

PRODUCT MONOGRAPH

Pr Piperacillin and Tazobactam for Injection

Piperacillin and Tazobactam Powder for Injection

Lyophilized Powder for Injection

Manufacturer's Standard

Piperacillin 2 g (as piperacillin sodium) and Tazobactam 0.25 g (as tazobactam sodium) per vial
Piperacillin 3 g (as piperacillin sodium) and Tazobactam 0.375 g (as tazobactam sodium) per vial
Piperacillin 4 g (as piperacillin sodium) and Tazobactam 0.5 g (as tazobactam sodium) per vial
Piperacillin 12 g (as piperacillin sodium) and Tazobactam 1.5 g (as tazobactam sodium) per vial
Piperacillin 36 g (as piperacillin sodium) and Tazobactam 4.5 g (as tazobactam sodium) per vial

Antibiotic/ β -lactamase Inhibitor

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PrPIPERACILLIN AND TAZOBACTAM FOR INJECTION

Piperacillin Sodium/Tazobactam Sodium

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intravenous	Lyophilized Powder for Injection 2.25g/vial (2g piperacillin as piperacillin sodium, 0.25g tazobactam as tazobactam sodium) 3.375g/vial (3g piperacillin as piperacillin sodium, 0.375g tazobactam as tazobactam sodium) 4.5g/vial (4g piperacillin as piperacillin sodium, 0.50g tazobactam as tazobactam sodium) 13.5g/vial (12g piperacillin as piperacillin sodium, 1.50g tazobactam as tazobactam sodium) 40.5g/vial (36g piperacillin as piperacillin sodium, 4.5g tazobactam as tazobactam sodium)	There are no clinically relevant nonmedicinal ingredients. <i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>

INDICATIONS AND CLINICAL USE

Piperacillin and Tazobactam for Injection (piperacillin sodium/tazobactam sodium) is indicated for the treatment of patients with systemic and/or local bacterial infections, caused by piperacillin resistant, piperacillin/tazobactam susceptible, β -lactamase producing strains of the designated microorganisms in the specified conditions listed below:

a) INTRA-ABDOMINAL INFECTIONS

Appendicitis (complicated by rupture or abscess) and peritonitis caused by piperacillin resistant, β -lactamase producing strains of *Escherichia coli* or members of the *Bacteroides fragilis* group.

b) SKIN AND SKIN STRUCTURE INFECTIONS

Uncomplicated and complicated skin and skin structure infections, including cellulitis, cutaneous abscess, acute ischemic/diabetic foot infections caused by piperacillin resistant β -lactamase producing strains of *Staphylococcus aureus* (not methicillin-resistant strains).

c) GYNECOLOGICAL INFECTIONS

Postpartum endometritis or pelvic inflammatory disease caused by piperacillin resistant, β -lactamase producing strains of *Escherichia coli*.

d) COMMUNITY-ACQUIRED LOWER RESPIRATORY TRACT INFECTIONS

Community-acquired pneumonia (moderate severity only) caused by piperacillin resistant, β -lactamase producing strains of *Haemophilus influenzae*.

e) NOSOCOMIAL PNEUMONIA

Nosocomial pneumonia (moderate to severe) caused by piperacillin-resistant, β -lactamase producing strains of *Staphylococcus aureus* and by piperacillin/tazobactam-susceptible *Acinetobacter baumannii*, *Haemophilus influenzae*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*. Nosocomial pneumonia caused by *P. aeruginosa* should be treated in combination with an aminoglycoside (see **DOSAGE AND ADMINISTRATION**).

While Piperacillin and Tazobactam for Injection is indicated only for the conditions listed above, infections caused by piperacillin susceptible organisms are also amenable to Piperacillin and Tazobactam for Injection treatment due to its piperacillin content. The tazobactam component of this combination product does not decrease the activity of the piperacillin component against piperacillin susceptible organisms. Therefore, the treatment of polymicrobial infections caused by piperacillin susceptible organisms and β -lactamase producing organisms susceptible to Piperacillin and Tazobactam for Injection should not require the addition of another antibiotic.

Piperacillin and Tazobactam for Injection may be useful as presumptive therapy in the indicated conditions prior to identification of causative organisms because of its broad spectrum of bactericidal activity against gram-positive and gram-negative aerobic and anaerobic organisms.

Appropriate cultures should usually be performed before initiating antimicrobial treatment in order to isolate and identify the organisms causing infection and to determine their susceptibility to Piperacillin and Tazobactam for Injection. Antimicrobial therapy should be adjusted, if appropriate, once results of culture(s) and antimicrobial susceptibility testing are known.

Geriatrics (> 65 years of age):

Patients over 65 years of age are not at an increased risk of developing adverse effects solely because of age. However, dosage should be adjusted in the presence of renal insufficiency (see **WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics** and **DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment, Renal Insufficiency**).

Pediatrics (< 12 years of age):

Safety and efficacy in children below the age of 12 years have not been established (see **WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics**).

CONTRAINDICATIONS

The use of Piperacillin and Tazobactam for Injection (piperacillin sodium/tazobactam sodium) is contraindicated in:

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section.
- Patients with a history of allergic reactions to any of the penicillins and/or cephalosporins or β -lactamase inhibitors.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- Serious and occasionally fatal hypersensitivity (anaphylactoid reaction, anaphylactic reaction, anaphylactoid shock, anaphylactic shock) reactions have been reported in individuals receiving therapy with penicillins. These reactions are more apt to occur in individuals with a history of sensitivity to multiple allergens. There have been reports of individuals with a history of penicillin hypersensitivity who have experienced severe hypersensitivity reactions when treated with cephalosporins.
- Before initiating therapy with Piperacillin and Tazobactam for Injection (piperacillin sodium/tazobactam sodium), careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins or other allergens. If an allergic reaction occurs during therapy with Piperacillin and Tazobactam for Injection, the antibiotic should be discontinued and appropriate therapy instituted. Serious anaphylactoid reactions require immediate emergency treatment with epinephrine, oxygen and intravenous steroids and airway management, including intubation, should also be administered as indicated.

General

As with other semisynthetic penicillins, piperacillin therapy has been associated with an increased incidence of fever and rash in cystic fibrosis patients.

Because of chemical instability, Piperacillin and Tazobactam for Injection should not be used for intravenous administration with solutions containing only sodium bicarbonate (see **DOSAGE AND ADMINISTRATION**, **Administration**, **Reconstitution**).

Piperacillin and Tazobactam for Injection should not be added to blood products or albumin hydrolysates.

Use of Piperacillin and Tazobactam for Injection with other drugs may lead to drug-drug interactions (see **DRUG INTERACTIONS**, **Drug-Drug Interactions**).

Ability to Drive and use Machines

No studies on the effect of ability to drive or use machines have been performed.

Carcinogenesis and Mutagenesis

Long-term carcinogenicity studies in animals have not been conducted with piperacillin/tazobactam, piperacillin, or tazobactam (see **TOXICOLOGY**).

Gastrointestinal

***Clostridium difficile*-Associated Disease**

Clostridium difficile-associated disease (CDAD) has been reported with use of many antibacterial agents, including piperacillin and tazobactam for injection. CDAD may range in severity from mild diarrhea to fatal colitis. It is important to consider this diagnosis in patients who present with diarrhea, or symptoms of colitis, pseudomembranous colitis, toxic megacolon, or perforation of colon subsequent to the administration of any antibacterial agent. CDAD has been reported to occur over 2 months after the administration of antibacterial agents.

Treatment with antibacterial agents may alter the normal flora of the colon and may permit overgrowth of *Clostridium difficile*. *Clostridium difficile* produces toxins A and B, which contribute to the development of CDAD. CDAD may cause significant morbidity and mortality. CDAD can be refractory to antimicrobial therapy.

If the diagnosis of CDAD is suspected or confirmed, appropriate therapeutic measures should be initiated. Mild cases of CDAD usually respond to discontinuation of antibacterial agents not directed against *Clostridium difficile*. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial agent clinically effective against *Clostridium difficile*. Surgical evaluation should be instituted as clinically indicated, as surgical intervention may be required in certain severe cases (see **ADVERSE REACTIONS**).

Hematologic

Bleeding manifestations or significant leukopenia following prolonged administration have occurred in some patients receiving β -lactam antibiotics, including 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.

Leukopenia and neutropenia may occur, especially during prolonged therapy. Therefore, periodic assessment of hematopoietic function should be performed (see **WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests**).

Neurologic

As with other penicillins, patients may experience neuromuscular excitability or convulsions if higher than recommended doses are given intravenously (particularly in the presence of renal failure).

Renal

In patients with creatinine clearance <40 mL/min and dialysis patients [hemodialysis and chronic ambulatory peritoneal dialysis (CAPD)], the intravenous dose should be adjusted to the degree of renal function impairment (see **DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment, Renal Insufficiency**). Also see **Hematologic** and **Neurologic** above.

Sensitivity/Resistance

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

Sexual Function/Reproduction

Studies in animals have shown reproductive and developmental toxicity in rats at maternally toxic doses when administered intravenously or intraperitoneally but have not shown teratogenicity of the piperacillin/tazobactam combination when administered intravenously (see **TOXICOLOGY**).

Skin Reactions

Serious skin reactions, such as Stevens-Johnson syndrome and toxic epidermal necrolysis, have been reported in patients receiving piperacillin/tazobactam (see **ADVERSE REACTIONS**). If patients develop a skin rash they should be monitored closely and piperacillin/tazobactam discontinued if lesions progress.

Special Populations

Pregnant Women: Studies in animals have shown reproductive and developmental toxicity, but no evidence of teratogenicity, at doses that are maternally toxic (see **TOXICOLOGY**). There are no adequate and well-controlled studies with the piperacillin/tazobactam combination or with

piperacillin or tazobactam alone in pregnant women. Piperacillin and tazobactam cross the placenta. Because animal reproduction studies are not always predictive of human response pregnant women should be treated with Piperacillin and Tazobactam for Injection only if the expected benefit outweighs the possible risks to the pregnant woman and fetus.

Nursing Women: Caution should be exercised when Piperacillin and Tazobactam for Injection is administered to nursing mothers. Piperacillin is excreted in low concentrations in human milk; tazobactam concentrations in milk have not been studied. Women who are breast-feeding should be treated only if the expected benefit outweighs the possible risks to the woman and child.

Pediatrics (< 12 years of age): Safety and efficacy in children below the age of 12 have not been established.

Geriatrics (> 65 years of age): Patients over 65 years of age are not at an increased risk of developing adverse effects solely because of age. However, dosage should be adjusted in the presence of renal insufficiency (see **DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment, Renal Insufficiency**).

In general, dose selection for an elderly patient should be approached with caution, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Piperacillin and Tazobactam for Injection contains 54.28 mg (2.36 mEq) of sodium per gram of piperacillin in the combination product. At the usual recommended doses, patients would receive between 651 and 868 mg/day (28.3 and 37.7 mEq) of sodium. The geriatric population may respond with a blunted natriuresis to salt loading. This may be clinically important with regard to diseases such as congestive heart failure.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Elderly patients are more likely to have decreased renal function and therefore care should be taken in dose selection. It may be useful to monitor renal function.

Monitoring and Laboratory Tests

Piperacillin and Tazobactam for Injection contains a total of 2.36 mEq (54.28 mg) of sodium (Na⁺) per gram of piperacillin in the combination product. This should be considered when treating patients requiring restricted salt intake. Periodic electrolyte determinations should be performed in patients with low potassium reserves, and the possibility of hypokalemia should be kept in mind with patients who have potentially low potassium reserves and who are receiving cytotoxic therapy or diuretics.

Periodic assessment of hematopoietic function should be performed, especially with prolonged therapy (see **WARNINGS AND PRECAUTIONS, Hematologic** and **ADVERSE REACTIONS, Abnormal Hematologic and Clinical Chemistry Findings**).

Coagulation parameters should be tested more frequently and monitored regularly, during simultaneous administration of Piperacillin and Tazobactam for Injection and high doses of heparin, oral anticoagulants and/or other drugs that may affect the blood coagulation system and/or the thrombocyte function (see **DRUG INTERACTIONS, Drug-Drug Interactions**).

Piperacillin may reduce the excretion of methotrexate. Therefore, to avoid drug toxicity, serum levels of methotrexate should be monitored in patients simultaneously treated with Piperacillin and Tazobactam for Injection and methotrexate (see **DRUG INTERACTIONS, Drug-Drug Interactions**).

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Clinical Trials (except Nosocomial Pneumonia)

During the clinical investigations, 2621 patients worldwide were treated with piperacillin and tazobactam for injection in phase 3 trials. In the key North American clinical trials (n=830 patients), 90% of the adverse events reported were mild to moderate in severity and transient in nature. However, in 3.2% of the patients treated worldwide, piperacillin and tazobactam for injection was discontinued because of adverse events primarily involving the skin (1.3%), including rash and pruritus; the gastrointestinal system (0.9%), including diarrhea, nausea, and vomiting; and allergic reactions (0.5%).

Adverse local reactions that were reported, irrespective of relationship to therapy with piperacillin and tazobactam for injection, were phlebitis (1.3%), injection site reaction (0.5%), pain (0.2%), inflammation (0.2%), thrombophlebitis (0.2%), and edema (0.1%).

Based on patients from the North American trials (n=1063), the events with the highest incidence in patients, irrespective of relationship to piperacillin and tazobactam for injection therapy, were diarrhea (11.3%); headache (7.7%); constipation (7.7%); nausea (6.9%); insomnia (6.6%); rash (4.2%), including maculopapular, bullous, urticarial, and eczematoid; vomiting (3.3%); dyspepsia (3.3%); pruritus (3.1 %); stool changes (2.4%); fever (2.4%); agitation (2.1 %); pain (1.7%); moniliasis (1.6%); hypertension (1.6%); dizziness (1.4%); abdominal pain (1.3%); chest pain (1.3%); edema (1.2%); anxiety (1.2%); rhinitis (1.2%); and dyspnea (1.1%).

Nosocomial Pneumonia Trials

In a completed study of nosocomial pneumonia, 222 patients were treated with piperacillin and tazobactam for injection in a dosing regimen of 4.5 g every 6 hours in combination with an aminoglycoside and 215 patients were treated with a comparator in combination with an

aminoglycoside. In this trial, treatment-emergent adverse events were reported by 402 patients, 204 (91.9%) in the piperacillin/ tazobactam group and 198 (92.1%) in the comparator group. Twenty-five (25, 11.0%) patients in the piperacillin/tazobactam group and 14 (6.5%) in the comparator group ($p > 0.05$) discontinued treatment due to an adverse event.

In this study of piperacillin and tazobactam for injection in combination with an aminoglycoside, adverse events that occurred in more than 1% of patients and were considered by the investigator to be drug-related were: diarrhea (17.6%), fever (2.7%), vomiting (2.7%), urinary tract infection (2.7%), rash (2.3%), abdominal pain (1.8%), generalized edema (1.8%), moniliasis (1.8%), nausea (1.8%), oral moniliasis (1.8%), BUN increased (1.8%), creatinine increased (1.8%), peripheral edema (1.8%), abdomen enlarged (1.4%), headache (1.4%), constipation (1.4%), liver function tests abnormal (1.4%), thrombocythemia (1.4%), excoriations¹ (1.4%), and sweating (1.4%).

Less Common Clinical Trial Adverse Drug Reactions ($\leq 1\%$)

Clinical Trials (except Nosocomial Pneumonia)

Additional adverse systemic clinical events reported in 1.0% or less of the patients are listed below within each body system:

Blood and lymphatic system disorders: mesenteric embolism, purpura, epistaxis, pulmonary embolism (see **WARNINGS AND PRECAUTIONS, Hematologic**).

Cardiac disorders: tachycardia, including supraventricular and ventricular; bradycardia; arrhythmia, including atrial fibrillation, ventricular fibrillation, cardiac arrest, cardiac failure, circulatory failure, myocardial infarction.

Ear and labyrinth disorders: vertigo, tinnitus.

Eye disorders: photophobia.

Gastrointestinal disorders: ileus, melena, flatulence, hemorrhage, gastritis, hiccough, ulcerative stomatitis.

Pseudomembranous colitis was reported in one patient during the clinical trials. The onset of pseudomembranous colitis symptoms may occur during or over 2 months after the administration of antibacterial treatment (see **WARNINGS AND PRECAUTIONS, Gastrointestinal**).

General disorders and administration site conditions: rigors, malaise, thirst.

Hepatobiliary disorders: jaundice.

Immune system disorders: anaphylaxis (including shock). Incidence of rash and fever is higher in patients with cystic fibrosis.

Infections and Infestations: candidiasis, vaginitis, pharyngitis.

¹These were coded under the COSTART term skin necrosis in CSR-44881, Supportive Table 10-3.

Metabolism and nutrition disorders: symptomatic hypoglycemia.

Musculoskeletal and connective tissue and bone disorders: myalgia, arthralgia, back pain.

Nervous system disorders: syncope, tremor, convulsions, taste perversion.

Psychiatric disorders: confusion, hallucination, depression.

Renal and urinary disorders: retention, dysuria, oliguria, hematuria, incontinence.

Reproductive system and breast disorders: leucorrhea, genital pruritus.

Respiratory, thoracic and mediastinal disorders: pulmonary edema, bronchospasm, coughing.

Skin and subcutaneous tissue disorders: diaphoresis, toxic epidermal necrolysis.

Vascular disorders: flushing, hypotension.

Nosocomial Pneumonia Trials

Drug-related adverse events reported in 1% or less of patients in the nosocomial pneumonia study of piperacillin and tazobactam for injection with an aminoglycoside were: acidosis, acute kidney failure, agitation, alkaline phosphatase increased, anemia, asthenia, atrial fibrillation, chest pain, CNS depression, colitis, confusion, convulsion, cough increased, thrombocytopenia, dehydration, depression, diplopia, drug level decreased, dry mouth, dyspepsia, dysphagia, dyspnea, dysuria, eosinophilia, fungal dermatitis, gastritis, glossitis, grand mal convulsion, hematuria, hyperglycemia, hypernatremia, hypertension, hypertonia, hyperventilation, hypochromic anemia, hypoglycemia, hypokalemia, hyponatremia, hypophosphatemia, hypoxia, ileus, injection site edema, injection site pain, injection site reaction, kidney function abnormal, leukocytosis, leukopenia, local reaction to procedure, melena, pain, prothrombin decreased, pruritus, respiratory disorder, AST (SGOT) increased, ALT (SGPT) increased, sinus bradycardia, somnolence, stomatitis, stupor, tremor, tachycardia, ventricular extrasystoles, and ventricular tachycardia.

Abnormal Hematologic and Clinical Chemistry Findings

Changes in laboratory parameters, without regard to drug relationship, were reported in all studies, including studies of nosocomial pneumonia in which a higher dose of piperacillin and tazobactam for injection was used in combination with an aminoglycoside. The changes in laboratory parameters include:

Hematologic: agranulocytosis, pancytopenia, anemia, decreases in hemoglobin and hematocrit, thrombocytopenia, increases in platelet count, eosinophilia, leukopenia, neutropenia. The leukopenia/neutropenia associated with piperacillin and tazobactam for injection administration appears to be reversible and most frequently associated with prolonged administration, i.e., > 21 days of therapy. These patients were withdrawn from therapy; some had accompanying systemic symptoms (e.g., fever, rigors, chills).

Coagulation: positive direct Coombs test, prolonged prothrombin time, activated partial thromboplastin time prolonged, bleeding time prolonged.

Hepatic: Increase of AST (SGOT), ALT (SGPT), alkaline phosphatase, blood bilirubin and gamma-glutamyltransferase.

Renal: increases in serum creatinine, blood urea nitrogen, renal failure.

Urinalysis: proteinuria, hematuria, pyuria.

Additional laboratory events include abnormalities in electrolytes (i.e., increases and decreases in sodium, potassium, and calcium), hyperglycemia, decreases in albumin, protein total decreased. In individuals with liver disease or those receiving cytotoxic therapy or diuretics, piperacillin and tazobactam for injection has been reported rarely to produce a decrease in serum potassium levels at high doses of piperacillin.

The following adverse reactions have also been reported for PIPRACIL[®] (piperacillin sodium):

Hepatobiliary disorders: cholestatic hepatitis.

Nervous system disorders: prolonged muscle relaxation (see **DRUG INTERACTIONS, Drug-Drug Interactions, Vecuronium**).

Renal and urinary disorders: rarely tubulointerstitial nephritis.

Skin and subcutaneous tissue disorders: erythema multiforme and Stevens-Johnson syndrome, rarely reported.

Post-Market Adverse Drug Reactions

Additional adverse events reported from worldwide marketing experience with piperacillin and tazobactam for injection occurring under circumstances where causal relationship to piperacillin and tazobactam for injection is uncertain:

Blood and lymphatic system disorders: hemolytic anemia, anemia, thrombocytosis, agranulocytosis, pancytopenia.

Hepatobiliary disorders: hepatitis, cholestatic jaundice.

Immune system disorders: hypersensitivity, anaphylactoid reaction, anaphylactic reaction, anaphylactoid shock, anaphylactic shock.

Infections and infestations: candidiasis.

Renal and urinary disorders: tubulointerstitial nephritis, renal failure.

Skin and subcutaneous tissue disorders: erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, dermatitis bullous.

DRUG INTERACTIONS

Drug-Drug Interactions

Aminoglycosides

The mixing of beta-lactam antibiotics with aminoglycosides *in vitro* can result in substantial inactivation of the aminoglycoside. Therefore, Piperacillin and Tazobactam for Injection and the aminoglycoside must be administered separately, when concomitant therapy with aminoglycosides is indicated.

The inactivation of aminoglycosides in the presence of penicillin-class drugs has been recognized. It has been postulated that penicillin-aminoglycoside complexes form; these complexes are microbiologically inactive and of unknown toxicity. Sequential administration of piperacillin and tazobactam for injection with tobramycin to patients with normal renal function and mild to moderate renal impairment has been shown to modestly decrease serum concentrations of tobramycin but does not significantly affect tobramycin pharmacokinetics. When aminoglycosides are administered in combination with piperacillin to patients with end-stage renal disease requiring hemodialysis, the concentrations of the aminoglycosides (especially tobramycin) may be significantly altered and should be monitored. Since aminoglycosides are not equally susceptible to inactivation by piperacillin, consideration should be given to the choice of the aminoglycoside when administered in combination with piperacillin to these patients.

Probenecid

Concomitant administration of piperacillin and tazobactam for injection and probenecid results in prolonged half-life of piperacillin (21%), and tazobactam (71%) and lower renal clearance for both piperacillin and tazobactam; however, peak plasma concentrations of either drug are unaffected.

Vancomycin

No pharmacokinetic interactions are found between piperacillin and tazobactam for injection and vancomycin.

Heparin

Coagulation parameters should be tested more frequently and monitored regularly, 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 (see **WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests**).

Vecuronium

Piperacillin used concomitantly with vecuronium has been implicated in the prolongation of the neuromuscular blockade of vecuronium. Piperacillin and Tazobactam for Injection 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-depolarizing muscle relaxants could be prolonged in the presence of piperacillin. See package insert for vecuronium bromide.

Methotrexate

Piperacillin may reduce the excretion of methotrexate; therefore, serum levels of methotrexate should be monitored in patients to avoid drug toxicity (see **WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests**).

Where Piperacillin and Tazobactam for Injection is administered concurrently with another antibiotic the drugs should not be mixed in the same solution but must be administered separately.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

As with other penicillins, the administration of Piperacillin and Tazobactam for Injection may result in a false-positive reaction for glucose in the urine using a copper-reduction method (CLINITEST^{®*}). It is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as DIASTIX^{®*} or TES-TAPE^{®**}) be used².

There have been reports of positive test results using the 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.

Drug-Lifestyle Interactions

Interactions with lifestyle have not been established.

DOSAGE AND ADMINISTRATION**Recommended Dose and Dosage Adjustment**

The usual total daily dose of Piperacillin and Tazobactam for Injection for adults is 3.375 g (3.0 g piperacillin sodium/0.375 g tazobactam sodium) every six hours totalling 13.5 g (12.0 g piperacillin sodium/1.5 g tazobactam sodium).

² *CLINITEST[®] and DIASTIX[®] are registered trademarks of Ames Division, Miles Laboratories, Inc.

** TES-TAPE[®] is a registered trademark of Eli Lilly and Company.

Clinical trial data in the treatment of intra-abdominal infections support the efficacy of 4.5 g piperacillin and tazobactam for injection (4.0 g piperacillin sodium/0.5 g tazobactam sodium) given every eight hours.

Nosocomial Pneumonia

Initial presumptive treatment of patients with nosocomial pneumonia should start with Piperacillin and Tazobactam for Injection at a dosage of 4.5 g (4.0 g piperacillin sodium/0.5 g tazobactam sodium) every six hours plus an aminoglycoside, totalling 18.0 g (16.0 g piperacillin sodium/2.0 g tazobactam sodium). Treatment with the aminoglycoside should be continued in patients from whom *Pseudomonas aeruginosa* is isolated. If *Pseudomonas aeruginosa* is not isolated, the aminoglycoside may be discontinued at the discretion of the treating physician.

Due to the *in vitro* inactivation of the aminoglycoside by beta-lactam antibiotics, Piperacillin and Tazobactam for Injection and the aminoglycoside are recommended for separate administration. Piperacillin and Tazobactam for Injection and the aminoglycoside should be reconstituted, diluted, and administered separately when concomitant therapy with aminoglycosides is indicated (see **DRUG INTERACTIONS, Drug-Drug Interactions, Aminoglycosides**).

Piperacillin and Tazobactam for Injection is not compatible with tobramycin for simultaneous coadministration via Y-site infusion. Compatibility of Piperacillin and Tazobactam for Injection with other aminoglycosides has not been established.

Renal Insufficiency

In patients with renal insufficiency, the intravenous dose of Piperacillin and Tazobactam for Injection (piperacillin sodium/tazobactam sodium) should be adjusted to the degree of actual renal function impairment. In patients with nosocomial pneumonia receiving concomitant aminoglycoside therapy, the aminoglycoside dosage should be adjusted according to the recommendations of the aminoglycoside used. The recommended daily doses of Piperacillin and Tazobactam for Injection for patients with renal insufficiency are as follows:

Recommended Dosing of Piperacillin and Tazobactam for Injection in Patients with Normal Renal Function and Renal Insufficiency (As total grams piperacillin/tazobactam)

Renal Function (Creatinine Clearance, mL/min)	All Indications (except Nosocomial Pneumonia)	Nosocomial Pneumonia
>40 mL/min	3.375 q6h	4.5 q6h
20-40 mL/min*	2.25 q6h	3.375 q6h
<20 mL/min*	2.25 q8h	2.25 q6h
Hemodialysis**	2.25 q12h	2.25 q8h
CAPD***	2.25 q12h	2.25 q8h

* Creatinine clearance for patients not receiving hemodialysis

** 0.75g should be administered following each hemodialysis session on hemodialysis days

*** CAPD: Continuous Ambulatory Peritoneal Dialysis

For patients on hemodialysis, the maximum dose is 2.25 g Piperacillin and Tazobactam for Injection (2.0 g piperacillin sodium/0.25 g tazobactam sodium) given every twelve hours for all indications other than nosocomial pneumonia and 2.25 g (2.0 g piperacillin sodium/0.25 g tazobactam sodium) every eight hours for nosocomial pneumonia. In addition, because hemodialysis removes 30% to 40% of Piperacillin and Tazobactam for Injection dose in four hours, one additional dose of 0.75 g (0.67 g piperacillin sodium/0.08 g tazobactam sodium) should be administered following each dialysis period. For patients with renal failure, measurement of serum levels of Piperacillin and Tazobactam for Injection will provide additional guidance for adjusting dosage.

Dosage adjustment is based on pharmacokinetic data. Clinical studies with Piperacillin and Tazobactam for Injection have not been performed in patients with impaired renal function.

Duration of Therapy

The usual duration of Piperacillin and Tazobactam for Injection treatment is from seven to ten days. However, the recommended duration of Piperacillin and Tazobactam for Injection treatment of nosocomial pneumonia is 7 to 14 days. In all conditions, the duration of therapy should be guided by the severity of the infection and the patient's clinical and bacteriological progress.

Administration

Piperacillin and Tazobactam for Injection should be administered by slow intravenous infusion over 30 minutes (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics**).

Reconstitution of single dose and pharmacy bulk vials:

Reconstitute Piperacillin and Tazobactam for Injection with at least 5 mL of a suitable diluent per gram of piperacillin from the list of diluents provided below. Swirl until dissolved. It should be further diluted to the desired final volume with an acceptable diluent.

Reconstitution for Single Dose Vial

Vial Size (piperacillin/ tazobactam)	Volume of diluent to be added to vial	Approximate available volume	Nominal concentration per mL
2.25g (2g/0.25g)	10 mL	11.60 mL	0.194 g/mL (0.172g/mL/0.022g/mL)
3.375g (3g/0.375g)	15 mL	17.36 mL	0.194 g/mL (0.172g/mL/0.022g/mL)
4.50g (4g/0.50g)	20 mL	23.15 mL	0.194 g/mL (0.172g/mL/0.022g/mL)

Reconstitute Piperacillin and Tazobactam for Injection per gram of piperacillin with 5 mL of a <i>Compatible Reconstitution Diluent</i> (listed below)	Further dilute the reconstituted Piperacillin and Tazobactam for Injection with 50 mL to 150 mL of a <i>Compatible Intravenous Solution</i> (listed below)
0.9% Sodium Chloride Injection Sterile Water for Injection 5% Dextrose Injection	0.9% Sodium Chloride Injection ^a Sterile Water for Injection* 5% Dextrose Injection 6% Dextran in Saline ^a Lactated Ringer's Injection ^β *Maximum recommended volume per dose of Sterile Water for Injection is 50 mL. ^a Compatibility studied in PVC and Polyolefin I.V. bags ^β Compatibility studied in PVC I.V. bags

Lactated Ringer's solution is compatible with Piperacillin and Tazobactam for Injection.

Reconstitution for Pharmacy Bulk Vial – Piperacillin 12 g (as piperacillin sodium) and Tazobactam 1.5 g (as tazobactam sodium):

Reconstitute the pharmacy bulk vial with exactly 51 mL of a compatible reconstitution diluent listed below, to a concentration of 200 mg/mL of piperacillin and 25 mg/mL of tazobactam. Swirl well until dissolved. It should be further diluted to the desired final volume with an acceptable diluent.

Reconstitution for Pharmacy Bulk Vial – Piperacillin 12 g (as piperacillin sodium) and Tazobactam 1.5 g (as tazobactam sodium)

Reconstitute Piperacillin and Tazobactam for Injection per pharmacy bulk vial with 51 mL of a <i>Compatible Reconstitution Diluent</i> (listed below)	Further dilute the reconstituted Piperacillin and Tazobactam for Injection with 50 mL to 150 mL of a <i>Compatible Intravenous Solution</i> (listed below)
0.9% Sodium Chloride Injection Sterile Water for Injection 5% Dextrose Injection	0.9% Sodium Chloride Injection ^a Sterile Water for Injection* 5% Dextrose Injection 6% Dextran in Saline ^a Lactated Ringer's Injection ^β *Maximum recommended volume per dose of Sterile Water for Injection is 50 mL. ^a Compatibility studied in PVC and Polyolefin I.V. bags ^β Compatibility studied in PVC I.V. bags

Reconstitution for Pharmacy Bulk Vial – Piperacillin 36 g (as piperacillin sodium) and Tazobactam 4.5 g (as tazobactam sodium)

Reconstitute the pharmacy bulk vial with exactly 152 mL of a compatible reconstitution diluent listed below, to yield a concentration of 200 mg/mL of piperacillin and 25 mg/mL of tazobactam. Swirl well until dissolved. Then it should be further diluted to the desired final volume with an acceptable diluent.

Reconstitution for Pharmacy Bulk Vial – Piperacillin 36 g (as piperacillin sodium) and Tazobactam 4.5 g (as tazobactam sodium)

Reconstitute Piperacillin and Tazobactam for Injection per pharmacy bulk vial with 152 mL of a <i>Compatible Reconstitution Diluent</i> (listed below)	Further dilute the reconstituted Piperacillin and Tazobactam for Injection with 50 mL to 150 mL of a <i>Compatible Intravenous Solution</i> (listed below)
0.9% Sodium Chloride Injection Sterile Water for Injection 5% Dextrose Injection	0.9% Sodium Chloride Injection ^a Sterile Water for Injection* 5% Dextrose Injection 6% Dextran in Saline ^a Lactated Ringer's Injection ^β *Maximum recommended volume per dose of Sterile Water for Injection is 50 mL. ^a Compatibility studied in PVC and Polyolefin I.V. bags ^β Compatibility studied in PVC I.V. bags

Lactated Ringer's Injection is compatible with Piperacillin and Tazobactam for Injection.

Intermittent Intravenous Infusion - Reconstitute as previously described, with 5 mL of an acceptable diluent per 1 gram of piperacillin and then further dilute in the desired volume (at least 50 mL). This diluted solution must be used immediately. Administer by infusion over a period of at least 30 minutes. During the infusion it is desirable to discontinue the primary infusion solution.

Stability of Piperacillin and Tazobactam for Injection Following Reconstitution

Piperacillin and Tazobactam for Injection is stable in glass-and plastic-containers (I.V. bags) when reconstituted with acceptable diluents.

Stability studies of Piperacillin and Tazobactam for Injection in glass vials have demonstrated chemical stability [potency, pH of reconstituted solution, appearance and description, and clarity of solution] for up to 24 hours at room temperature and up to 48 hours at refrigerated temperatures. Discard unused portions after storage for 24 hours at room temperature or 48 hours when refrigerated.

Stability studies of Piperacillin and Tazobactam for Injection in PVC bags have demonstrated chemical stability with Lactated Ringer's Injection [potency, pH of reconstituted solution,

appearance, and clarity of solution] for up to 24 hours at room temperature or 72 hours when refrigerated. Discard unused portions.

DUE TO MICROBIAL CONSIDERATIONS, INTRAVENOUS ADMIXTURES ARE USUALLY RECOMMENDED FOR USE WITHIN A MAXIMUM OF 24 HOURS AT ROOM TEMPERATURE OR 72 HOURS WHEN REFRIGERATED (2-8°C).

Stability and compatibility of Piperacillin and Tazobactam for Injection in polyolefin I.V. bags and PVC I.V. bags have demonstrated chemical stability (potency, appearance and clarity of solution) for up to 24 hours at room temperature and up to 72 hours at refrigerated temperature. Piperacillin and Tazobactam for Injection contains no preservatives. Appropriate consideration of aseptic technique should be used.

As with all parenteral drug products, intravenous admixtures should be inspected visually for clarity, particulate matter, precipitate, discolouration and leakage prior to administration, whenever solution and container permit. Solutions showing haziness, particulate matter, precipitate, discolouration or leakage should not be used. Discard unused portion.

Directions for dispensing from pharmacy bulk vial

The use of pharmacy bulk vial is restricted to hospitals with a recognized intravenous admixture program. The pharmacy bulk vial is intended for single puncture, multiple dispensing.

Incompatibilities

Piperacillin and Tazobactam for Injection should not be added to blood products or albumin hydrolysates.

Because of chemical instability, Piperacillin and Tazobactam for Injection should not be used for intravenous administration with solutions containing sodium bicarbonate alone or solutions that significantly alter the pH. It may be used with intravenous admixtures containing other ingredients as well as sodium bicarbonate for up to 24 hours at room temperature and 48 hours refrigerated.

Solutions containing Piperacillin and Tazobactam for Injection and protein hydrolysates or amino acids should be used within 12 hours if stored at room temperature and 24 hours if refrigerated.

Piperacillin and Tazobactam for Injection should not be mixed with other drugs in a syringe or infusion bottle since compatibility has not been established.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

There have been post-marketing reports of overdose with piperacillin and tazobactam for injection.

The majority of those events experienced, including nausea, vomiting, and diarrhea 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).

Treatment should be supportive and symptomatic according to the patient's clinical presentation.

Excessive serum levels of either tazobactam or piperacillin may be reduced by hemodialysis, although no specific antidote is known. As with other penicillins, neuromuscular excitability or convulsions have occurred following large intravenous doses, primarily in patients with impaired renal function.

In the case of motor excitability or convulsions, general supportive measures, including administration of anticonvulsive agents (e.g., diazepam or barbiturates) may be considered.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Piperacillin and Tazobactam for Injection (piperacillin sodium/tazobactam sodium) is an injectable antibacterial combination of the semisynthetic antibiotic piperacillin sodium and the β -lactamase inhibitor tazobactam sodium for intravenous administration. Thus, piperacillin/tazobactam combines the properties of a broad-spectrum antibiotic and a β -lactamase inhibitor.

Piperacillin sodium exerts bactericidal activity by inhibiting septum formation and cell wall synthesis. Piperacillin and other β -lactam antibiotics block the terminal transpeptidation step of cell wall peptidoglycan biosynthesis in susceptible organisms by interacting with the 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.

Pharmacodynamics

Tazobactam sodium has little clinically relevant *in vitro* activity against bacteria due to its reduced affinity to penicillin-binding proteins. It is, however, a β -lactamase inhibitor of the Richmond-Sykes class III (Bush class 2b & 2b') penicillinases and cephalosporinases. It varies in its ability to inhibit class II and IV (2a & 4) penicillinases. Tazobactam does not induce chromosomally-mediated β -lactamases at tazobactam concentrations achieved with the recommended dosage regimen.

Pharmacokinetics

Absorption: Peak plasma concentrations of tazobactam and piperacillin are attained immediately after completion of an intravenous infusion of piperacillin and tazobactam for injection (piperacillin sodium/tazobactam sodium). Piperacillin plasma concentrations, following a 30 minute infusion of piperacillin and tazobactam for injection are similar to those obtained when equivalent doses of piperacillin are administered alone, with mean peak plasma concentrations of approximately 134, 242, and 298 $\mu\text{g/mL}$ for the 2.0 g/0.25 g, 3.0 g/0.375 g and 4.0 g/0.5 g (piperacillin sodium/tazobactam sodium) doses, respectively. The corresponding mean peak plasma concentrations of tazobactam are 15, 24 and 34 $\mu\text{g/mL}$.

After 3.0 g/0.375 g (piperacillin sodium /tazobactam sodium) 30 minute IV infusions administered

every 6 hours, steady state plasma concentrations of tazobactam and piperacillin are similar to those obtained after the first dose. In like manner, after 4.0 g/0.5 g or 2.0 g/0.25 g piperacillin sodium /tazobactam sodium 30 minute infusions given every 6 hours, from those obtained after the first dose. Steady state plasma concentrations after 30 minute infusions every 6 hours are provided in **Table 1 (A, B)**, respectively.

TABLE 1(A,B)

STEADY STATE MEAN PLASMA CONCENTRATIONS IN ADULTS AFTER 30-MINUTE INTRAVENOUS INFUSION OF PIPERACILLIN/TAZOBACTAM EVERY 6 HOURS

A) TAZOBACTAM

Dose*	PLASMA CONCENTRATIONS (µg/mL)						AUC (µg•hr/mL)
	30 min	1 hr	2 hr	3 hr	4 hr	6 hr	AUC 0-6
2 g/0.25 g	14.8 (14)	7.2 (22)	2.6 (30)	1.1 (35)	0.7 (6) ^b	<0.5	16.0 (21)
3 g/0.375 g	24.2 (14)	10.7 (7)	4.0 (18)	1.4 (21)	0.7 (16) ^a	<0.5	25.0 (8)
4 g/0.5 g	33.8 (15)	17.3 (16)	6.8 (24)	2.8 (25)	1.3 (30)	<0.5	39.8 (15)

* piperacillin/tazobactam

^a N=4

^b N=3

B) PIPERACILLIN

Dose*	PLASMA CONCENTRATIONS (µg/mL)						AUC (µg•hr/mL)
	30 min	1 hr	2 hr	3 hr	4 hr	6 hr	AUC 0-6
2 g/0.25 g	134 (14)	57 (14)	17.1 (23)	5.2 (32)	2.5 (35)	0.9 (14) ^a	131 (14)
3 g/0.375	242 (12)	106 (8)	34.6 (20)	11.5 (19)	5.1 (22)	1.0 (10)	242 (10)
4 g/0.5 g	298 (14)	141 (19)	46.6 (28)	16.4 (29)	6.9 (29)	1.4 (30)	322 (16)

* piperacillin/tazobactam

^a N=4

24 (2.25 g and 4.5 g) and 22 (3.375g) subjects were enrolled in the study and all were evaluable for pharmacokinetic analysis.

In healthy subjects, following single or multiple piperacillin and tazobactam for injection doses, the plasma half-lives of tazobactam and piperacillin range from 0.7 to 1.2 hours and are unaffected by dose or duration of infusion.

Distribution: Tazobactam and piperacillin are widely distributed into tissues and body fluids including, but not limited to, intestinal mucosa, gallbladder, lung, female reproductive tissues (uterus, ovary and fallopian tube), interstitial fluid and bile. Mean tissue concentrations were generally 50-100% of those in plasma. Distribution of tazobactam and piperacillin into cerebrospinal fluid is low in subjects with non-inflamed meninges, as with other penicillins.

Metabolism: Piperacillin is metabolized to a minor microbiologically active desethyl metabolite. Tazobactam is metabolized to a single metabolite which lacks pharmacological and antibacterial activities.

Excretion: Both tazobactam and piperacillin are eliminated by the kidney via glomerular filtration and tubular secretion. Tazobactam and its metabolite are eliminated primarily by renal excretion with 80% of the dose as unchanged drug and the remainder as the single metabolite. Piperacillin is excreted rapidly as unchanged drug, with 68% of the dose in the urine. Piperacillin, tazobactam and desethyl piperacillin are also secreted into the bile.

Special Populations and Conditions

Hepatic Insufficiency: Tazobactam and piperacillin half-lives increase by approximately 18% and 25% respectively, in patients with hepatic cirrhosis compared to healthy subjects. However, dosage adjustment of Piperacillin and Tazobactam for Injection due to hepatic cirrhosis is not necessary.

Renal Insufficiency: In subjects with renal impairment, the half-lives of tazobactam and piperacillin, after single doses, increase with decreasing creatinine clearance. At creatinine clearance below 20 mL/min., the increase in half-life is four-fold for tazobactam and two-fold for piperacillin compared to subjects with normal renal function. Dosage adjustments for Piperacillin and Tazobactam for Injection are recommended when creatinine clearance is below 40 mL/min in patients receiving the recommended daily dose of Piperacillin and Tazobactam for Injection (see **DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment, Renal Insufficiency**).

Hemodialysis removes 30-40% of a piperacillin and tazobactam for injection dose with an additional 5% of the tazobactam dose removed as the tazobactam metabolite. Peritoneal dialysis removes approximately 21% and 6% of the tazobactam and piperacillin doses, respectively, with up to 16% of the tazobactam dose removed as the tazobactam metabolite. For dosage recommendations for patients undergoing hemodialysis, see **DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment, Renal Insufficiency**.

STORAGE AND STABILITY

Piperacillin and Tazobactam for Injection vials should be stored at controlled room temperature 15-25°C.

For single dose vials and pharmacy bulk vial, discard unused portions.

SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Piperacillin and Tazobactam for Injection (sterile piperacillin sodium/tazobactam sodium parenteral combination) is a white to off-white sterile, cryodesiccated powder or cake consisting of piperacillin and tazobactam as their sodium salts packaged in glass vials.

Each Piperacillin and Tazobactam for Injection 2.25 g vial provides piperacillin sodium equivalent to 2 grams of piperacillin and tazobactam sodium equivalent to 0.25 gram of tazobactam. Each vial contains 4.72 mEq (109 mg) of sodium.

Each Piperacillin and Tazobactam for Injection 3.375 g vial provides piperacillin sodium equivalent to 3 grams of piperacillin and tazobactam sodium equivalent to 0.375 gram of tazobactam. Each vial contains 7.08 mEq (163 mg) of sodium.

Each Piperacillin and Tazobactam for Injection 4.5 g vial provides piperacillin sodium equivalent to 4 grams of piperacillin and tazobactam sodium equivalent to 0.5 gram of tazobactam. Each vial contains 9.44 mEq (217 mg) of sodium.

Each pharmacy bulk vial of 13.5 g Piperacillin and Tazobactam for Injection provides piperacillin sodium equivalent to 12 grams of piperacillin and tazobactam sodium equivalent to 1.5 gram of tazobactam. Each vial contains 28.32 mEq (651 mg) of sodium.

Each pharmacy bulk vial of 40.5 g Piperacillin and Tazobactam for Injection provides piperacillin sodium equivalent to 36 grams of piperacillin and tazobactam sodium equivalent to 4.5 grams of tazobactam. Each vial contains 84.96 mEq (1953 mg) of sodium.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

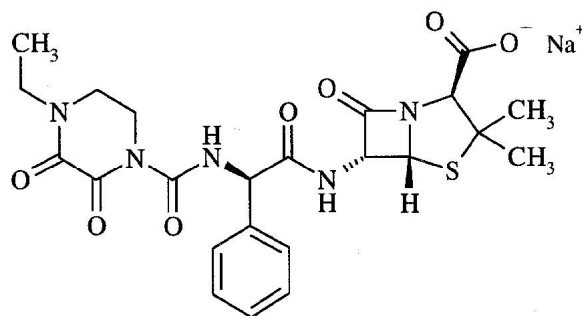
Drug Substance

Proper name: Piperacillin Sodium

Chemical name: Sodium (2*S*,5*R*,6*R*)-6-[(*R*)-2-(4-ethyl-2,3-dioxo-1-piperazine-carboxyamido)-2-phenylacetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]-heptane-2-carboxylate

Molecular formula and molecular mass: C₂₃H₂₆N₅NaO₇S and 539.5

Structural formula:



Physicochemical properties: Piperacillin monohydrate is a white to off-white crystalline powder. The aqueous solubility of its sodium salt is 1g/1.4mL and the pH of 25% w/v solution is 5.5-7.0. The melting point of the piperacillin sodium is 183° -185°C with decomposition.

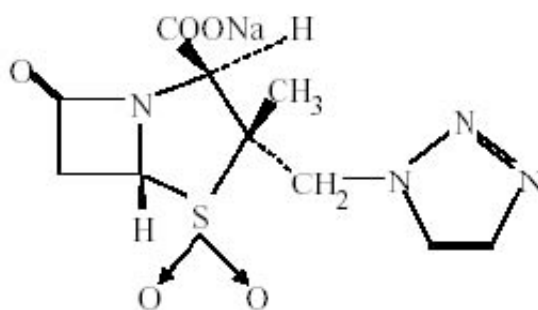
Drug Substance

Proper name: Tazobactam Sodium.

Chemical name: Sodium (2*S*, 3*S*, 5*R*)-3-methyl-7-oxo-3-(1*H*-1,2,3-triazol-1-ylmethyl)-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate 4,4-dioxide

Molecular formula and molecular mass: C₁₀H₁₁N₄NaO₅S and 322.29

Structural formula:



Physicochemical properties: Tazobactam is a white to pale-yellow crystalline powder. Its solubility in water is 5.5mg/mL with a resulting pH of 1.9, and the aqueous solubility of sodium salt is at least 500mg/mL. There is no melting point; the material decomposes at above 176°C.

CLINICAL TRIALS

DETAILED PHARMACOLOGY

Animal Pharmacology

Enzyme Induction:

Hepatic mixed function oxidase studies in the rat and dog indicated that tazobactam did not induce the hepatic drug metabolizing enzymes in these species.

Toxicokinetics:

Evaluation of the pharmacokinetic disposition of tazobactam and piperacillin following dose administration disclosed no evidence of alteration in the disposition of either agent. Plasma concentrations of tazobactam following intraperitoneal administration, the route of administration in rat toxicity studies, were proportional to the dose increment from 20 to 500 mg/kg. Similarly, plasma concentrations of piperacillin were dose proportional up to 1000 mg/kg but were greater than dose proportional at higher doses.

In pharmacokinetics studies, as well as in the acute and long-term rat and dog toxicity studies, the extent of piperacillin and tazobactam exposure was much higher than that observed in man. The disposition of tazobactam in the rat differed considerably from the disposition in the dog and man, with the dog closely resembling man in the extent of distribution, elimination half-life, and systemic clearance of tazobactam.

Both species employed in the safety assessment studies (rat, dog) produced a metabolite (M-1) from tazobactam. Plasma concentrations of M-1 following single IV doses of 25, 150, and 400 mg/kg of M-1 were dose proportional.

Placental Transfer:

The penetration of tazobactam and its metabolites through the placental barrier was moderate in pregnant rats. Tazobactam and its metabolites initially attained concentrations in the uterus, placenta, ovary, and amnion that were 20-50% of the plasma concentrations, while concentrations attained in the fetus were about 3%.

Excretion in Breast Milk:

Although drug-related concentrations of radioactivity were detected in milk of lactating rats, the concentrations of unchanged tazobactam in pup plasma and tissues were very low.

The effects seen in these studies with piperacillin/tazobactam are similar to those seen with other β -lactam antibiotics in combination with β -lactamase inhibitors. Results of preclinical studies support the use piperacillin/tazobactam in patients with infectious diseases.

Human Pharmacology

Bioavailability:

Twelve, healthy, male volunteers were given a single IM injection of 2 g piperacillin/0.25 g tazobactam to determine absolute bioavailability. Within one hour peak plasma concentrations of 125 $\mu\text{g/mL}$ and 15.6 $\mu\text{g/mL}$ for piperacillin and tazobactam, respectively, were attained. The absolute bioavailability (F) was 71% for piperacillin and 84% for tazobactam.

Distribution:

The distribution volume at steady-state (V_{ss}) for tazobactam ranged from 12.8 to 15.8 L following 30 minute infusion dose of 0.1 to 1.0 g. Co-administration of piperacillin significantly decreased tazobactam V_{ss} by approximately 16%. Piperacillin V_{ss} (range 12 to 17 L) following a 30 minute infusion dose of 4 g was unaffected by tazobactam. In studies using radio-labelled tazobactam the blood to plasma concentration ratios of radioactivity were approximately 0.5 to 0.8 at each sampling time suggesting that tazobactam and its metabolite do not preferentially distribute into the cellular components of blood.

After a 30 minute IV infusion of piperacillin/tazobactam to subjects undergoing elective surgery, both compounds were well distributed into tissues with mean tissue concentrations generally 50 to 100% of plasma concentrations. Tissue concentrations of tazobactam and piperacillin were generally greater than 19 and 6 µg/g, respectively, in lung, intestinal mucosa, gallbladder, and appendix for up to 2.5 hours after a dose of either 0.5 g/4 g or 0.5 g/2 g piperacillin/tazobactam. Similarly, after a 2 g/0.5 g piperacillin/tazobactam dose, concentrations up to 3.5 hours after dosing were greater than 5.6 µg/g for piperacillin and 3.7 µg/g for tazobactam in intestine, gallbladder and stomach mucosa.

A dose of 4 g piperacillin/0.5 g tazobactam produced peak concentrations of 94.2 µg/g for piperacillin and 7.7 µg/g for tazobactam in skin. Concentrations in bile from gallbladder aspirates ranged from 1.3 to 42.9 µg/mL for tazobactam and from 220 to 1045 µg/mL for piperacillin after an infusion dose of 3 g piperacillin/0.375 g tazobactam. Following a 4 g piperacillin/0.5 g tazobactam 30 minute infusion, peak blister levels of tazobactam and piperacillin were 11.3 and 77.2 µg/mL, respectively. The blister fluid AUC was, on average, about 90% of the plasma AUC for either compound. As seen with other penicillins, concentrations in cerebral spinal fluid are low. They reached 2 to 3% of plasma values, 2 hours after start of a 5 g piperacillin/0.625 g tazobactam 30 minute infusion.

Dose Proportionality:

To investigate the change in C_{max} with increasing dosage, two single dose studies, involving 32 healthy volunteers, were performed using doses of 2 g/0.25 g, 3 g/0.375 g, 4 g/0.5 g piperacillin/tazobactam given as either a 5 minute infusion or a 30 minute infusion. For both compounds, the increase in C_{max} was proportional. AUC was proportional between the 3 g/0.375 g and 4 g/0.5 g piperacillin/tazobactam doses. However, increases in AUC were more than proportional (up to 30%) as the dose increased from 2 g/0.25 g to 3 g/0.375 g or 4 g/0.5 g piperacillin/ tazobactam.

Metabolism and Excretion:

Piperacillin undergoes biotransformation in the gastrointestinal tract, where minor (<1% total dose) microbiologically inactive metabolites are formed via bacterial hydrolysis.

Tazobactam is metabolized to a single metabolite (M1) which lacks pharmacological and antibacterial activities and circulates at approximately 10% of the parent concentrations in subjects with normal renal function. Following an IV infusion of 3 g piperacillin and 0.377 g ¹⁴C-tazobactam (60 microcuries), tazobactam was excreted about 80% as unchanged drug and the remainder as M1. Up to 4 hours post-dose, total radioactivity concentrations in plasma could be accounted for by unchanged tazobactam and M1 while, after 4 hours, they are primarily accounted for by M1.

Piperacillin from piperacillin and tazobactam for injection is eliminated by renal pathways, and recovery of piperacillin from piperacillin and tazobactam for injection in bile is < 1% (HPLC assay) of the dose administered. About 50% - 70% of the dose is excreted unchanged by the kidney. The excretion is unaffected by co-administration of tazobactam. Urine concentrations of piperacillin from piperacillin and tazobactam for injection generally exceeded 1500 µg/mL over the dosing interval following a 30 minute IV infusion of 3 g piperacillin/0.375 tazobactam.

There are no significant changes in piperacillin pharmacokinetics due to tazobactam.

Tazobactam and its M1 metabolite are eliminated primarily by renal excretion. The magnitude of renal clearance of each compound suggests renal excretion is via glomerular filtration and net active tubular secretion. Urinary excretion of tazobactam is decreased in the presence of piperacillin, presumably due to competition for renal tubular secretion. Urinary concentrations generally exceeded 200 µg/mL over the dosing interval after a 30 minute IV infusion of 3 g piperacillin/0.375 g tazobactam.

Following an IV infusion of 3 g piperacillin and 0.375 g tazobactam (60 microcuries), recovery of total radioactivity in urine and feces over the 5 day collection period was 94%. The majority (84%) of the radioactivity was recovered in urine within 6 hours post-dose. Fecal recovery of radioactivity was <1% of the dose.

Protein Binding:

Both piperacillin and tazobactam are approximately 30% bound to plasma proteins. The binding of both tazobactam and piperacillin was not affected by the presence of the other compound. The protein binding of M1 was negligible (< 3%) in human plasma.

Elimination Half-Life:

In healthy subjects, following single or multiple doses, the plasma elimination $T_{1/2}$ of tazobactam and piperacillin ranged from 0.7 to 1.2 hours and was independent of dose level and duration of infusion. Given concomitantly, piperacillin $T_{1/2}$ was unchanged, whereas an increase of about 18% in tazobactam $T_{1/2}$ was observed. Following an IV infusion of 3 g piperacillin and 0.377 g ^{14}C -tazobactam (60 microcuries), the $T_{1/2}$ of total radioactivity in plasma was 3.2 hours reflecting the elimination of M1.

Piperacillin appears to reduce the rate of elimination of tazobactam.

Renal/Hepatic Impairment:

Mean plasma concentrations of piperacillin and tazobactam in subjects with decreased renal impairment are shown in **Table 2 (A, B)**. With decreasing renal function from $\text{CL}_{\text{cr}} > 90$ to < 20 mL/min., peak plasma concentrations of both piperacillin and tazobactam increased approximately 30%, while the mean C_{max} of the M1 metabolite increased about 4-fold. Plasma clearance of piperacillin and tazobactam was decreased (up to 2.7- and 4.4-fold, respectively) and $T_{1/2}$ increased (up to 2- and 4-fold, respectively) as renal function decreased. Dosage regimen adjustments are recommended at $\text{CL}_{\text{cr}} < 40$ mL/min.

TABLE 2(A,B)

**MEAN PLASMA CONCENTRATION IN SUBJECTS WITH DECREASED RENAL FUNCTION FOLLOWING
A 30 MINUTE INTRAVENOUS INFUSION**

A) TAZOBACTAM

Creatinine Clearance	Time (hours)								
	0.5	1	2	3	4	6	8	12	24
>90	23.6	12.5	5.2	2.3	1.3	BQL	BQL	BQL	BQL
60-90	29.4	16.7	8.1	4.7	3.0	1.6	BQL	BQL	BQL
40-59	31.5	19.5	11.0	7.3	4.9	2.4	1.6	BQL	BQL
20-39	28.8	21.1	14.9	10.6	7.6	4.0	2.2	1.4	BQL
<20	31.5	24.4	18.2	14.7	12.1	8.2	5.4	3.3	2.3

B) PIPERACILLIN

Creatinine Clearance	Time (hours)								
	0.5	1	2	3	4	6	8	12	24
>90	209	96.3	35.8	15.0	7.2	2.1	1.2	BQL	BQL
60-90	235	138	57.2	27.8	15.0	4.7	1.1	BQL	BQL
40-59	288	154	80.0	45.4	27.0	9.2	3.8	1.4	BQL
20-39	245	165	92.1	53.9	30.6	10.4	4.1	1.5	BQL
<20	253	179	120.0	84.3	56.3	28.8	15.9	6.0	1.4

BQL: Below Quantifiable Limit

Hemodialysis removed approximately 30 to 40% of the piperacillin and tazobactam doses; M1 was removed from the systemic circulation similarly to tazobactam. To maintain pre-dialysis plasma concentrations an additional one-third of the piperacillin/tazobactam unit dose is recommended following hemodialysis therapy. On average, peritoneal dialysis removed up to 6% and 21% of the dose for piperacillin and tazobactam with up to 16% of the tazobactam dose removed as M1. For dosage recommendations for patients undergoing hemodialysis, see **DOSAGE AND ADMINISTRATION**.

The single dose pharmacokinetic profiles of piperacillin and tazobactam are affected by cirrhosis with significantly lower CL_T (29%) and longer T_{1/2} (25%) for piperacillin. Similar changes in tazobactam CL_T (25%) and T_{1/2} (18%) were observed, although only the difference in CL_T was significant. Since the predicted steady-state plasma concentrations of both compounds after multiple

dosing were only 10% different between cirrhotic and normal subjects, no adjustment in dosage regimen is recommended due to cirrhosis.

Drug Interactions:

Probenecid, tobramycin and vancomycin were investigated for potential pharmacokinetic interaction with piperacillin/tazobactam.

Co-administration of a 1 g oral dose of probenecid did not significantly change C_{max} but lowered CL_R (20 to 25%) and increased $T_{1/2}$ for piperacillin by 21% and tazobactam by 71%. Co-administration of probenecid did not result in any significant increase in the plasma concentration of piperacillin/tazobactam.

Vancomycin (500 mg) given as a 60 minute infusion prior to piperacillin/tazobactam did not significantly change the pharmacokinetic profiles for either piperacillin or tazobactam. Similarly, no significant change in vancomycin pharmacokinetics was observed.

These studies indicate that adjustment in dosage regimen for piperacillin/tazobactam, tobramycin or vancomycin is not warranted when these compounds are co-administered.

Neutropenic:

In neutropenic subjects, after 30 minute infusions of 3 g piperacillin/0.375 g tazobactam every 4 hours for 5 days, the elimination $T_{1/2}$ was 40 to 80% longer and CL_T was 20 to 40% lower for both piperacillin and tazobactam. After multiple dosing, the mean C_{max} and AUC_{0-4} values were about 40% higher than after the first dose. However, this difference is not large enough to warrant adjustment of the dosage regimen in neutropenic patients.

MICROBIOLOGY

Piperacillin sodium exerts bactericidal activity by inhibiting septum formation and cell wall synthesis of susceptible bacteria. Piperacillin and other β -lactam antibiotics block the terminal transpeptidation step of cell wall peptidoglycan biosynthesis in susceptible organisms by interacting with the 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. Tazobactam sodium, which has very little intrinsic microbiologic activity due to its very low level of binding to penicillin-binding proteins, is a β -lactamase inhibitor of the Richmond-Sykes class III (Bush class 2b & 2b') penicillinases and cephalosporinases. It varies in its ability to inhibit class II and IV (2a & 4) penicillinases. Tazobactam does not induce chromosomally-mediated β -lactamases at tazobactam levels achieved with the recommended dosing regimen.

Mechanism of resistance:

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

In gram-positive bacteria, changes in PBPs are the primary 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* and viridans group streptococci. Resistance caused by changes in PBPs also occurs in fastidious gram-negative species such as *Haemophilus influenzae* and *Neisseria gonorrhoeae*. Piperacillin/tazobactam is not active against strains in which resistance to β -lactam antibiotics is determined by altered PBPs. As indicated above, there are some β -lactamases that are not inhibited by tazobactam.

Spectrum of Activity

Piperacillin/tazobactam has been shown to be **active against most strains** of the following microorganisms both *in vitro* and in clinical infections as described in the **INDICATIONS AND CLINICAL USE** section.

Aerobic and facultative gram-positive microorganisms:

Staphylococcus aureus (methicillin-susceptible strains only)

Aerobic and facultative gram-negative microorganisms:

Acinetobacter baumannii

Escherichia coli

Haemophilus influenzae (excluding β -lactamase negative, ampicillin-resistant isolates)

Klebsiella pneumoniae

Pseudomonas aeruginosa (given in combination with an aminoglycoside to which the isolate is susceptible)

Gram-negative anaerobes:

Bacteroides fragilis group (*B. fragilis*, *B. ovatus*, *B. thetaiotaomicron*, and *B. vulgatus*)

The following *in vitro* data are available, **but their clinical significance is unknown.**

At least 90% of the following microorganisms exhibit an *in vitro* minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for piperacillin/tazobactam. However, the safety and effectiveness of piperacillin/tazobactam in treating clinical infections due to these bacteria have not been established in adequate and well-controlled clinical trials.

Aerobic and facultative gram-positive microorganisms:

Enterococcus faecalis (ampicillin or penicillin-susceptible isolates only)

Staphylococcus epidermidis (methicillin-susceptible isolates only)

Streptococcus agalactiae†

Streptococcus pneumoniae† (penicillin-susceptible isolates only)

Streptococcus pyogenes†

Viridans group streptococci†

Aerobic and facultative gram-negative microorganisms:

Citrobacter koseri

Moraxella catarrhalis

Morganella morganii

Neisseria gonorrhoeae

Proteus mirabilis
Proteus vulgaris
Serratia marcescens
Providencia stuartii
Providencia rettgeri
Salmonella enterica

Gram-positive anaerobes:

Clostridium perfringens

Gram-negative anaerobes:

Bacteroides distasonis
Prevotella melaninogenica

† These are not β -lactamase producing bacteria and, therefore, are susceptible to piperacillin alone.

Susceptibility Testing Methods

As is recommended with all antimicrobials, the results of in vitro susceptibility tests, when available, should be provided to the physician as periodic reports, which describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting the most effective antimicrobial.

Dilution Techniques:

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of piperacillin and tazobactam powders.^{23,24} MIC values should be determined using serial dilutions of piperacillin combined with a fixed concentration of 4 μ g/mL tazobactam. For anaerobic bacteria, the susceptibility to piperacillin/tazobactam can be determined by the reference agar dilution method.²⁵ The MIC values obtained should be interpreted according to criteria provided in **Table 3**.

Diffusion Techniques:

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure^{23,26} requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 100 μ g of piperacillin and 10 μ g of tazobactam to test the susceptibility of microorganisms to piperacillin/tazobactam. The disk diffusion interpretation criteria are provided in **Table 3**.

TABLE 3 SUSCEPTIBILITY INTERPRETIVE CRITERIA FOR PIPERACILLIN/TAZOBACTAM						
Pathogen	Minimal Inhibitory Concentration (MIC) in mg/L of Piperacillin ^a			Disk ^b Diffusion Inhibition Zone (mm Diameter)		
	S	I	R	S	I	R

<i>Enterobacteriaceae</i> and <i>Acinetobacter baumannii</i>	≤ 16	32-64	≥ 128	≥ 21	18-20	≤ 17
<i>Pseudomonas aeruginosa</i>	≤ 16	32-64	≥ 128	≥ 21	15-20	≤ 14
<i>Haemophilus influenzae</i> ^c	≤ 1	-	≥ 2	≥ 21	-	-
<i>Staphylococcus aureus</i>	≤ 8	-	≥ 16	≥ 18	-	≤ 17
<i>Bacteroides fragilis</i> group ^d	≤ 32	64	≥ 128	-	-	-

S = Susceptible. I = Intermediate. R = Resistant.
^a MICs are determined using a fixed concentration of 4 mg/L tazobactam
^b Interpretive criteria are based on disks containing 100 µg of piperacillin and 10 µg of tazobactam.
^c These interpretive criteria for *Haemophilus influenzae* are applicable only to tests performed using Haemophilus Test Medium inoculated with a direct colony suspension and incubated at 35°C in ambient air for 20 to 24 hours.
^d With the exception of *Bacteroides fragilis* itself MICs are determined by agar dilution only.

A report of S (“Susceptible”) indicates that the pathogen is likely to be inhibited by usually achievable concentrations of the antimicrobial compound in the blood. A report of I (“Intermediate”) indicates that the result should be considered equivocal and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone that prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of R (“Resistant”) indicates that usually achievable concentrations of the antimicrobial compound in the blood are unlikely to be inhibitory and other therapy should be selected.

Quality Control

Standardized susceptibility test procedures require the use of quality control microorganisms to control the technical aspects of the test procedures.^{23,24,25,26} Standard piperacillin/tazobactam lyophilized powder should provide the following ranges of values noted in **Table 4**. 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.

TABLE 4 QUALITY CONTROL RANGES FOR PIPERACILLIN/TAZOBACTAM TO BE USED IN CONJUNCTION WITH SUSCEPTIBILITY TEST INTERPRETIVE CRITERIA		
Quality Control Strain	Minimal Inhibitory Concentration Range in mg/L of piperacillin	Disk Diffusion Inhibition Zone Diameter Range in mm
<i>Escherichia coli</i> ATCC 25922	1 -4	24 – 30
<i>Escherichia coli</i> ATCC 35218	0.5 – 2	24 – 30
<i>Pseudomonas aeruginosa</i> ATCC 27853	1 – 8	25 – 33
<i>Haemophilus influenzae</i> ^a ATCC 49247	0.06 – 0.5	33 – 38
<i>Staphylococcus aureus</i> ATCC 29213	0.25 – 2	-
<i>Staphylococcus aureus</i> ATCC 25923	-	27 – 36

<i>Bacteroides fragilis</i> ATCC 25285	0.12 – 0.5 ^b	-
<i>Bacteroides thetaiotaomicron</i> ATCC 29741	4 – 16 ^b	

^a This quality control range for *Haemophilus influenzae* is applicable only to tests performed using Haemophilus Test Medium inoculated with a direct colony suspension and incubated at 35°C in ambient air for 20 to 24 hours.

^b Agar dilution only.

TOXICOLOGY

Acute Toxicity

In mice (10/sex), IV doses of 2000/500 mg/kg of piperacillin/tazobactam resulted in no mortality and no signs of toxicity or treatment-related effects while 4000/1000 mg/kg of piperacillin/tazobactam resulted in death in 1 of 10 male mice and 5 of 10 female mice within 6 hours after dosing. At this dose, muscular hypertonia, tachypnea and convulsions were observed. In mice, IV doses of 4500/562.5 mg/kg of piperacillin/tazobactam resulted in death of 2 of 10 males within 6 hours and 3 of 10 females (2 females died 2 days and 1 female died 7 days after dosing). At this dose, shallow and frequent respiration, muscular hypertonia, reduced mobility and convulsions were observed. In mice (10/sex), IV doses of tazobactam up to 3500 mg/kg resulted in no mortality and no signs of toxicity or treatment-related effects while an IV piperacillin dose of 4500 mg/kg in mice resulted in death in 4 of 10 females within 6 hours after dosing. At this dose, shallow and frequent respiration, muscular hypertonia, reduced mobility and convulsions were observed. In 1 of 10 male mice, the right kidney was white in colour. In addition, partial papillary necrosis and partial tubular necrosis of the cortex accompanied by mononuclear leucocyte infiltration were observed.

In rats, IV doses of piperacillin/tazobactam resulted in death in 7 of 10 females at 2000/250 mg/kg, in 3 of 10 males at 2200/275 mg/kg, and in 10 of 10 males and 9 of 10 females at 2400/300 mg/kg, within 6 hours after dosing. In rats dosed IV, shallow and frequent respiration, muscular hypertonia, staggering, and convulsions were observed. Following administration of IP doses of 4000/1000 mg/kg of tazobactam/piperacillin, there was no mortality. At this IP dose, transient wet perianal area and decreased body-weight gain and food consumption in male rats occurred during the first week after dosing. Distended cecum occurred in two females.

In rats, IV doses of piperacillin resulted in death in 8 of 10 females at 1000 mg/kg (twice daily), 4 of 10 males and 8 of 10 females at 2200 mg/kg, and 8 of 10 males and 9 of 10 females at 2400 mg/kg, within 6 hours after dosing. At these doses, shallow and frequent respiration, muscular hypertonia, staggering and convulsions occurred. Following administration of IP doses of 5000 mg/kg of tazobactam, there was no mortality. At this dose, transient wet perianal area and decreased body-weight gain and food consumption in male and/or female rats occurred during the first week after dosing.

In dogs (1/sex), IV doses resulted in salivation at 2600/330 mg/kg of piperacillin/tazobactam; emesis, salivation and conjunctival congestion at 4000/500 mg/kg of piperacillin/tazobactam; and death in 1 male and 1 female within 2 hours after dosing at 5200/650 mg/kg of piperacillin/tazobactam.

In dogs, IV doses of tazobactam at 3000 or 5000 mg/kg resulted in no deaths. At these doses, erythema, edema, emesis, loose stools, slight changes in hematology (decreased red blood cell parameters, platelets and lymphocytes) and in serum chemistry (decreased potassium and increased AST) parameters occurred. In addition, salivation occurred at 3000 mg/kg of tazobactam and decreased motor activity occurred at 5000 mg/kg of tazobactam. An IV dose of 5200 mg/kg of piperacillin resulted in no deaths. At this dose, emesis and salivation occurred.

Long-Term Toxicity

Long-term toxicity studies in the rat and dog established target organ toxicity. In both species, altered hepatocellular glycogen distribution, a well-known effect of β -lactamase inhibitors, was observed. This finding occurred in drug-treated rats in 5-day, 1-, 3-, and 6-month studies at doses > 80 mg/kg/day of tazobactam alone or in combination with piperacillin. In dogs, it occurred with tazobactam alone or in combination with piperacillin at 3000 mg/kg/day for 5 days, > 40 mg/kg/day for 1 and 3 months and > 80 mg/kg/day for 6 months. Additionally, enlarged ceca were observed in rats. Enlarged ceca, caused by suppression of intestinal microflora, is a non-specific effect of antimicrobials in rodents. Other drug-related effects observed in rats and dogs in long-term toxicity studies were decreased red blood cell parameters and decreased cholesterol and serum triglycerides.

Decreased platelets and total protein, and increased alkaline phosphatase, ALT, and AST were also seen in dogs. The effect on red blood cell parameters, cholesterol and triglyceride levels, and altered distribution of hepatocellular glycogen were reversible or diminished following a recovery period.

Genotoxicity and Carcinogenicity

Long-term studies in animals to evaluate carcinogenic potential have not been performed with piperacillin/tazobactam, piperacillin or tazobactam.

Piperacillin/tazobactam:

Piperacillin/tazobactam was negative in microbial mutagenicity assays at concentrations up to 14.84/1.86 mcg/plate. Piperacillin/tazobactam was negative in the unscheduled DNA synthesis (UDS) test at concentrations up to 5689/711 mcg/mL. Piperacillin/tazobactam was negative in a mammalian point mutation (Chinese hamster ovary cell HPRT) assay at concentration up to 8000/1000 mcg/mL. Piperacillin/tazobactam was negative in a mammalian cell (BALB/c-3T3) transformation assay at concentrations up to 8/1 mcg/mL. In vivo, piperacillin/tazobactam did not induce chromosomal aberrations in rats dosed IV with 1500/187.5 mg/kg; this dose is similar to the maximum recommended human daily dose on a body-surface-area basis (mg/m^2).

Piperacillin:

Piperacillin was negative in microbial mutagenicity assays at concentrations up to 50 mcg/plate. There was no DNA damage in bacteria (Rec assay) exposed to piperacillin at concentrations up to 200 mcg/disc. Piperacillin was negative in the UDS test at concentrations up to 10,000 mcg/mL, which is 26 times the human plasma concentration of piperacillin. In mammalian point mutation (mouse lymphoma cells) assay, piperacillin was positive at concentrations ≥ 2500 mcg/mL, which is 7 times the human plasma concentration. Piperacillin was negative in a cell (BALB/c-3T3) transformation assay at concentrations up to 3000 mcg/mL, which is 8 times the human plasma concentration. In vivo, piperacillin did not induce chromosomal aberrations in mice at IV doses up to 2000 mg/kg/day or rats at IV doses up to 1500 mg/kg/day. These doses are 6 (mice) and 4 (rats) times the maximum recommended human daily dose based on body weight, and half (mice) or

similar to (rats) the human dose based on body-surface area (mg/m^2). In another in vivo test, there was no dominant lethal effect when piperacillin was given to rats at IV doses up to 2000 $\text{mg}/\text{kg}/\text{day}$, which is similar to the human dose based on body-surface area. When mice were given piperacillin at IV doses up to 2000 $\text{mg}/\text{kg}/\text{day}$, which is half the human dose based on body-surface area (mg/m^2), urine from these animals was not mutagenic when tested in a microbial mutagenicity assay. Bacteria injected into the peritoneal cavity of mice given piperacillin at IV doses up to 2000 $\text{mg}/\text{kg}/\text{day}$ did not show increased mutation frequencies.

Tazobactam:

Tazobactam was negative in microbial mutagenicity assays at concentrations up to 333 mcg/plate . Tazobactam was negative in the UDS test at concentrations up to 2000 mcg/mL . Tazobactam was negative in a mammalian point mutation (Chinese hamster ovary cell HPRT) assay at concentrations up to 5000 mcg/mL . In another mammalian point mutation (mouse lymphoma cells) assay, tazobactam was positive at concentrations ≥ 3000 mcg/mL . Tazobactam was negative in a cell (BALB/c-3T3) transformation assay at concentrations up to 900 mcg/mL . In an in vitro cytogenetics (Chinese hamster lung cells) assay, tazobactam was negative at concentrations up to 3000 mcg/mL . In vivo, tazobactam did not induce chromosomal aberrations in rats at IV doses up to 5000 mg/kg , which is 23 times the human dose based on body-surface area (mg/m^2).

Reproductive and Development Toxicity

A fertility and general reproduction study in rats using intraperitoneal administration of tazobactam or the combination piperacillin/tazobactam reported a decrease in litter size and an increase in fetuses with ossification delays and variations of ribs (skeletal anomalies such as delays in bone ossification), concurrent with maternal toxicity. Fertility of the F1 generation and embryonic development of F2 generation were not impaired.

Teratogenicity studies using intravenous administration of tazobactam or the combination piperacillin/tazobactam in mice and rats resulted in slight reductions in rat fetal weights at maternally toxic doses but did not show teratogenic effects.

Peri/postnatal development was impaired (reduced pup weights, increase in stillbirths, increase in pup mortality) concurrent with maternal toxicity after intraperitoneal administration of tazobactam or the combination piperacillin/tazobactam in the rat.

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PART III: CONSUMER INFORMATION

^{Pr}Piperacillin and Tazobactam for Injection

This leaflet is part III of a three-part "Product Monograph" published when Piperacillin and Tazobactam for Injection was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Piperacillin and Tazobactam for Injection. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

Piperacillin and Tazobactam for Injection is used by doctors to treat bacterial infections in different parts of the body.

What it does:

Piperacillin and Tazobactam for Injection belongs to a group of injectable antibiotic combinations containing piperacillin sodium and tazobactam sodium. Piperacillin is a penicillin-type antibiotic that interferes with bacterial cell wall formation and tazobactam reduces the action of bacteria which inactivate piperacillin. Both work together to reduce the bacterial infection.

When it should not be used:

Piperacillin and Tazobactam for Injection should not be used in patients with a history of allergic reactions to any of the penicillins and/or cephalosporins, beta lactamase inhibitors.

What the medicinal ingredients are:

Piperacillin and Tazobactam for Injection contains the active ingredients Piperacillin (as Piperacillin Sodium) and Tazobactam (as Tazobactam Sodium).

What dosage forms it comes in:

Piperacillin and Tazobactam for Injection is available as a lyophilized powder for injection.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Notify your doctor if you are allergic to penicillin, cephalosporins or other allergens. If an allergic reaction occurs during therapy with Piperacillin and Tazobactam for Injection stop taking the drug and seek immediate medical attention.

BEFORE you use Piperacillin and Tazobactam for Injection talk to your doctor if you:

- are allergic to Piperacillin and Tazobactam for Injection, penicillin, cephalosporins or beta-lactamase inhibitors

- have kidney or liver problems
- have gall bladder problems
- have low levels of potassium in blood or taking diuretics
- are on a low sodium diet as this product contains sodium
- are pregnant or could become pregnant during treatment
- are breast feeding. Piperacillin is excreted at low levels in human milk.
- have cystic fibrosis or bleeding problems
- have a history of severe diarrhea or bowel problems due to an antibiotic
- are being treated for gonorrhea
- are taking any medicines including: Aminoglycosides, Probenecid, blood thinners (e.g. Heparin), Vecuronium or Methotrexate

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with Piperacillin and Tazobactam for Injection include:

- Aminoglycosides (a type of antibiotic, e.g. tobramycin)
- Probenecid (a drug used to treat gout)
- Drugs used to thin blood (e.g. Heparin)
- Vecuronium (a muscle relaxant)
- Methotrexate (a drug used to treat cancer)

PROPER USE OF THIS MEDICATION

Piperacillin and Tazobactam for Injection will be administered by your doctor.

Usual dose:

The usual total daily dose of Piperacillin and Tazobactam for Injection for adults is 12g/1.5g, given as 3g/0.375g intravenously every six hours, as administered by the healthcare professional.

Overdose:

There have been post-marketing reports of overdose with piperacillin and tazobactam for injection. The majority of those events experienced including nausea, vomiting, and diarrhea have also been reported with the usual recommended dosages. You may experience neuromuscular excitability (increased sensitivity of muscles and nerves) or convulsions if higher than recommended doses are given intravenously (particularly in the presence of kidney failure).

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

Piperacillin and Tazobactam for Injection is often administered by a doctor. If you suspect a missed dose talk to your physician.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines Piperacillin and Tazobactam for Injection may have side effects. The most common side effects are:

- Nausea or indigestion
- Vomiting
- diarrhea or constipation
- rash, itchy or red skin
- allergic reaction such as hives
- a new infection caused by bacteria that are resistant to Piperacillin and Tazobactam for Injection (superinfection)
- difficulty sleeping
- headache, dizziness or light-headedness
- anxiety, sweating, agitation
- shortness of breath
- chest pain
- abdominal pain or swelling
- fever
- pain

Serious skin reactions have occurred in patients taking piperacillin/tazobactam combinations. If you develop symptoms such as peeling or blistering skin or severe rash, contact your doctor immediately.

If you suffer severe, persistent, watery or bloody diarrhea, with or without fever and abdominal pain, you may have Clostridium difficile colitis (bowel inflammation). If this happens, stop taking Piperacillin and Tazobactam for Injection and contact your doctor immediately.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common	Chest pain		✓	
	Diarrhea			✓
Uncommon	Confusion		✓	
	Convulsions		✓	
	Hallucinations		✓	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your
	Jaundice (yellowing of skin or eyes)		✓	
Rare	Allergic reactions such as: Chest tightness, dizziness, faintness, hives, itching, shortness of breath, skin rash, swollen face, lips, mouth or tongue, trouble breathing, wheezing.		✓	

This is not a complete list of side effects. For any unexpected effects while taking Piperacillin and Tazobactam for Injection, contact your doctor or pharmacist.

HOW TO STORE IT

Piperacillin and Tazobactam for Injection vials should be stored at controlled room temperature 15-25°C.

Reporting Side Effects

You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:

- Online at MedEffect (<http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php>);
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
 - Fax to 1-866-678-6789 (toll-free), or
 - Mail to: Canada Vigilance Program
Health Canada, Postal Locator 0701E
Ottawa, ON
K1A 0K9

Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect (<http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php>).

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:

<http://www.sterimaxinc.com>

or by contacting the sponsor, SteriMax Inc. at:
1-800-881-3550

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