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. 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 and 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-AFT 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.

The following compatibility information does not apply to the piperacillin/tazobactam formulation not containing EDTA.

In circumstances where co-administration is preferred, the reformulated piperacillin/tazobactam containing EDTA supplied in vials is compatible for simultaneous co- administration via Y-site infusion only with the following aminoglycosides under the following conditions:

Aminoglycoside	Piperacillin/ tazobactam (grams) dose	Piperacillin/ tazobactam Diluent Volume (mL)	Aminoglycoside Concentration Range‡ (mg/mL)	Acceptable Diluents
Amikacin	2.25,3.375,4.5	50,100,150	1.75 – 7.5	0.9% sodium chloride or 5% dextrose
Gentamicin	2.25,3.375,4.5	100,150	0.7 – 3.32	0.9% sodium chloride

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

Compatibility of piperacillin/tazobactam with other aminoglycosides has not been established. Only the concentration and diluents for amikacin and gentamicin with the dosages of piperacillin/tazobactam listed in the above table 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.

Method of administration

Reconstitution directions

For intravenous use only

Diluents for Reconstitution:

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

- Sterile Water for Injections
- 0.9% Sodium Chloride Injection
- Glucose 5% injection

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

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

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

Compatible Intravenous Diluents:

1. Saline
2. Sterile Water for Injection.*
3. Glucose 5%.
4. Dextran 6% in Saline.
5. Hartmann's solution for injection (only compatible with piperacillin/tazobactam and is compatible for co-administration via a Y-site).

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

4.3 Contraindications

The use of PipTaz-AFT is contraindicated in:

- Patients with a history of allergic reactions to any of the penicillins and/or cephalosporins or β-lactamaase 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.

PipTaz-AFT 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-AFT. 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-AFT 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, PipTaz-AFT 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 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 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 non-susceptible organisms, including fungi. Patients should be carefully monitored during therapy. If superinfection 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 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 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 PipTaz-AFT 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-AFT.

Check the following before use

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

For patients with renal impairment and/or hepatic insufficiency, measurement of serum levels of piperacillin will provide guidance for adjusting dosage. In patients with creatinine clearance ≤ 40 mL/min and dialysis patients (haemodialysis and CAPD), the intravenous dose should be adjusted to the degree of renal function impairment. (See 4.2 Dose and method of administration).

PipTaz-AFT contains 214 mg of sodium per vial, which may increase a patient's overall sodium intake.

Periodic electrolyte determinations should be made in patients with low potassium reserves and the possibility of hypokalaemia should be kept in mind with patients who have potentially low potassium reserves and who are receiving cytotoxic therapy or diuretics. Because of its poor penetration into the CSF, piperacillin is not advised in the treatment of meningitis and brain abscess. Antimicrobials used in high doses for short periods to treat gonorrhoea may mask or delay symptoms of incubating syphilis. Therefore, prior to treatment, patients with gonorrhoea should also be evaluated for syphilis. Specimens for darkfield examination should be obtained from patients with any suspected primary lesion and serological tests should be made for a minimum of four months.

Paediatric Population

Safety and efficacy of the use of PipTaz-AFT 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 piperacillin/tazobactam 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 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 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 could produce the same phenomenon if given along with vecuronium. Due to their similar mechanism of action, it is expected that the neuromuscular blockade produced by any of the non- depolarising muscle relaxants could be prolonged in the presence of piperacillin.

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

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

During simultaneous administration of 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 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 during lactation or in breastfeeding women are not available. Low quantities of piperacillin/ tazobactam 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 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 postmarketing 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://nzphvc.otago.ac.nz/reporting/.

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

Microbiology

PipTaz-AFT is active against most strains of the following β-lactamase producing and non β-lactamase producing microorganisms:

Gram-negative bacteria

Escherichia coli, Citrobacter spp., Klebsiella spp. (including K. pneumoniae), Enterobacter spp., (including E. cloacae), Proteus vulgaris, Proteus mirabilis, Serratia spp. (including S. marcescens), Pseudomonas aeruginosa and other Pseudomonas spp., Neisseria gonorrhoeae, Neisseria meningitidis, Moraxella catarrhalis, Acinetobacter spp., Haemophilus influenza.

Gram-positive bacteria

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

Anaerobic bacteria

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

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 states[1].

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 latest NCCL references are:

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

For anaerobes:

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

Clinical efficacy and safety

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 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	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.

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 (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)	$T_{½}$ (h)
Piperacillin 100 mg/kg	2-5 mo 6-23 mo 2-5 y 6-12 y	382(15) 344(15) 408(80) 394(24)	539(29) 373(27) 331(21) 404(17	3.3(24) 4.8(29) 5.2(19) 4.2(21)	0.28(32) 0.25(27) 0.23(36) 0.24(42)	1.3(16) 1.0(24) 0.9(26) 0.8(27)
Tazobactam 12.5 mg/kg	2-5 mo 6-23 mo 2-5 y 6-12 y	43(49) 35(22) 45(42) 45(25)	63(32) 42(23) 37(24) 57(27)	3.6(28) 5.2(24) 5.8(19) 3.9(36)	0.32(31) 0.33(29) 0.27(33) 0.28(36)	1.3(15) 1.1(23) 0.9(29) 1.3(57)

5.3 Preclinical safety data

Genotoxicity

Mutagenicity studies with piperacillin and tazobactam showed no evidence of genotoxicity in assays for chromosomal and DNA damage. One assay for gene mutations (Mouse lymphoma assay) was weakly positive at tazobactam and piperacillin concentrations ≥3200 µg/mL and 2500 µg/mL, respectively.

Carcinogenicity

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium bicarbonate

6.2 Incompatibilities

PipTaz-AFT 4 g/0.5 g should not be mixed with other drugs in a syringe or infusion bottle since compatibility has not been established. Whenever PipTaz-AFT 4 g/0.5 g is used concurrently with another antibiotic, the drugs must be administered separately.

Because of chemical instability, PipTaz-AFT 4 g/0.5 g should not be used with solutions containing only sodium bicarbonate or having a pH in the basic range.

PipTaz-AFT 4 g/0.5 g should not be added to blood products or albumin hydrolysates.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store below 25 °C.
PipTaz-AFT 4 g/0.5 g must be reconstituted with not less than 20 mL of diluent prior to use.

From a microbiological point of view, the diluted solution should be used immediately. To reduce microbiological hazard, use as soon as practicable after dilution. If storage is necessary, hold at 2- 8 °C for not more than 24 hours.

PipTaz-AFT 4 g/0.5 g contains no antimicrobial preservative. For single use in one patient only. Discard any remaining residue.

6.5 Nature and contents of container

PipTaz-AFT 4 g/0.5 g powder for injection is available as a vial containing piperacillin sodium equivalent to 4 g piperacillin and tazobactam sodium equivalent to 500 mg tazobactam.

It is available in packs of 1 and 10 vials.

6.6 Special precautions for disposal and other handling

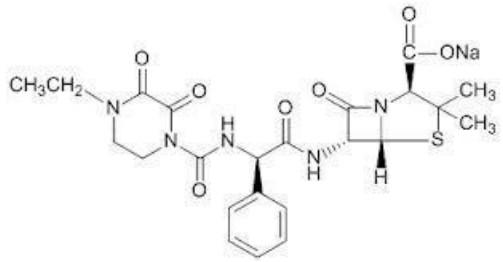
Any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 Physicochemical properties

Piperacillin sodium

Chemical structure

Piperacillin sodium has the chemical name 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



The empirical formula is $C_{23}H_{26}N_5NaO_7S$.

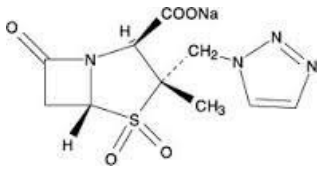
The molecular weight is 539.54.

CAS number
59703-84-3

Tazobactam sodium

Chemical structure

Tazobactam sodium has the chemical name sodium (2S-(2α,3β,5α)-3-methyl-7-oxo-3-(1H-1,2,3- triazol-1-ylmethyl)-4-thia-1-azabicyclo[3.2.0] heptane-2-carboxylic acid 4,4-dioxide.



The empirical formula is $C_{10}H_{11}N_4O_5S$.

The molecular weight is 322.28.

CAS number
89785-84-2

7. MEDICINE SCHEDULE

Prescription

8. SPONSOR

AFT Pharmaceuticals Limited
PO Box 33-203
Auckland 0740, New Zealand.

9. DATE OF FIRST APPROVAL

March 2015

10. DATE OF REVISION OF THE TEXT

Reference

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

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
All	Reformatted to align with the revised format and with the reference product