

NEW ZEALAND DATA SHEET

PIPTAZ SANDOZ (PIPERACILLIN/TAZOBACTAM)

1. PRODUCT NAME

PIPTAZ SANDOZ; 4 g/0.5 g; injection, powder

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

PIPTAZ SANDOZ contains piperacillin (as sodium salt) 4 g and tazobactam (as sodium salt) 0.5 g.

One bottle of powder for solution for infusion contains 9.44 mmol (217 mg) of sodium.

Excipient(s) with known effect: Not applicable

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Powder for injection.

White to off-white sterile, cryodesiccated powder in glass bottles.

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS

PIPTAZ SANDOZ (piperacillin/tazobactam) is indicated for the treatment of the following systemic and/or local bacterial infections in which susceptible organisms have been detected or are suspected:

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
7. Bacterial infections in neutropenic patients. Full therapeutic doses of PIPTAZ SANDOZ (piperacillin/tazobactam) plus an aminoglycoside should be used.
8. Bone and joint infections
9. Polymicrobial infections: PIPTAZ SANDOZ (piperacillin/tazobactam) is indicated for polymicrobial infections including those where aerobic and anaerobic organisms are suspected (intra-abdominal, skin and skin structure, upper and lower respiratory tract, gynaecological).

While PIPTAZ SANDOZ (piperacillin/tazobactam) is indicated only for the conditions listed above, infections caused by piperacillin susceptible organisms are also amenable to PIPTAZ SANDOZ (piperacillin/tazobactam) treatment due to its piperacillin content. Therefore, the treatment of mixed infections caused by piperacillin susceptible organisms and β -lactamase

producing organisms susceptible to PIPTAZ SANDOZ (piperacillin/tazobactam) should not require the addition of another antibiotic.

Appropriate culture and susceptibility tests should be performed before treatment in order to identify organisms causing infections and to determine their susceptibilities to PIPTAZ SANDOZ (piperacillin/tazobactam). Because of its broad-spectrum of activity against Gram-positive and Gram-negative aerobic and anaerobic organisms as listed above, PIPTAZ SANDOZ (piperacillin/tazobactam) is particularly useful in the treatment of mixed infections and in presumptive therapy prior to the availability of the results of sensitivity tests. Therapy with PIPTAZ SANDOZ (piperacillin/tazobactam) may, however, be initiated before results of such tests are known. Modification of the treatment may be required once these results become available or if there is no clinical response.

In serious infections, presumptive therapy with PIPTAZ SANDOZ (piperacillin/tazobactam) may be initiated before susceptibility test results are available.

PIPTAZ SANDOZ (piperacillin/tazobactam) acts synergistically with aminoglycosides against certain strains of *Pseudomonas aeruginosa*. Combined therapy has been successful, especially in patients with impaired host defences. 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.

Children under the age of 12 years

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

4.2. DOSE AND METHOD OF ADMINISTRATION

Dosage

PIPTAZ SANDOZ (piperacillin/tazobactam) may be given by slow intravenous injection, by 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 (PIPTAZ SANDOZ) 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 (PIPTAZ SANDOZ) administered every six, eight or twelve hours.

Use in neutropenic patients - adults and children over the age of 12:

In neutropenic patients, the usual intravenous dosage for adults and children with normal renal function is 4.5 g PIPTAZ SANDOZ given every eight hours as a 30 minute infusion, in conjunction with an aminoglycoside. 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 administered every six or eight hours.

Piperacillin/tazobactam has been shown to have a synergistic effect with an aminoglycoside against *Pseudomonas* infection. Therefore combination therapy is recommended for use in

neutropenic patients, in whom infection is attributed predominantly to *Pseudomonas* organisms.

Children under the age of 12 years:

Recommended Intravenous Dosage

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.

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.

Paediatric Population Safety and efficacy of the use of piperacillin and tazobactam in children under the age of 2 years has not yet been established.

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:

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 Dose 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 piperacillin/1 g tazobactam/day PIPTAZ SANDOZ. 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 PIPTAZ SANDOZ (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 PIPTAZ SANDOZ (piperacillin/tazobactam) 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 the β -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.

Method of administration

Instructions for use/handling

The reconstitution and dilution is to be made under aseptic conditions. The solution is to be inspected visually for particulate matter and discoloration prior to administration. The solution should only be used if the solution is clear and free from particles.

For intravenous use

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

| Bottle Size (piperacillin/tazobactam) | Minimum volume of diluent to be added to bottle |
|--|--|
| 4.50 g (4 g/0.5 g) | 20 mL |

Diluents for Reconstitution:

- Sterile Water for Injections
- Sodium Chloride Injection
- Dextrose 5% in Water
- Dextrose 5% in Saline

When swirled constantly, reconstitution generally occurs within 5 to 10 minutes. The reconstituted solution should be withdrawn from the bottle by syringe. When reconstituted as directed, the bottle contents withdrawn by syringe will provide the labelled amount of piperacillin and tazobactam. Solutions of PIPTAZ SANDOZ prepared in this manner appear clear to slightly yellow in colour.

Administration Directions

The reconstituted solution may be further diluted to the desired volume (e.g. 50 mL to 150 mL) with one of the compatible diluents for intravenous use listed below.

1. 0.9% Sodium Chloride for Injection.
2. Sterile Water for Injection.*
3. Dextrose 5%.
4. Dextran 6% in Saline.

*Maximum recommended volume of Sterile Water for Injection per dose is 50 mL.

Diluted solutions should be used immediately. Product is for single use in one patient only. Discard any residue.

4.3. CONTRAINDICATIONS

The use of PIPTAZ SANDOZ (piperacillin/tazobactam) is contraindicated in patients with a history of allergic reactions to any of the penicillins and/or cephalosporins or β -lactamase inhibitors.

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Warnings

Hypersensitivity reactions

Serious and occasionally fatal hypersensitivity (anaphylactic/anaphylactoid [including shock]) reactions have been reported in patients on penicillin/cephalosporin therapy. Although anaphylaxis is more frequent following parenteral therapy, it has occurred in patients on oral penicillins/cephalosporins. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity and/or a history of sensitivity to multiple allergens. There have been reports of individuals with a history of penicillin/cephalosporin hypersensitivity who have experienced severe reactions when treated with either a penicillin or cephalosporin.

PIPTAZ SANDOZ should be given with caution to patients who have previously experienced signs and symptoms of allergy associated with a cephalosporin or penicillin treatment. Past history of a severe allergic reaction to penicillin/cephalosporin is a contraindication to the use of PIPTAZ SANDOZ (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, PIPTAZ SANDOZ (piperacillin/tazobactam) should be discontinued and the appropriate therapy instituted. Serious 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 system symptoms (DRESS), and acute generalised exanthematous pustulosis (AGEP) have been reported in patients taking β -lactam antibiotics. When SCAR is suspected, PIPTAZ SANDOZ (piperacillin/tazobactam) should be discontinued immediately and an alternative treatment should be considered.

Pseudomembranous colitis

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

Leucopenia and neutropenia

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 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.

Precautions

Use in patients with renal impairment

Due to its potential nephrotoxicity (see Section 4.8 Undesirable effects), piperacillin/tazobactam should be used with care in patients with renal impairment or in hemodialysis 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).

In a secondary analysis using data from a large multicenter, 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 with caution in the following circumstances

Bleeding manifestations, especially in patients with renal impairment

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.

Superinfections, particularly during prolonged treatment

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.

Neuromuscular excitability or convulsions

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

Patients with severe liver disease or decreased hepatic blood flow

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).

Increased hepatic adverse reactions

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 PIPTAZ SANDOZ (piperacillin/tazobactam).

Check the following before use

Organ system functions

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

Patients with renal impairment and/or hepatic insufficiency

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

Patients requiring sodium restriction; 2.35 mEq of sodium per gram

The theoretical sodium content of each 4.5 g bottle of PIPTAZ SANDOZ (piperacillin/tazobactam) is 216 mg sodium (9.4 mmol), which may increase a patient's overall sodium intake.

Patients with low potassium

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.

Massive doses of PIPTAZ SANDOZ can cause hypokalaemia and sometimes hypernatraemia. In patients undergoing high-dose treatment for more than 5 days, electrolyte balance, blood counts, and renal function should be monitored. Additionally, use of a potassium-sparing diuretic may be helpful.

Treatment of meningitis and brain abscess is not advisable

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

Patients with gonorrhoea

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.

Cystic fibrosis patients; increased risk for fever and rash

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

Paediatric Population

Safety and efficacy of the use of piperacillin and tazobactam in children under the age of 2 years has not yet been established.

Effects on Laboratory tests

Penicillins may interfere with:

- Urinary glucose test
- Coomb's tests

- Tests for urinary or serum proteins
- Tests which use bacteria e.g. Guthrie test.

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 PIPTAZ SANDOZ (piperacillin/tazobactam) should be interpreted cautiously and confirmed by other diagnostic methods.

4.5. INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Other medicines

Probenecid

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

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.

No kinetic interaction is found between piperacillin/tazobactam and vancomycin.

Aminoglycosides

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

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 β -lactam penicillin is only clinically significant in patients with severe renal dysfunction.

Vecuronium

Piperacillin when used concomitantly with vecuronium has been implicated in the prolongation of the neuromuscular blockade of vecuronium. PIPTAZ SANDOZ (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 high doses of heparin, oral anticoagulants and other drugs that may affect the blood coagulation system and/or the thrombocyte function, the coagulation parameters should be tested more frequently and monitored regularly.

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

Assigned Category B1 by the Australian Drug Evaluation Committee.

Adequate human studies on the use of piperacillin and 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 and tazobactam during lactation or in breastfeeding are not available. Low quantities of PIPTAZ SANDOZ can be detected in breast milk with the potential for hypersensitivity reactions (e.g. drug rashes) or gastrointestinal disorders (e.g. diarrhoea or candidosis) in the breast-fed infant. Consequently, breastfeeding might have to be discontinued.

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

No studies on the effects on the ability to drive and use machines have been performed.

4.8. 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, pruritis, vomiting, allergic reactions, nausea, urticaria, superinfection, phlebitis, thrombophlebitis, dyspepsia, and insomnia.

Adverse reactions are listed in the Table in CIOMS frequency categories:

| | |
|--------------|---|
| Very Common: | ≥ 10% |
| Common: | ≥ 1% and < 10% |
| Uncommon: | ≥ 0.1% and < 1% |
| Rare: | ≥ 0.01% and < 0.1% |
| Very rare: | < 0.01% |
| Not known: | frequency could not be accurately estimated from clinical studies |

The following table of suspected undesirable effects is based on clinical trials and/or spontaneous post-marketing reporting rates:

| <i>Body System</i> | <i>Adverse Reaction</i> |
|---|---|
| <i>Infections and infestations</i> | |
| Common: | Candida infection [†] |
| Rare: | Pseudomembranous colitis |
| <i>Blood and lymphatic system disorders</i> | |
| Common: | Thrombocytopenia, anaemia [†] . |
| Uncommon: | Leucopenia |
| Rare: | Agranulocytosis. |
| Not known: | Pancytopenia [†] , neutropenia, haemolytic anaemia [†] , eosinophilia [†] , thrombocytosis [†] |
| <i>Immune system disorders</i> | |
| Not known: | Hypersensitivity [†] , anaphylactic reaction [†] , anaphylactoid reaction [†] , anaphylactic shock [†] , anaphylactoid shock [†] |
| <i>Metabolism and Nutrition Disorders</i> | |
| Uncommon: | Hypokalaemia |
| <i>Nervous system disorders</i> | |
| Common: | Headache, insomnia |
| Uncommon: | Seizure [†] |
| Not known: | Dizziness |
| <i>Vascular disorders</i> | |
| Uncommon: | Hypotension, phlebitis, thrombophlebitis, flushing |
| <i>Respiratory, thoracic and mediastinal disorders</i> | |
| Rare: | Epistaxis |
| Not known: | Eosinophilic pneumonia [†] |
| <i>Gastrointestinal disorders</i> | |
| Very common: | Diarrhoea |

| Body System | Adverse Reaction |
|--|---|
| Common: | Abdominal pain, nausea, vomiting, constipation, dyspepsia |
| Rare: | Stomatitis |
| Not known: | Bloody diarrhoea, dry mouth |
| Hepatobiliary disorders | |
| Not known: | Jaundice, hepatitis [†] |
| Skin and subcutaneous tissue disorders | |
| Common: | Rash, pruritis |
| Uncommon: | Erythema multiforme [†] , urticaria, rash maculopapular [†] |
| Rare: | Toxic epidermal necrolysis (TEN) [†] |
| Not known: | Dermatitis bullous, Stevens-Johnson Syndrome (SJS) [†] , hyperhidrosis, eczema, drug reaction with eosinophilia and systemic symptoms (DRESS) [†] , acute generalised exanthematous pustulosis (AGEP) [†] , dermatitis exfoliative [†] , purpura, cutaneous vasculitis. |
| Musculoskeletal, connective tissue and bone disorders | |
| Uncommon: | Arthralgia, myalgia |
| Not known: | Muscular weakness, prolonged muscle relaxation |
| Renal and urinary disorders | |
| Not known: | Tubulointerstitial nephritis [†] , renal failure |
| General disorders and administration site conditions | |
| Common: | Pyrexia, injection site reaction |
| Uncommon: | Chills |
| Not known: | Oedema, fatigue |
| Psychiatric Disorders | |
| Common: | Insomnia |
| Not known: | Hallucinations, delirium [†] |
| Investigations | |
| Common: | Alanine aminotransferase increased, aspartate aminotransferase increased, protein total decreased, blood albumin decreased, Coombs direct test positive, blood creatinine increased, blood alkaline phosphatase increased, blood urea increased, activated partial thromboplastin time prolonged |
| Uncommon: | Blood glucose decreased, blood bilirubin increased, prothrombin time prolonged |
| Not known: | Bleeding time prolonged, gamma-glutamyltransferase increased |

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

[†] Adverse event identified post-marketing.

Reporting suspected adverse effects

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>.

4.9. OVERDOSE

Signs and symptoms

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).

Management

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.

For advice on the management of overdose, please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES

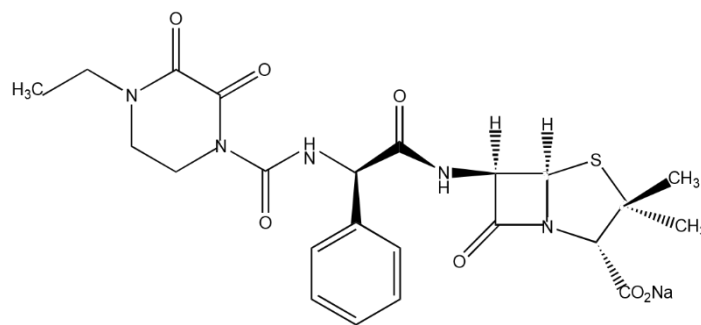
Mechanism of action

Pharmacotherapeutic group

Antibacterials for systemic use, Combinations of penicillins, including betalactamase inhibitors.

ATC code: J01C R05.

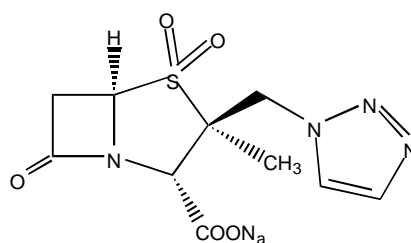
Piperacillin sodium is derived from D(-)- α -aminobenzylpenicillin. The chemical name of piperacillin sodium is sodium (2S,5R,6R)-6-[(R)-2-(4-ethyl-2,3-dioxo-1-piperazine carboxamido)-2-phenylacetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane - 2-carboxylic acid. Its structural formula is:



Piperacillin sodium

CAS: [59703-84-3] Molecular formula: $C_{23}H_{26}N_5NaO_7S$ MW: 539.54

Tazobactam sodium is a derivative of the penicillin nucleus. Chemically, tazobactam is a penicillanic acid sulfone. Its chemical name is sodium (2S-(2 α ,3 β ,5 α)-3-methyl-7-oxo-3-(1H1,2,3-triazol-1-ylmethyl)-4-thia-1-azabicyclo[3.2.0] heptane-2-carboxylic acid 4,4-dioxide. The chemical structure of tazobactam sodium is:



Tazobactam sodium

CAS: [89785-84-2] Molecular formula: $C_{10}H_{11}N_4NaO_5S$ MW: 322.28

PIPTAZ SANDOZ is available as a white to off-white sterile, cryodesiccated powder of piperacillin and tazobactam as the sodium salts packaged in glass bottles. 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 PIPTAZ SANDOZ formulation enhances and extends the antibiotic spectrum of piperacillin to include many β -lactamase producing bacteria normally resistant to it. Thus, PIPTAZ SANDOZ (piperacillin/tazobactam) combines the properties of a broad-spectrum antibiotic and a β -lactamase inhibitor.

Microbiology

PIPTAZ SANDOZ (piperacillin/tazobactam) 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 influenzae*.

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.

Susceptibility

Local information of 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 states¹.

Table 1. MIC 90 for 1,952 clinically significant isolates

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

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.

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 M11-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 hospitalized 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 and plasma levels

Mean plasma concentrations of piperacillin and tazobactam at steady state of the combination appear in Tables 2. 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 2. Plasma levels in adults after a thirty-minute intravenous infusion of piperacillin/tazobactam (steady state)

| PIPERACILLIN PLASMA LEVELS (µg/mL) | | | | | | |
|------------------------------------|--------|------|--------|------|------|------|
| Piperacillin/Tazobactam Dose | 30*min | 1 hr | 1.5 hr | 2 hr | 3 hr | 4 hr |
| 4 g/500 mg | 298 | 141 | 87 | 47 | 16 | 7 |
| TAZOBACTAM PLASMA LEVELS (µg/mL) | | | | | | |
| Piperacillin/Tazobactam Dose | 30*min | 1 hr | 1.5 hr | 2 hr | 3 hr | 4 hr |
| 4 g/500 mg | 33.8 | 17.3 | 11.7 | 6.8 | 2.8 | 1.3 |

*Completion of 30 minute infusion

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

Biotransformation

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

Excretion

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

Impaired renal function

The half-life of piperacillin and tazobactam increases with decreasing creatinine clearance. The increase is two-fold and four-fold for piperacillin and tazobactam, respectively, at creatinine clearance below 20 mL/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/12.5 mg/kg tazobactam (Table 3). 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 3. 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 | 382(15) | 539(29) | 3.3(24) | 0.28(32) | 1.3(16) |
| | 6-23 mo | 344(15) | 373(27) | 4.8(29) | 0.25(27) | 1.0(24) |
| | 2-5 y | 408(80) | 331(21) | 5.2(19) | 0.23(36) | 0.9(26) |
| | 6-12 y | 394(24) | 404(17) | 4.2(21) | 0.24(42) | 0.8(27) |
| Tazobactam 12.5 mg/kg | 2-5 mo | 43(49) | 63(32) | 3.6(28) | 0.32(31) | 1.3(15) |
| | 6-23 mo | 35(22) | 42(23) | 5.2(24) | 0.33(29) | 1.1(23) |
| | 2-5 y | 45(42) | 37(24) | 5.8(19) | 0.27(33) | 0.9(29) |
| | 6-12 y | 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 \geq 3200 µg/mL and 2500 µg/mL, respectively.

Carcinogenicity

Long term carcinogenicity studies of piperacillin and tazobactam in animals have not been performed.

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS

The product contains no excipients or preservatives.

6.2. INCOMPATIBILITIES

This medicinal product must not be mixed with other medicinal products except those mentioned in Section 6.6 Special precautions for disposal.

This product must not be mixed or coadministered with any aminoglycoside. The mixing of β -lactam antibiotics with an aminoglycoside *in vitro* can result in substantial inactivation of the aminoglycoside.

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

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

Due to chemical instability, piperacillin/tazobactam should not be used in solutions containing only sodium bicarbonate.

Lactated Ringer's (Hartmann's) solution is not compatible with piperacillin/tazobactam.

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

6.3. SHELF LIFE

Unopened container:

2 years.

After dilution or reconstitution:

Chemical and physical in-use stability has been demonstrated for 24 hours at 20-25°C and for 48 hours at 2-8°C.

From a microbiological point of view, once opened, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2-8°C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

6.4. SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5. NATURE AND CONTENTS OF CONTAINER

Packed in 100 mL bottle size (Type II) closed with rubber stopper (latex-free) and flip-off aluminium crimp caps

Pack size of 1 and 10 bottles per carton.

Not all pack sizes may be marketed.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL

No special requirements for disposal.

7. MEDICINE SCHEDULE

Prescription Only Medicine

8. SPONSOR

Novartis New Zealand Limited

PO Box 99102, Newmarket,
Auckland 1149

Telephone: 0800 354 335

9. DATE OF FIRST APPROVAL

09 Feb 2017

10. DATE OF REVISION OF THE TEXT

06/11/2019

SUMMARY TABLE OF CHANGES

| Section Changed | Summary of new information |
|------------------------|---|
| All | Minor editorial changes |
| 4.4 | Updated information to warning on severe cutaneous adverse reactions (SCAR) Addition of "seizure" as neurological complication in high-dose administrations Addition of paragraph "Paediatric population" |
| 4.8 | Addition of "haemolytic anaemia", "seizure" and "derilium". |