New Zealand Data Sheet

1. PRODUCT NAME

Pipetam® 4g/0.5g powder for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains piperacillin (as sodium salt) equivalent to 4 g and tazobactam (as sodium salt) equivalent to 0.5 g.
Each vial of Pipetam® 4g/0.5g contains 8.99 mmol (206.6 mg) of sodium
For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Pipetam® vials: Type I glass vials containing a white to off-white sterile powder for reconstitution.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Pipetam® is indicated for the treatment of the following systemic and/or local bacterial infections in which susceptible organisms have been detected or are suspected in adults and children over 2 years of age *(see sections 4.2 and 5.1):*

Adults and adolescents

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 PIPETAM plus an aminoglycoside should be used.
8. Bone and joint infections
9. Polymicrobic infections: including those where aerobic and anaerobic organisms are suspected (intra-abdominal, skin and skin structure, upper and lower respiratory tract, gynaecological).

Children 2 to 12 years of age

Treatment of serious intra-abdominal infections.
Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2. Dose and method of administration

The dose and frequency depends on the severity and localisation of the infection. The usual routes of administration are by slow intravenous injection or intravenous infusion.

Dose

Adults and adolescents

Infections:

The usual intravenous dosage for adults and children with normal renal function is Pipetam®, 4 g piperacillin/0.5g tazobactam, given every eight hours. Dose can vary from Pipetam®, 2 g piperacillin/0.25g tazobactam to 4g piperacillin /0.5g tazobactam administered every six, eight or twelve hours.

In neutropenic patients, the usual intravenous dosage for adults with normal renal function is 4 g piperacillin/0.5 g tazobactam given every eight hours, 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/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.

Paediatric population-

Hospitalised children with intra-abdominal infection- aged 2 to 12 years

Children ≤ 40kg with normal renal function: the recommended dosage is 100 mg piperacillin/12.5 mg tazobactam per kilogram every 8 hours.

Children ≥ 40kg with normal renal function: follow the adult dose guidance i.e. 4 g piperacillin/0.5g tazobactam every 8 hours

Children with renal impairment: The pharmacokinetics have not been studied. Each patient must be monitored closely for signs of drug toxicity. Drug dose and interval should be adjusted accordingly.

Hospitalised children aged <2 years

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

Renal impairment

In patients with renal insufficiency, the intravenous dose should be adjusted to the degree of actual renal function impairment. The suggested daily doses are as per Table 1 below:

Creatinine Clearance (mL/min)	Recommended Pipetam® Dosage
> 40	No dosage adjustments necessary
20-40	4 g piperacillin/0.5 g tazobactam Every 8 hours.
< 20	4 g piperacillin/0.5 g tazobactam every 12 hours

For patients on haemodialysis, the maximum daily dose 8 g piperacillin/ 1g tazobactam per 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/ tazobactam will provide additional guidance for adjusting dosage *see section 5.2*.

Treatment duration

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/symptoms or the fever.

Method of Administration

For instructions on reconstitution of the medicinal product before administration, *see section 6.6*

Pipetam® may be administered either by slow intravenous injection over a period of 3 to 5 minutes or as a slow intravenous infusion over 20 to 30 minutes.

4.3. Contraindications

Pipetam® is contraindicated in patients who have had previous experience of a major allergy or anaphylaxis to a cephalosporin or penicillin.

Pipetam® is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients listed in section 6.1

4.4. Special warnings and precautions for use

Pipetam® should be given with caution to patients who have experienced symptoms of allergy associated with a cephalosporin or penicillin. Serious and occasionally fatal hypersensitivity (anaphylactoid including shock) reactions have been reported in patients on penicillin therapy, although anaphylaxis is more frequent following parenteral therapy. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity and/or a history of sensitivity to multiple allergens. Before commencing therapy with any penicillin, careful enquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins or other allergens. If an allergic reaction occurs; appropriate therapy should be instituted, Pipetam® therapy discontinued and other emergency measures given.

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

Serious skin reactions, such as Stevens-Johnson syndrome and toxic epidermal necrolysis, have been reported in patients receiving Pipetam®. If patients develop a skin rash they should be monitored closely and Pipetam® discontinued if lesions progress.

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 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 may occur when high doses are administered, especially in patients with impaired renal function.

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.

Hypokalaemia may occur in patients with low potassium reserves or who are receiving concomitant medicinal products that may lower potassium levels; periodic electrolyte determinations may be performed in such patients.

Pipetam® contains 8.99 mmol (206.6 mg) of sodium per vial of powder for solution for infusion. To be taken into consideration by patients on a controlled sodium diet

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.

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.

4.5. Interaction with other medicines and other forms of interaction

Oestrogen Containing Oral Contraceptives

The efficacy of oral contraceptives may be impaired under concomitant administration of Pipetam ®, which may result in unwanted pregnancy. Women taking oral contraceptives should be aware of this and should be informed about alternative methods of contraception.

Methotrexate

Penicillins reduce the excretion of methotrexate thereby increasing the risk of methotrexate toxicity.

Interference with diagnostic tests

Penicillins may interfere with:

-Urinary glucose test-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.

-Coomb's tests

-Tests for urinary or serum proteins

-Tests which use bacteria e.g.Guthrie test.
- Bio-Rad Laboratories Platelia Aspergillus EIA tests may lead to false-positive results for patients receiving Tazocin. 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.

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

Vancomycin
No kinetic interaction is found between Piperacillin/tazobactam and vancomycin.

Aminoglycosides
Concurrent administration of tobramycin with Pipetam ®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.

For information related to the administration of piperacillin / tazobactam with aminoglycosides please refer to section 6.2

Non-depolarising muscle relaxants
Piperacillin when used concomitantly with vecuronium has been implicated in the prolongation of the neuromuscular blockade of vecuronium. Pipetam ®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.

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

Pregnancy

Adequate human studies on the use of Piperacillin/tazobactam during pregnancy are not available. Limited studies with piperacillin alone in rats and mice revealed no teratogenic effects or harm to the foetus. Studies with tazobactam (doses up to 3000 mg/kg IV) or tazobactam and piperacillin (doses up to 750 mg/kg and 3000 mg/kg IV) in mice showed no evidence of teratogenicity or harm to the foetus. Studies in rats at these dose levels showed no evidence of teratogenicity though maternal toxicity, in the form of decreased weight gain, was noted at the dose levels tested. Piperacillin 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 foetus.

Breast-feeding

Adequate clinical studies on the use of Piperacillin/tazobactam during breast-feeding are not available. Trace quantities of penicillin 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.

Fertility

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

4.7. Effects on ability to drive and use machines

During treatment with Pipetam®, undesirable effects may occur (e.g. allergic reactions, dizziness, convulsions) which may influence the ability to drive and use machines. Patients should be cautious when driving or operating machinery.

4.8. Undesirable effects

The overall incidence of Pipetam ® 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.

The following convention has been used for the classification of frequency:-
Very common ≥ 10%, common ≥ 1% and < 10%, uncommon ≥ 0.1% and < 1%, rare ≥ 0.01% and <0.1%, very rare <0.01%. Frequency unknown: frequency could not be accurately estimated from clinical studies

The following Table 2 of suspected undesirable effects is based on clinical trials and/or spontaneous post-marketing reporting rates:

Infections and infestations	
Candidal superinfection	Uncommon
Blood and lymphatic system disorders	
Leucopenia, neutropenia, thrombocytopenia	Uncommon
Anaemia, bleeding manifestations (including purpura, epistaxis, bleeding time prolonged), eosinophilia, haemolytic anaemia	Rare
Agranulocytosis, Coombs direct test positive, Pancytopenia, prolonged partial thromboplastin time, prothrombin time prolonged,disturbed thrombocyte function, thrombocytosis	Very rare
Immune system disorders	
Hypersensitivity reaction	Uncommon
Anaphylactic/anaphylactoid reaction (including shock)	Rare
Metabolism and Nutrition Disorders	
Blood albumin decreased, blood glucose decreased, blood total protein decreased, hypokalaemia	Very rare
Nervous system disorders	
Headache, insomnia	Uncommon
Hallucination, dizziness, dry mouth	Frequency unknown
Vascular disorders	
Hypotension, phlebitis, thrombophlebitis	Uncommon
Flushing	Rare
Gastrointestinal body system	
Diarrhoea, nausea, vomiting	Common
Constipation, dyspepsia, jaundice, stomatitis	Uncommon
Abdominal pain, pseudomembranous colitis	Rare
Bloody diarrhoea	Frequency unknown
Hepatobiliary	
Alanine aminotransferase increased, aspartate aminotransferase increased	Uncommon
Bilirubin increased, blood alkaline phosphatase increased, gamma-glutamyltransferase increased, hepatitis	Rare

Skin and subcutaneous tissue disorders	
Rash	Common
Pruritis, urticaria	Uncommon
Bullous dermatitis, erythema multiforme and cutaneous vasculitis	Rare
Stevens-Johnson Syndrome, toxic epidermal necrolysis	Very rare
Increased sweating, eczema, exanthema	Frequency unknown
Musculoskeletal, Connective tissue and bone disorders	
Arthralgia	Rare
Myalgia, Muscular weakness, prolonged muscle relaxation	Frequency unknown
Renal and urinary disorders	
Blood creatinine increased	Uncommon
Interstitial nephritis, renal failure	Rare
Blood urea nitrogen increased	Very rare
General disorders and administration site conditions	
Fever, injection site reaction	Uncommon
Rigors	Rare
Oedema, tiredness, fatigue	Frequency unknown

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

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 reactions https://nzphvc.otago.ac.nz/reporting/

4.9. Overdose

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 doses. Patients may experience neuromuscular excitability or convulsions if higher than recommended doses are given intravenously (particularly in the presence of renal failure).

Treatment

In the event of an overdose, piperacillin / tazobactam treatment should be discontinued. Treatment should be supportive and symptomatic according to the

patient's clinical presentation. No specific antidote is known, however, 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 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic Group: BETA-LACTAM ANTIBACTERIALS, PENICILLINS- Beta-Combinations of penicillins, incl. beta-lactamase inhibitors

ATC code J01CR05

Mechanism of action

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

Microbiology

Piperacillin/tazobactam is active against most strains of the following ß-lactamase producing and non ß-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.

Table 3 MIC_{90} for 1,952 clinically significant isolates

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

The 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

5.2. Pharmacokinetic properties

Absorption: Mean plasma concentrations of Pipetam ® at steady state of the combination appear in the table below. Peak of Pipetam ® plasma concentrations are attained immediately after completion of an intravenous infusion. When given with tazobactam, piperacillin plasma levels are similar to those attained when equivalent doses of piperacillin are administered alone.

Table 4 Plasma levels in adults after a thirty-minute intravenous infusion of piperacillin/tazobactam (steady state)

	Time (hrs) after completion of 30 minutes intravenous infusion of Pipetam ® 4g/0.5g dose					
	0.5 hrs *	1 hrs	1.5 hrs	2 hrs	3 hrs	4 hrs
Piperacillin plasma levels (µg/mL)	298	141	87	47	16	7
Tazobectam plasma levels (µg/mL)	33.8	17.3	11.7	6.8	2.8	13
* Completion of 30 minute infusion						

Distribution: 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. Distribution into cerebrospinal fluid is poor, hence, piperacillin is not advised in the treatment of meningitis and brain abscess.

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

Elimination: 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 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.

Special populations

Renal impairment: The half-life Pipetam ® 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.*

Hepatic impairment: 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- 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 4).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 µg/mL to16 µg/mL commonly found in intra-abdominal infections in children.

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

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.

5.3. Preclinical safety data

Long term carcinogenicity studies of Piperacillin/tazobactam in animals have not been performed. 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. Piperacillin and tazobactam did not affect the fertility of male or female rats.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

None.

6.2. Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6

Pipetam ® should not be mixed with other drugs in a syringe or infusion bottle since compatibility has not been established.

Whenever Pipetam ® is used concurrently with another antibiotic e.g. aminoglycosides, the drugs must be administered separately.

The mixing of Pipetam ® with an aminoglycoside can result in substantial inactivation of the aminoglycoside. 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.

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

Pipetam ® should not be added to blood products or albumin hydrolysates

6.3. Shelf life

Un-reconstituted dry powder Injection Vials 24 months
Reconstituted/Diluted solution: When prepared under aseptic conditions chemical and physical in use stability has been demonstrated for 5 hours at 20-25°C and for

24 hours at 2-8°C. However, microbiological point of view must be considered and the injection should be prepared immediately before use and any unused solution discarded.

6.4. Special precautions for storage

Store the unprepared Pipetam ® Vials at or below 25°C and protect from light and moisture

6.5. Nature and contents of container

Pipetam ® is supplied in type I glass, 50mL vials with 32 mm bromothymol rubber stopper containing 4g / 0.5g piperacillin/tazobactam for injection in packs of 1 or 10 vials

6.6. Special precautions for disposal and other 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

Diluents for Reconstitution:
Sterile Water for Injections *
Sodium Chloride solution 9 mg/ml (0.9%)
Dextrose solution 5 mg/ml (5%)

Preparation:

Each vial of Pipetam® 4g/0.5g should be reconstituted with a minimum volume of 20mL of the above diluents. [Maximum recommended volume of Sterile Water for Injection per dose is 50 mL]

Shake the contents until dissolved. When swirled constantly, reconstitution generally occurs within 5 to 8 minutes

The reconstituted solution may be further diluted to the desired volume (e.g. 50 mL to 150 mL) with one of the following compatible diluents: 0.9% sodium chloride for injection or Dextrose solution 5 mg/ml (5%)

Displacement value is 3.5 ml.

7. MEDICINE SCHEDULE

Prescription Medicine.

8. SPONSOR

Douglas Pharmaceuticals Ltd
P O Box 45 027
Auckland 0651
New Zealand
Phone: (09) 835 0660

9. DATE OF FIRST APPROVAL

14 March 2013

10. DATE OF REVISION OF THE TEXT

19 May 2017

Summary table of changes

Section Changed	Summary of new information
2	Amended sodium content
4.3	Added contraindication in patients with previous allergy and hypersensitivity to excipients as requested by Medsafe
4.4	Added caution to patients with previous allergy and hypokalaemia/ hypernatraemia statement as requested by Medsafe
4.5	Oral contraceptive interactions statement added as well as interference with diagnostic tests section as requested by Medsafe
4.6	Breast-feeding statement added; fertility statement added as requested by Medsafe
4.7	Added statement under effects on ability to drive and use machines as requested by Medsafe
4.8	Cutaneous vasculitis added as an adverse event
4.9	Poison Centre contacts added