-administration of piperacillin/tazobactam with aminoglycosides

Due to the *in vitro* inactivation of the aminoglycoside by beta-lactam antibiotics, piperacillin/tazobactam and the aminoglycoside are recommended for separate administration. Piperacillin/tazobactam and the aminoglycoside should be reconstituted and diluted separately when concomitant therapy with aminoglycosides is indicated.

In circumstances where co-administration is preferred, TAZOPIP for injection is compatible for simultaneous co-administration via Y-site infusion only with the following aminoglycosides under the following conditions:

Table 2: The conditions where TAZOPIP for injection is compatible for simultaneous co-administration via Y-site infusion with aminoglycoside

Aminoglycoside	TAZOPIP (grams) dose	TAZOPIP Diluent Volume (mL)	Aminoglycoside Concentration* Range (mg/mL)	Acceptable Diluents
Amikacin	2.25, 4.5	50, 150	1.75 – 7.5	0.9% sodium chloride or 5% glucose
Gentamicin	2.25, 4.5	50, 150	0.7 – 3.32	0.9% sodium chloride or 5% glucose

* The dose of aminoglycoside should be based on patient weight, status of infection (serious or life threatening) and renal function (creatinine clearance).

Compatibility of TAZOPIP for injection with other aminoglycosides has not been established. Only the concentration and diluents for amikacin and gentamicin with the dosages of TAZOPIP listed in Table 2 have been established as compatible for co-administration via Y-site infusion. Simultaneous co-administration via Y-site in any manner other than listed above may result in inactivation of the aminoglycoside by piperacillin/tazobactam.

Administration

Reconstitution directions:

Use sterile water for injections or Sodium chloride injection as diluents for reconstitution. Product is for single use in one patient only. Discard any residue.

A needle with 21G [0.8 mm] diameter size is advised to be used for reconstitution. When inserting syringe into the vial, via the rubber stopper, it is recommended to slice the bung with the beveled edge facing upwards (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

For intravenous use:

Reconstitute each vial with the volume of diluent shown in Table 3, using one of the above diluents. Shake until dissolved.

Table 3: 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 50 mL with saline, 5% glucose or Dextran 6% in Saline.

To reduce microbiological hazard, use as soon as possible after preparation. If storage is necessary, hold at 2°C to 8ºC for not more than 24 hours.

4.3 CONTRAINDICATIONS

The use of TAZOPIP for injection is contraindicated in patients with a history of allergic reaction to any of the penicillins and/or cephalosporins or beta-lactamase inhibitors.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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.

The theoretical sodium content of each vial of TAZOPIP for injection is 54 mg sodium (2.35 mEq) per gram of piperacillin, which may increase a patient's overall sodium intake. 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. As with other penicillins, patients may experience neuromuscular excitability or convulsions if higher than recommended doses are given intravenously.

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.

Repeated use of lidocaine as diluent should be avoided in patients with severe liver disease or decreased hepatic blood flow due to the possibility of lidocaine toxicity (resulting from decreased metabolism and accumulation).

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

It is advised to use a needle with 21G [0.8 mm] diameter size, for reconstitution. When inserting syringe into the vial, via the rubber stopper, it is recommended to slice the bung with the beveled edge facing upwards (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Hypersensitivity Reactions

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 TAZOPIP for injection. 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, TAZOPIP for injection should be discontinued and the appropriate therapy instituted. Serious anaphylactic/anaphylactoid reactions (including shock) require immediate emergency treatment with adrenaline (epinephrine). 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, TAZOPIP 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.

Rhabdomyolysis has been reported with the use of piperacillin/tazobactam. If signs or symptoms of rhabdomyolysis are observed, piperacillin/tazobactam should be discontinued and appropriate therapy initiated.

Pseudomembranous Colitis

Antibiotic-associated pseudomembranous colitis has been reported with many antibiotics including piperacillin. A toxin produced by *Clostridioides 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 e.g. opiates and diphenoxylate with atropine (Lomotil) may prolong and/or worsen the condition and should not be used.

Bleeding Manifestations

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.

Hepatic Effects

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 TAZOPIP for injection 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 TAZOPIP for injection.

Prolonged Therapy

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.

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

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

Use in Renal Impairment

Due to its potential nephrotoxicity (see 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). In patients with renal insufficiency and dialysis patients, the intravenous dose and administration interval should be adjusted to the degree of renal function impairment (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION). Measurement of serum levels of piperacillin will provide guidance for adjusting dosage (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

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)).

In a secondary analysis using data from a large multicenter, randomised-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 TAZOPIP for 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* enzyme immunoassay (EIA) test in patients receiving TAZOPIP for 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 TAZOPIP for injection should be interpreted cautiously and confirmed by other diagnostic methods.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Probenecid

Concurrent administration of probenecid and TAZOPIP for injection 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.

Aminoglycosides

The mixing of beta-lactam antibiotics with aminoglycosides *in vitro* can result in substantial inactivation of the aminoglycoside. However, amikacin and gentamicin were determined to be compatible *in vitro* with TAZOPIP for injection in certain diluents at specific concentrations for a simultaneous Y-site infusion (See Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

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.

Other Antibiotics

If TAZOPIP for injection 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.

Non-depolarising muscle relaxants

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

Heparin and Anticoagulants

During simultaneous administration of high doses of heparin, oral anticoagulants and other medicines that may affect the blood coagulation system and/or the thrombocyte function, the coagulation parameters should be tested 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

Category B1. Adequate human studies on the use of TAZOPIP for injection 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 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 fetus. 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 has been found to cross the placenta in humans. Pregnant women should be treated only if the expected benefit outweighs the possible risks to the pregnant woman and fetus.

Australian categorisation definition of Category B1: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage.

Use in Lactation

Adequate clinical studies on the use of TAZOPIP for 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 breastfeeding 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)

TAZOPIP for injection 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.

Clinical Experience

The following adverse reactions have been reported in clinical trials and are listed in Council for International Organisations of Medical Sciences (CIOMS) frequency categories as follows:

Very common: $\geq$ 10%

Common: $\geq$ 1% and < 10%

Uncommon: $\geq$ 0.1% and < 1%

Rare: $\geq$ 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 bullous dermatitis), 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, connective tissue and bone disorders

Rare: Arthralgia

Unknown: Muscular weakness, muscle pain, 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 (ALT) increased, aspartate aminotransferase (AST) increased, blood creatinine increased

Rare: Bleeding manifestations (including 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 of such rises is higher than with piperacillin alone.

Post-marketing Experience

Additional adverse events reported from worldwide marketing experience with TAZOPIP for injection, occurring under circumstances where causal relationship with TAZOPIP 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

Not known: Kounis syndrome*

Psychiatric disorders

Unknown: 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

Musculoskeletal and connective tissue disorders

Not known: Rhabdomyolysis

Hepatobiliary disorders

Uncommon: Jaundice

Rare: Hepatitis

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

*Acute coronary syndrome associated with an allergic reaction

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 symptoms 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 (epinephrine), antihistamines, corticosteroids and, if required, oxygen and airway management). Excessive serum concentrations of either piperacillin or tazobactam may be reduced by haemodialysis.

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 beta-lactamases, including the plasmid and chromosomally mediated enzymes that commonly cause resistance to penicillins. The presence of tazobactam in the TAZOPIP formulation enhances and extends the antibiotic spectrum of piperacillin to include many beta-lactamase producing bacteria normally resistant to it. Thus, TAZOPIP combines the properties of a broad-spectrum antibiotic and a beta-lactamase inhibitor.

Piperacillin and other β-lactam antibiotics block the terminal transpeptidation step of cell wall peptidoglycan biosynthesis in susceptible bacteria by interacting with penicillin-binding proteins (PBPs), the bacterial enzymes that carry out this reaction. *In vitro*, piperacillin is active against a variety of gram-positive and gram-negative aerobic and anaerobic bacteria.

Piperacillin has reduced activity against bacteria harbouring certain β-lactamase enzymes, which chemically inactivate piperacillin and other β-lactam antibiotics. Tazobactam sodium, which has very little intrinsic antimicrobial activity, due to its low affinity for PBPs, can restore or enhance the activity of piperacillin against many of these resistant organisms. Tazobactam is a potent inhibitor of many class A β-lactamases (penicillinases, cephalosporinases and extended spectrum enzymes). It has variable activity against class A carbapenemases and class D β-lactamases. It is not active against most class C cephalosporinases and inactive against Class B metallo-β-lactamases.

Two features of piperacillin/tazobactam lead to increased activity against some organisms harbouring β-lactamases that, when tested as enzyme preparations, are less inhibited by tazobactam and other inhibitors: tazobactam does not induce chromosomally mediated β-lactamases at tazobactam levels achieved with the recommended dosing regimen and piperacillin is relatively refractory to the action of some β-lactamases.

Like other β-lactam antibiotics, piperacillin, with or without tazobactam, demonstrates time-dependent bactericidal activity against susceptible organisms.

Mechanism of Resistance

There are three major mechanisms of resistance to β-lactam antibiotics: changes in the target penicillin-binding proteins (PBPs) resulting in reduced affinity for the antibiotics, destruction of the antibiotics by bacterial β-lactamases, and low intracellular antibiotic levels due to reduced uptake or active efflux of the antibiotics.

In gram-positive bacteria, changes in PBPs are a major mechanism of resistance to β-lactam antibiotics, including piperacillin/tazobactam. This mechanism is responsible for methicillin resistance in staphylococci and penicillin resistance in *Streptococcus pneumoniae* as well as viridans group streptococci and enterococci. Resistance caused by changes in PBPs also occurs to a lesser extent in fastidious gram-negative species such as *Haemophilus influenzae* and *Neisseria gonorrhoeae*. Piperacillin/tazobactam is not active against strains in which resistance to β-lactam antibiotics is determined by altered PBPs. As indicated above, there are some β-lactamases that are not inhibited by tazobactam.

Antibacterial spectrum (Groupings of relevant species according to piperacillin/tazobactam susceptibility)

Commonly susceptible species

Aerobic gram-negative bacteria:

Citrobacter koseri
Haemophilus influenzae
Moraxella catarrhalis
Proteus mirabilis

Aerobic gram-positive bacteria:

Enterococcus faecalis (ampicillin-or penicillin-susceptible isolates only)
Listeria monocytogenes
Staphylococcus aureus (methicillin-susceptible isolates only)
Staphylococcus spp., coagulase-negative (methicillin-susceptible isolates only)
Streptococcus agalactiae (Group B streptococci)†
Streptococcus pyogenes (Group A streptococci)†

Anaerobic gram-positive bacteria:

Clostridium spp.
Eubacterium spp.
Anaerobic gram-positive cocci††

Anaerobic gram-negative bacteria:

Bacteroides fragilis group
Fusobacterium spp.
Porphyromonas spp.
Prevotella spp.

Species for which acquired resistance may be a problem

Aerobic gram-positive bacteria

Enterococcus faecium
Streptococcus pneumoniae††
Viridans group streptococci††

Aerobic gram-negative bacteria

Acinetobacter baumannii
Citrobacter freundii
Enterobacter spp.
Escherichia coli

Klebsiella pneumoniae
Morganella morganii
Proteus vulgaris
Providencia spp.
Pseudomonas aeruginosa
Serratia spp.

Anaerobic gram-positive bacteria

Clostridium perfringens

Anaerobic gram-negative bacteria

Bacteroides distasonis
Prevotella melaninogenica

Inherently resistant organisms

Aerobic gram-positive bacteria

Corynebacterium jeikeium

Aerobic gram-negative bacteria

Burkholderia cepacia
Legionella spp.
Stenotrophomonas maltophilia

Others

Chlamydophila pneumoniae
Mycoplasma pneumoniae

† Streptococci are not β-lactamase producing bacteria; resistance in these organisms is due to alterations in PBPs and, therefore, piperacillin/tazobactam-susceptible isolates are susceptible to piperacillin alone. Penicillin resistance has not been reported in *S. pyogenes*.

†† Including *Anaerococcus*, *Finegoldia*, *Peptococcus*, *Peptoniphilus*, and *Peptostreptococcus* spp. (CLSI M100 Ed. 29, 2019).

Disc susceptibility test:

Susceptibility testing should be conducted using standardised laboratory methods such as those described by the Clinical and Laboratory Standards Institute (CLSI). These include dilution methods (minimal inhibitory concentration [MIC] determination) and disk susceptibility methods. Standardised susceptibility test procedures require the use of quality control microorganisms to control the technical aspects of the laboratory procedures. Quality control microorganisms are specific strains with intrinsic biological properties relating to resistance mechanisms and their genetic expression within the microorganism; the specific strains used for susceptibility test quality control are not clinically significant.

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 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 of resistance is desirable, particularly when treating severe infections. This information provides guidance on microorganisms susceptible to piperacillin/tazobactam. The following MIC_{90} values were reported in 1996 for clinical isolates collected in 3 Australian states (see Table 4).

Table 4: MIC_{90} for 1,952 clinically significant isolates

Organism (number)	**MIC_{90} (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
Staphyloccus 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 CLSI interpretive criteria for susceptibility testing of piperacillin/tazobactam are listed in Table 5:

Table 5: CLSI Susceptibility Interpretive Criteria for Piperacillin/Tazobactam

Pathogen	**Minimal Inhibitory Concentration (mg/L of Piperacillin)[a]**			**Disk[b] Diffusion Inhibition Zone (mm Diameter)**		
	S	I	R	S	I	R
Enterobacteriaceae	≤16	32-64	≥128	≥21	18-20	≤17
Acinetobacter spp.	≤16	32-64	≥128	≥21	18-20	≤17
Pseudomonas aeruginosa	≤16	32-64	≥128	≥21	15-20	≤14
Certain other non-fastidious gram-negative bacilli[c]	≤16	32-64	≥128	-	-	-
Haemophilus influenzae and *Haemophilus parainfluenzae*	≤1	-	≥2	≥21	-	-
Anaerobes[d]	≤16	32-64	≥128	-	-	-

Source: Clinical and Laboratory Standards Institute. *Performance Standards for Antimicrobial Susceptibility Testing*; CLSI document M100:ED29. CLSI, Wayne, PA, 2019. This document is updated annually and may be accessed at http://clsi-m100.com/.

S = Susceptible. I = Intermediate. R = Resistant.

[a] MICs are determined using a fixed concentration of 4 mg/L tazobactam and by varying the concentration of piperacillin.

[b] CLSI interpretive criteria are based on disks containing 100 µg of piperacillin and 10 µg of tazobactam.

[c] Refer to CLSI Document M100 Table 2B-5 for the list of organisms included.

[d] With the exception of *Bacteroides fragilis*, MICs are determined by agar dilution only.

Organisms and quality control ranges for piperacillin/tazobactam to be utilised with CLSI methodology and susceptibility test interpretive criteria are listed in Table 6:

Table 6: Quality Control Ranges for Piperacillin/Tazobactam to be Used in Conjunction with CLSI Susceptibility Test Interpretive Criteria

Quality Control Strain	Minimal Inhibitory Concentration (mg/L of piperacillin)	Disk Diffusion Inhibition Zone (mm Diameter)
Escherichia coli ATCC 25922	1-4	24-30
Escherichia coli ATCC 35218	0.5-2	24-30
Pseudomonas aeruginosa ATCC 27853	1-8	25-33
Haemophilus influenzae ATCC 49247	0.06-0.5	33-38
Staphylococcus aureus ATCC 29213	0.25-2	-
Staphylococcus aureus ATCC 25923	-	27-36
Bacteroides fragilis ATCC 25285	0.125-0.5[a]	-
Enterococcus faecalis ATCC 29212	1-4	
Bacteroides thetaiotaomicron ATCC 29741	4-16[a]	-
Clostridioides (formerly *Clostridium*) difficile ATCC 700057	4-16[a]	
Eggerthella lenta (formerly *Eubacterium lentum*) ATCC 43055	4-16[a]	

Source: Clinical and Laboratory Standards Institute. *Performance Standards for Antimicrobial Susceptibility Testing*, CLSI document M100ED29. CLSI, Wayne, PA, 2019.
[a] Agar dilution only.

Clinical Trials

MERINO trial (blood stream infections due to ESBL producing organisms):

In a prospective, randomised non-inferiority clinical trial, definitive (i.e. based on susceptibility confirmed *in vitro*) treatment with piperacillin/tazobactam did not meet non-inferiority versus meropenem in regard to 30-day mortality in the treatment of blood stream infections due to ESBL producing *E. coli* or *Klebsiella pneumoniae* in critically ill adult patients. A total of 23 of 187 patients (12.3%) randomised to piperacillin/tazobactam met the primary outcome of mortality at 30 days compared with 7 of 191 (3.7%) randomised to meropenem (risk difference, 8.6% [1-sided 97.5% CI: − ∞ to 14.5%]; P = 0.90 for non-inferiority). Clinical and microbiological resolution by day 4 occurred in 121 of 177 patients (68.4%) in the piperacillin/tazobactam group compared with 138 of 185 (74.6%), randomised to meropenem (risk difference, −6.2% [95% CI: −15.5 to 3.1%]; P = 0.19). The cause of the mortality imbalance is not clear.

Paediatric:

A study was performed to compare the safety, tolerance, and efficacy of 100 mg/kg piperacillin plus 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/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/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 Table 7 and 8. 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 7: Plasma levels in adults after a 30-minute intravenous infusion of piperacillin/tazobactam (steady state)						
Piperacillin plasma levels (microgram/mL)						
Piperacillin/tazobactam Dose	30 min*	1 hr	1.5 hr	2 hr	3 hr	4 hr
2 g/250 mg	134	57	29	17	5	2
4 g/500 mg	298	141	87	47	16	7
Tazobactam plasma levels (microgram/mL)						
Piperacillin/Tazobactam Dose	30 min*	1 hr	1.5 hr	2 hr	3 hr	4 hr
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						

Table 8: Plasma levels in adults after an intramuscular injection of piperacillin/tazobactam (steady state)						
Piperacillin plasma levels (microgram/mL)						
Piperacillin/tazobactam Dose	30 min	1 hr	1.5 hr	2 hr	3 hr	4 hr
2 g/250 mg	55	45	31	19	8	4
Tazobactam plasma levels (microgram/mL)						
Piperacillin/tazobactam Dose	30 min	1 hr	1.5 hr	2 hr	3 hr	4 hr
2 g/250 mg	10.5	7.4	4.9	3.2	1.4	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 (see 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, see 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 plus 12.5 mg/kg tazobactam (Table 9). 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 plus 12.5 mg/kg tazobactam administered every 8 hours is predicted to provide coverage 31 - 61% of the time for the range of MIC values of 2 - 16 microgram/mL commonly found in intra-abdominal infections in children.

Table 9: Piperacillin and tazobactam pharmacokinetics in children (CV%) following single doses

	Patient age	C_{max} (mg/L)	AUC (mg.h/L)	CL (mL/min/kg)	V_{ss} (L/kg)	$T_{½}$ (h)
Dose						
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)

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 greater than or equal to 3200 microgram/mL and 2500 microgram/mL, respectively.

Carcinogenicity

Long term carcinogenicity studies of TAZOPIP for injection in animals have not been performed.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Each vial contains a total of 2.35 mEq (54 mg) of sodium per gram of piperacillin. The product contains no excipients or preservatives.

6.2 INCOMPATIBILITIES

TAZOPIP for injection should not be mixed with other drugs in a syringe or infusion bottle since compatibility has not been established. Whenever TAZOPIP for injection is used concurrently with another antibiotic, the drugs must be administered separately. Due to the *in vitro* inactivation of aminoglycosides by beta-lactam

antibiotics, TAZOPIP for injection and the aminoglycoside should be reconstituted and diluted separately when concomitant therapy with aminoglycosides is indicated.

Because of chemical instability, TAZOPIP for injection should not be used with lactated Ringer's solution, solutions containing only sodium bicarbonate or having a pH in the basic range.

TAZOPIP for 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

TAZOPIP 2 g/0.25 g Powder for Injection: Store below 25ºC. Protect from light.

TAZOPIP 4 g/0.5 g Powder for Injection: Store below 25ºC. Protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

TAZOPIP 2 g/0.25 g Powder for Injection	:	2.25 g vial containing piperacillin sodium 2.085 g equivalent to 2 g piperacillin and tazobactam sodium 0.2683 g equivalent to 0.25 g tazobactam. Packs of 1, glass type I clear vial.
TAZOPIP 4 g/0.5 g Powder for Injection	:	4.5 g vial containing piperacillin sodium 4.170 g equivalent to 4 g piperacillin and tazobactam sodium 0.5366 g equivalent to 0.5 g tazobactam. Packs of 1 and 10, glass type I clear vial. Some strengths, pack sizes and/or pack types may not be marketed.

Australian Register of Therapeutic Goods (ARTG)

AUST R 144969 – TAZOPIP 2 g/0.25 g piperacillin (as sodium) 2 g and tazobactam (as sodium) 0.25 g powder for injection vial

AUST R 144970 – TAZOPIP 4 g/0.5 g piperacillin (as sodium) 4 g and tazobactam (as sodium) 0.5 g powder for injection vial

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

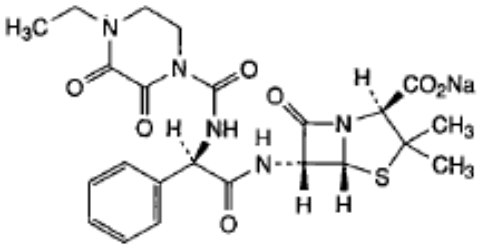
6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Structure

Piperacillin (as sodium)

Chemical name	:	sodium (*2S,5R,6R*)-6-[[(*2R*)-2-[[(4-ethyl-2,3-dioxopiperazin-1-yl)carbonyl]amino]-2-phenylacetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0] heptane-2-carboxylic acid

Structural formula :



Molecular formula : $C_{23}H_{26}N_5NaO_7S$

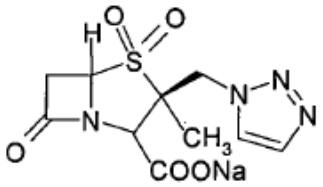
Molecular weight : 539.54

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

Tazobactam (as sodium)

Chemical name : sodium (*2S,3S,5R*)-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

Structural formula :



Molecular formula : $C_{10}H_{11}N_4NaO_5S$

Molecular weight : 322.28

Tazobactam sodium, a derivative of the penicillin nucleus, is a penicillanic acid sulfone.

CAS Number

Piperacillin sodium: CAS Registry no. 59703-84-3

Tazobactam sodium: CAS Registry no. 89785-84-2

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

Alphapharm Pty Ltd trading as Viatris

Level 1, 30 The Bond

30 – 34 Hickson Road

Millers Point NSW 2000

www.viatris.com.au

Phone: 1800 274 276

9 DATE OF FIRST APPROVAL

21/09/2009

10 DATE OF REVISION

17/06/2024

Summary Table of Changes

Section Changed	Summary of New Information
All	Minor editorial changes.
4.4	Addition of rhabdomyolysis warning/precaution.
4.8	Addition of post-marketing adverse drug reaction – rhabdomyolysis.

TAZOPIP_pi\Jun24/00