NEW ZEALAND DATA SHEET

1. PRODUCT NAME

Piperacillin/Tazobactam Eugia 4.0g/0.5 g powder for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 4 g/0.5 g single dose vial contains piperacillin sodium (4.170g) equivalent to 4 grams of piperacillin and tazobactam sodium (536.6mg) equivalent to 500 mg of tazobactam.

Pharmacotherapeutic group: Antibacterials for systemic use, Combined of penicillins inc. beta-lacatamase inhibitors; ATC code: J01C R05.

There are no excipients.

3. PHARMACEUTICAL FORM

Powder for injection

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Piperacillin/ Tazobactam Eugia 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 Piperacillin/ Tazobactam Eugia plus an aminoglycoside should be used.

8. Bone and joint infections

9. Polymicrobic infections: Piperacillin/ Tazobactam Eugia is indicated for polymicrobic infections including those where aerobic and anaerobic organisms are suspected (intraabdominal, skin and skin structure, upper and lower respiratory tract, gynaecological).

While Piperacillin/ Tazobactam Eugia is indicated only for the conditions listed above, infections caused by piperacillin susceptible organisms are also amenable to Piperacillin/ Tazobactam Eugia treatment due to its piperacillin content. Therefore, the treatment of mixed infections caused by piperacillin susceptible organisms and beta-lactamase producing organisms susceptible to Piperacillin/ Tazobactam Eugia 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 Piperacillin/ Tazobactam Eugia. Because of its broad-spectrum of activity against Gram-positive and Gram-negative aerobic and anaerobic

organisms as listed above, Piperacillin/ Tazobactam Eugia 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 Piperacillin/ Tazobactam Eugia 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 Piperacillin/ Tazobactam Eugia may be initiated before susceptibility test results are available.

Piperacillin/ Tazobactam Eugia 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, Piperacillin/ Tazobactam Eugia 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

Dose

Piperacillin/ Tazobactam Eugia 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 (Piperacillin/ Tazobactam Eugia) given every eight hours.

The total daily dose depends on the severity and localisation of the infection and can vary from 2 g piperacillin/0.25 g tazobactam to 4g piperacillin/0.5g tazobactam (Piperacillin/ Tazobactam Eugia) 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 Piperacillin/ Tazobactam Eugia 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 2.25 g to 4.5 g Piperacillin/ Tazobactam Eugia administered every six or eight hours.

Piperacillin/ Tazobactam Eugia 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 hour

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.

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/1 g/day Piperacillin/ Tazobactam Eugia. In addition, because haemodialysis removes 30%-50% of piperacillin in 4 hours, one additional dose of 2 g piperacillin/0.25 g tazobactam (Piperacillin/ Tazobactam Eugia) should be administered following each dialysis period. For patients with renal failure and hepatic insufficiency, measurement of serum levels of Piperacillin/ Tazobactam Eugia will provide additional guidance for adjusting dosage.

Children aged 2 to 12 years

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

Duration of therapy

In acute infections, treatment with Piperacillin/ Tazobactam Eugia 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 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.

Method of administration

Reconstitution directions

For intravenous use:

Diluents for Reconstitution:

- Sterile Water for Injections
- 0.9% Sodium Chloride Injection

- Dextrose 5% in Water
- Dextrose 5% in 0.9% Sodium chloride

When swirled constantly, reconstitution generally occurs within 5 to 10 minutes. The reconstituted solution should be withdrawn from the vial by syringe. When reconstituted as directed, the vial contents withdrawn by syringe will provide the labelled amount of Piperacillin/ Tazobactam Eugia. Solutions of Piperacillin/ Tazobactam Eugia prepared in this manner appear clear to slightly yellow in colour.

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

Vial Size (piperacillin/tazobactam)	Minimum volume of diluent to be added to vial
4.50 g (4 g/0.5 g)	20 mL

Administration directions

For intravenous use:

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.

Compatible Intravenous Diluents:

1. 0.9% Sodium Chloride for Injection.

2. Sterile Water for Injection.

3. Dextrose 5% in water.

4. Dextrose 5% in 0.9% Sodium chloride

4.3 Contraindications

The use of Piperacillin/ Tazobactam Eugia is contraindicated in:

• Patients with a history of allergic reactions to any of the penicillins and/or cephalosporins or Beta-lactamase inhibitors.

• Patients with hypersensitivity to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

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

Piperacillin/ Tazobactam Eugia should be given with caution to patients who have previously experienced signs and symptoms of allergy associated with a cephalosporin or penicillin 6 treatment. Past history of a severe allergic reaction to penicillin/cephalosporin is a contraindication to the use of Piperacillin/ Tazobactam Eugia. Before initiating therapy with any penicillin/cephalosporin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins or other allergens. If an allergic reaction occurs, Piperacillin/ Tazobactam Eugia should be discontinued and the appropriate therapy

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

Severe cutaneous adverse reactions (SCAR), such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalised exanthematous pustulosis (AGEP) have been reported in patients taking beta-lactam antibiotics. When SCAR is suspected, Piperacillin/ Tazobactam Eugia should be discontinued immediately and an alternative treatment should be considered.

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 Clostridioides 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 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).

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

Use in renal impairment

Due to its potential nephrotoxicity (see section 4.8), 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).

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 7 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).

Use with caution in the following circumstances

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

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

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

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

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

Check the following before use

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

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

The theoretical sodium content of each vial of Piperacillin/ Tazobactam Eugia is 2.84 mEq (65 mg) of sodium per gram of piperacillin which may increase a patient's overall sodium intake.

2.25 g vial: 130 mg sodium (5.65 mmol)

4.5 g vial: 260 mg sodium (11.31 mmol)

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 Piperacillin/ Tazobactam Eugia 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.

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 dark field examination should be obtained from patients with any suspected primary lesion and serological tests should be made for a minimum of 4 months.

Paediatric Population

Safety and efficacy of the use of Piperacillin/ Tazobactam Eugia 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 falsepositive 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 Eugia injection, who were subsequently found to be free of Aspergillus infection. Cross-reactions with non-Aspergillus polysaccharides and polyfuranoses with Bio-Rad Laboratories Platelia Aspergillus EIA test have been reported. Therefore, positive test results in patients receiving Piperacillin/ Tazobactam Eugia should be interpreted cautiously and confirmed by other diagnostic methods.

4.5 Interaction with other medicines and other forms of interaction

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

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). 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 Eugia and vancomycin.

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

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

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

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

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

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

During simultaneous administration of 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

Fertility

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

Pregnancy - Category B1

Adequate human studies on the use of Piperacillin/ Tazobactam Eugia 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 has been found to cross the placenta in rats. Pregnant women should be treated only if the expected benefit outweighs the possible risks to the pregnant woman and fetus.

Lactation

Adequate clinical studies on the use of Piperacillin/ Tazobactam Eugia during lactation or in breastfeeding women are not available. Low quantities of Piperacillin/ Tazobactam Eugia 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 effect on the ability to drive or use machines have been performed.

4.8 Undesirable effects

Piperacillin/ Tazobactam Eugia 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:

Body System	**Adverse Reaction Infections and infestations**
Common:	Candida infection†
Rare:	Pseudomembranous colitis
Blood and lymphatic system disorders	
Common:	Thrombocytopenia, anaemia†
Uncommon:	Leucopenia
Rare:	Agranulocytosis
Not known:	Pancytopenia†, neutropenia, haemolytic† anaemia†, thrombocytosis†, eosinophilia†
Immune system disorders	
Not known:	Anaphylactoid shock†, anaphylactic shock† anaphylactoid reaction†, anaphylactic reaction†, hypersensitivity†
Metabolism and nutrition disorders	
Uncommon:	Hypokalaemia
Nervous system disorders	
Common:	Headache
Uncommon:	Seizure†
Not known:	Dizziness
Vascular disorders	
Uncommon:	Hypotension, phlebitis, thrombophlebitis, flushing
Respiratory, thoracic and mediastinal disorders	
Body System	**Adverse Reaction**
Rare:	Epistaxis
Not known:	Eosinophilic pneumonia†
Gastrointestinal disorders	
Very common:	Diarrhoea

Common :	Abdominal pain, vomiting, constipation, nausea, dyspepsia
Rare:	Stomatitis
Not Known:	Bloody diarrhoea, dry mouth
Hepatobiliary disorders	
Not known:	Hepatitis†, jaundice
Skin and subcutaneous tissue disorders	
Common:	Rash, pruritus
Uncommon:	Erythema multiforme†, urticaria, rash maculopapular†
Rare:	Toxic epidermal necrolysis (TEN)†
Not known:	Stevens-Johnson syndrome (SJS)†, drug reaction with eosinophilia and systemic symptoms (DRESS)†, acute generalised exanthematous pustulosis (AGEP)†, dermatitis exfoliative†, dermatitis bullous, purpura, eczema, hyperhidrosis, cutaneous vasculitis
Musculoskeletal and connective tissue disorders	
Uncommon:	Arthralgia, myalgia
Not known:	Muscular weakness, prolonged muscle relaxation
Renal and urinary disorders	
Not known:	Renal failure, tubulointerstitial nephritis†
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
Body System	**Adverse Reaction**
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 of suspected adverse reactions

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://pophealth.my.site.com/carmreportnz/s/.

4.9 Overdose

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

No specific antidote is known. 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

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 J3 -lactamases, including the plasmid and chromosomally mediated enzymes that commonly cause resistance to penicillins. The presence of tazobactam in the formulation enhances and extends the antibiotic spectrum of piperacillin to include many J3-lactamase producing bacteria normally resistant to it. Thus, combines the properties of a broad spectrum antibiotic and a J3-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 harboring 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 βlactamases. 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 harboring β-lactamases that, when tested as enzyme preparations, are less inhibited by tazobactam and other inhibitors: tazobactam does not induce chromosomally mediated βlactamases 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 15 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 βlactam antibiotics is determined by altered PBPs. As indicated above, there are some βlactamases 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 influenza

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 pneumonia

† 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).

Susceptibility

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.

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 states.

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

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

The CLSI interpretive criteria for susceptibility testing of piperacillin/tazobactam are listed in the following table:

CLSI Susceptibility Interpretive Criteria for Piperacillin/ Tazobactum						
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
P**se**udomonas aeruginosa	≤16	32-64	≥128	≥21	15-20	≤14
Certain other non-fastidious gram-negative bacilli[c]	-	-	-	≥21	18-20	≤17
Haemophilus influenza and Haemophilus parainfluenzae	≤1	-	≥2	≥21	-	-
Anaerobes[d]	≤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.

Standardised susceptibility test procedures require the use of quality control microorganisms to control the technical aspects of the test 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.

Organisms and quality control ranges for piperacillin/tazobactam to be utilized with CLSI methodology and susceptibility test interpretive criteria are listed in the following table:

Quality Control Rangers for Piperacillin/ Tazobactum to be Used in Cinjunction 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 influenza ATCC 49247	0.06-0.5	33-38
Staphylococcus aureus ATCC 29213	0.25-2	-
Staphylococcus aureus ATCC 29213	-	27-36
Staphylococcus aureus ATCC 25923	0.12-0.5[a]	-
Bacteroides fragilis ATCC 25285	1-4	
Enterococcus faecalis ATCC 29212	4-16[a]	
Bacteroides thetaiotaomicron ATCC 29741	4-16[a]	-
Clostridiodes (formerly Clostridium difficile ATCC 700057	4-16[a]	
Eggerthella lenta (foemerly Eubacterium lentum) ATCC 43055	4-16[a]	

Source: Clinica and laboratory Standards Institute. Performance standards for Antimicrobial Susceptibility Testing. CLSI document MI00ED29. CLSI, Wayne, PA, 2019.
a Agar dilution only.

Clinical efficacy and safety

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 in Version: pfdtazev10820 Supersedes: pfdtazev10719 Page 19 of 23 regard to 30day 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%) randomized 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%), randomized 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. This study was not sponsored by Pfizer.

Paediatric population

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 (Piperacillin/ Tazobactam Eugia) administered intravenously was at least as effective as cefotaxime plus metronidazole in the treatment of children aged 2 to 12 years with severe IAIs.

5.2 Pharmacokinetic properties

Distribution

Mean plasma concentrations of piperacillin and tazobactam at steady state of the combination appear in Table 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 4 g/500 mg	30*min 298	1 hr 141	1.5 hr 87	2 hr 47	3 hr 16	4 hr 7
TAZOBACTAM PLASMA LEVELS (µg/mL)						
Piperacillin/Tazobactam Dose 4 g/500 mg	30*min 33.8	1 hr 17.3	1.5 hr 11.7	2 hr 6.8	3 hr 2.8	4 hr 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.

Elimination

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.

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.

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.

Paediatric population

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 (Cmax) 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 tg/mL to 16 tg/mL commonly found in intraabdominal infections in children.

Table 3. Piperacillin and tazobactam pharmacokinetics in children (cv%) following single doses

Dose	Patient age	Cmax (mg/L)	AUC (mg.h/L)	CL (mL/min/kg)	Vss (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)	3.9(36)	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 3200 tg/mL and 2500 tg/mL, respectively.

Carcinogenicity

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipient

Sodium Hydrogen Carbonate

6.2 Incompatibilities

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

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

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

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store below 25°C.

The reconstituted/diluted solutions of drug product are physically compatible and chemically stable over a period of 24 hours at controlled room temperature (25°C) and 48 hours at 2 – 8°C. For compatible solvents see section 4.2.

From a microbiological point of view, the reconstituted and diluted solutions 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 12 hours at 2-8°C, unless reconstitution and dilution have taken place in controlled and validated aseptic conditions.

6.5 Nature and contents of container

Piperacillin/ Tazobactam Eugia 4g/0.5g Powder for Injection

Type-I clear glass vials of 48 mL stoppered with grey colour bromo butyl rubber stopper and sealed with red colour Polypropylene and Aluminum flip off seal.
Pack sizes: 1 and 10 vials.

*Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription

8. SPONSOR

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9. DATE OF FIRST APPROVAL

22 October 2026

10. DATE OF REVISION OF THE TEXT

NA

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
N/A	New product registration