PRODUCT MONOGRAPH

Pr PIPERACILLIN/TAZOBACTAM FOR INJECTION

Sterile piperacillin sodium/tazobactam sodium

Lyophilized Powder for Injection

For Intravenous Use

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

Antibiotic/ß-lactamase Inhibitor

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March 7, 2011

Control No. 144852

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form/Strength	Clinically Relevant Nonmedicinal Ingredients
Intravenous	Powder for solution, 2.25 g, 3.375 g, 4.5 g	There are no clinically relevant nonmedicinal ingredients. *For a complete listing, see* **DOSAGE FORMS, COMPOSITION AND PACKAGING** *section.*

INDICATIONS AND CLINICAL USE

Piperacillin/Tazobactam for Injection (sterile 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, ß-lactamase-producing strains of the designated microorganisms in the specified conditions listed below:

- **Intra-abdominal Infections:** Appendicitis (complicated by rupture or abscess) and peritonitis caused by piperacillin-resistant, ß-lactamase-producing strains of *Escherichia coli* or members of the *Bacteroides fragilis* group.
- **Skin and Skin Structure Infections:** Uncomplicated and complicated skin structure infections, including cellulitis, cutaneous abscess, acute ischemic/diabetic foot infections caused by piperacillin-resistant, ß-lactamase-producing strains of *Staphylococcus aureus* (not methicillin-resistant strains).
- **Gynecological Infections:** Postpartum endometritis or pelvic inflammatory disease caused by piperacillin-resistant, ß-lactamase-producing strains of *Escherichia coli*.
- **Community-acquired Lower Respiratory Tract Infections:** Community-acquired pneumonia (moderate severity only) caused by piperacillin-resistant, ß-lactamase-

producing strains of *Haemophilus influenzae*.

- **Nosocomial Pneumonia:** Nosocomial pneumonia (moderate to severe) caused by piperacillin-resistant, ß-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/Tazobactam for Injection is indicated only for the conditions listed above, infections caused by piperacillin-susceptible organisms are also amenable to piperacillin/tazobactam 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 ß-lactamase-producing organisms susceptible to piperacillin/tazobactam should not require the addition of another antibiotic.

Piperacillin/tazobactam 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/tazobactam. 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

- 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 ß-lactamase inhibitors.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- **Serious and occasionally fatal hypersensitivity [anaphylactic/anaphylactoid (including 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/Tazobactam for Injection, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, or other allergens. If an allergic reaction occurs during therapy with piperacillin/tazobactam, 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

Clostridium difficile-associated disease (CDAD) has been reported with use of many antibacterial agents, including Piperacillin/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 antibactieral 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** section).

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/tazobactam should not be used for intravenous

administration with solutions containing only sodium bicarbonate (see **DOSAGE AND ADMINISTRATION, Administration, Reconstitution**).

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

Hematologic

Bleeding manifestations or significant leukopenia following prolonged administration have occurred in some patients receiving ß-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.

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

Reproduction studies have been performed in rats and have revealed no evidence of impaired fertility due to piperacillin/tazobactam administered up to a dose which is similar to the maximum recommended human daily dose based on body surface area (mg/m^2). Teratology studies have been performed in mice and rats and have revealed no evidence of harm to the fetus due to piperacillin/tazobactam at doses 1 - 2 and 2 - 3 times the human dose of piperacillin and tazobactam, respectively, based on body surface area (mg/m^2).

Piperacillin: Reproduction and teratology studies have been performed in mice and rats and have revealed no evidence of impaired fertility or harm to the fetus due to piperacillin administered up to a dose which is half (mice) or similar (rats) to the human dose based on body surface area (mg/m^2).

Tazobactam: Reproduction studies have been performed in rats and have revealed no evidence of impaired fertility due to tazobactam administered up to a dose 3 times the human dose based on body surface area (mg/m^2). Teratology studies have been performed in mice and rats and have revealed no evidence of harm to the fetus due to tazobactam up to a dose which is 6 (mice) and 14 (rats) times the human dose based on body surface area (mg/m^2). In rats, tazobactam crosses the placenta. Concentrations in the fetus are less than or equal to 10% of that found in maternal plasma.

Special Populations

Pregnant Women: 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. Reproduction and teratology studies in animals have not revealed any adverse effects to the fetus (see **WARNINGS AND PRECAUTIONS, Sexual Function/Reproduction**). Because animal reproduction studies are not always predictive of human response, pregnant women should be treated with Piperacillin/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/tazobactam 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/Tazobactam for Injection contains 54 mg (2.35 m Eq) of sodium per gram of piperacillin in the combination product. At the usual recommended doses, patients would receive between 648 and 864 mg/day (28.2 and 37.6 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/Tazobactam for Injection contains a total of 2.35 mEq (54 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.

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*.

During the clinical investigations, 2621 patients worldwide were treated with piperacillin/ tazobactam 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/tazobactam 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/tazobactam, 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/tazobactam 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/tazobactam 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/tazobactam 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%); excoriations* (1.4%); and sweating (1.4%).

Less Common Clinical Trial Adverse Drug Reactions (≤ 1%)

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

Autonomic nervous system: hypotension, ileus, syncope.

Body as a whole: rigors, back pain, malaise, candidal superinfection.

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

Central nervous system: tremor, convulsions, vertigo.

Gastrointestinal: melena, flatulence, hemorrhage, gastritis, hiccough, ulcerative stomatitis, jaundice.

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, General**.)

Hearing: tinnitus.

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

Metabolic and nutritional: symptomatic hypoglycemia, thirst.

Musculoskeletal: myalgia, arthralgia.

* Coded under the COSTART term skin necrosis.

Platelet, bleeding, clotting: mesenteric embolism, purpura, epistaxis, pulmonary embolism. (See **WARNINGS AND PRECAUTIONS, Hematologic**.)

Psychiatric: confusion, hallucination, depression.

Reproductive, female: leukorrhea, vaginitis.

Respiratory: pharyngitis, pulmonary edema, bronchospasm, coughing.

Skin and appendages: genital pruritus, diaphoresis, toxic epidermal necrolysis.

Special senses: taste perversion.

Urinary: retention, dysuria, oliguria, hematuria, incontinence.

Vision: photophobia.

Vascular (extracardiac): flushing.

Nosocomial Pneumonia Trials:

Drug-related adverse events reported in 1% or less of patients in the nosocomial pneumonia study of piperacillin/tazobactam 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/tazobactam 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/tazobactam administration appears to be reversible and most frequently associated with prolonged administration, i.e., $\geq$ 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, prolonged partial thromboplastin time, bleeding time prolonged.

Hepatic: Transient elevations of AST (SGOT), ALT (SGPT), alkaline phosphatase, bilirubin, gamma-glutamyltransferase increased.

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, and decreases in total protein or albumin. In individuals with liver disease or those receiving cytotoxic therapy or diuretics, piperacillin/ tazobactam 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 sterile piperacillin sodium:

Skin and appendages: erythema multiforme and Stevens-Johnson syndrome, rarely reported.

Gastrointestinal: cholestatic hepatitis.

Renal: rarely, interstitial nephritis.

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

Postmarket Adverse Drug Reactions

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

Gastrointestinal: hepatitis, cholestatic jaundice.

Hematologic: hemolytic anemia, anemia, thrombocytosis, agranulocytosis, pancytopenia.

Immune: hypersensitivity reactions, anaphylactic/anaphylactoid reactions (including shock).

Infections: candidial superinfections.

Renal: interstitial nephritis, renal failure.

Skin and appendages: erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis.

DRUG INTERACTIONS

Drug-Drug Interactions

Aminoglycosides: The mixing of Piperacillin/Tazobactam for Injection with aminoglycosides *in vitro* can result in substantial inactivation of the aminoglycoside. Therefore, Piperacillin/Tazobactam for Injection and the aminoglycoside must be administered separately, when concomitant therapy with aminoglycosides is indicated. (See **DOSAGE AND ADMINISTRATION, Dosing Considerations**).

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/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/tazobactam 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/tazobactam 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.

Vecuronium: Piperacillin used concomitantly with vecuronium has been implicated in the prolongation of the neuromuscular blockade of vecuronium. Piperacillin/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.

Lactated Ringer's solution is not compatible with Piperacillin/Tazobactam for Injection (see **DOSAGE AND ADMINISTRATION, Administration, Reconstitution**).

When piperacillin/tazobactam is administered concurrently with another antibiotic, the drugs should not be mixed in the same solution and 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/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 used.

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.

DOSAGE AND ADMINISTRATION

Dosing Considerations
Due to the *in vitro* inactivation of aminoglycosides by beta-lactam antibiotics, piperacillin/tazobactam and the aminoglycoside should be reconstituted, diluted and administered separately when concomitant therapy with aminoglycosides is indicated (see **DRUG INTERACTIONS**).

Recommended Dose and Dosage Adjustment
The usual total daily dose of Piperacillin/Tazobactam for Injection (sterile piperacillin sodium/tazobactam sodium) for adults is 12 g/1.5 g given as 3 g/0.375 g every six hours.

† 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 g/0.5 g given every eight hours.

Initial presumptive treatment of patients with nosocomial pneumonia should start with piperacillin/tazobactam at a dosage of 4.5 g 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.

Renal Insufficiency: In patients with renal insufficiency, the intravenous dose 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/tazobactam for patients with renal insufficiency are as follows:

Recommended Dosing of Piperacillin/Tazobactam for Injection in Patients with Normal Renal Function and Renal Insufficiency (as total grams of 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. ** 0.75 g should be administered following each hemodialysis session on hemodialysis days.		

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

Dosage adjustment is based on pharmacokinetic data. Clinical studies with piperacillin/ tazobactam have not been performed in patients with impaired renal function.

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

Administration

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

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

Reconstitution

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

Reconstitute Piperacillin/Tazobactam for Injection per gram of piperacillin with 5 mL of a ***Compatible Reconstitution Diluent*** (listed below)	**Further dilute** the reconstituted Piperacillin/Tazobactam for Injection with 50 mL to 150 mL of a ***Compatible Intravenous Solution*** (listed below)
0.9% Sodium Chloride Injection Sterile Water for Injection 5% Dextrose Injection	0.9% Sodium Chloride Injection Sterile Water for Injection* 5% Dextrose Injection * Maximum recommended volume per dose of Sterile Water for Injection is 50 mL.
Bacteriostatic Sodium Chloride Injection (with benzyl alcohol) Bacteriostatic Water for Injection (with benzyl alcohol) Bacteriostatic Water for Injection (with parabens)	0.9% Sodium Chloride Injection

Lactated Ringer's solution is not compatible with Piperacillin/Tazobactam for Injection (see **DRUG INTERACTIONS**, **Drug-Drug Interactions**).

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/Tazobactam for Injection Following Reconstitution:
Piperacillin/Tazobactam for Injection is stable in glass and plastic containers (plastic syringes, i.v. bags and tubing) when reconstituted with acceptable diluents.

Stability studies of piperacillin/tazobactam in glass vials have demonstrated chemical stability

(potency, pH of reconstituted solution, 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.

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 studies of Piperacillin/Tazobactam for Injection in polyolefin i.v. bags have demonstrated chemical stability (potency, appearance and description, and clarity of solution) for up to 24 hours at room temperature and up to 72 hours at refrigerated temperature. Stability and compatibility of Piperacillin/Tazobactam for Injection in PVC i.v. bags have not been established. Piperacillin/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.

Incompatibilities: Not to be added to blood products or albumin hydrolysates.

Because of chemical instability, piperacillin/tazobactam should not be used for intravenous administration with solutions containing sodium bicarbonate alone. 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/tazobactam and protein hydrolysates or amino acids should be used within 12 hours if stored at room temperature and 24 hours if refrigerated.

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

OVERDOSAGE

There have been postmarketing reports of overdose with sterile piperacillin sodium/tazobactam sodium. 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.

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

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Piperacillin/Tazobactam for Injection is an injectable antibacterial combination consisting of the semisynthetic antibiotic piperacillin sodium and the ß-lactamase inhibitor tazobactam sodium for intravenous administration.

Pharmacodynamics

Piperacillin sodium exerts bactericidal activity by inhibiting septum formation and cell wall synthesis. *In vitro*, piperacillin is active against a variety of gram-positive and gram-negative aerobic and anaerobic bacteria. Tazobactam sodium is a ß-lactamase inhibitor. Tazobactam, in combination with piperacillin enhances and extends the antibiotic spectrum of piperacillin to include ß-lactamase producing bacteria normally resistant to piperacillin.

Pharmacokinetics

Absorption: Peak plasma concentrations of tazobactam and piperacillin are attained immediately after completion of an intravenous infusion of Piperacillin/Tazobactam for Injection. Piperacillin plasma concentrations, following a 30 minute infusion of piperacillin/tazobactam are similar to those obtained when equivalent doses of piperacillin are administered alone, with mean peak plasma concentrations of approximately 134, 242, and 298 µg/mL for the 2 g/0.25 g, 3 g/0.375 g and 4 g/0.5 g (piperacillin/tazobactam) doses, respectively. The corresponding mean peak plasma concentrations of tazobactam are 15, 24 and 34 µg/mL.

After 3 g/0.375 g (piperacillin/tazobactam) 30 minute i.v. 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 g/0.5 g or 2 g/0.25 g piperacillin/tazobactam 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 Six 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 g	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 (3.75 g) subjects were enrolled in the study and all were evaluable for pharmacokinetic analysis.

In healthy subjects, following single or multiple piperacillin/tazobactam 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 to 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/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/tazobactam are recommended when creatinine clearance is below 40 mL/min in patients receiving the recommended daily dose of piperacillin/tazobactam (see **DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment, Renal Insufficiency**).

Hemodialysis removes 30 to 40% of a piperacillin/tazobactam 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/Tazobactam for Injection vials should be stored at controlled room temperature between 15 and 30°C (59-86°F).

Single-dose vials. Discard unused portions.

SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Piperacillin/Tazobactam for Injection (sterile piperacillin sodium and tazobactam sodium) is

available in the following dosage forms:

- Piperacillin/Tazobactam for Injection 2.25 g vial: Each vial provides piperacillin sodium equivalent to 2 grams of piperacillin and tazobactam sodium equivalent to 0.25 gram of tazobactam. Each vial contains 4.69 mEq (108 mg) of sodium.
  2.25 g vial – 10 per carton.

- Piperacillin/Tazobactam for Injection 3.375 g vial: Each vial provides piperacillin sodium equivalent to 3 grams of piperacillin and tazobactam sodium equivalent to 0.375 gram of tazobactam. Each vial contains 7.03 mEq (162 mg) of sodium.
  3.375 g vial – 10 per carton.

- Piperacillin/Tazobactam for Injection 4.5 g vial: Each vial provides piperacillin sodium equivalent to 4 grams of piperacillin and tazobactam sodium equivalent to 0.5 gram of tazobactam. Each vial contains 9.37 mEq (216 mg) of sodium.
  4.5 g vial – 10 per carton.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Piperacillin Monohydrate and Tazobactam Acid are converted to their sodium salts during manufacture of the drug product.

Proper name: Tazobactam Acid
Tazobactam Sodium

Chemical name:

Tazobactam Acid
(2*S*,3S,5*R*)-3-Methyl-7-oxo-3-(1*H*-1,2,3-triazol-1-ylmethyl)-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 4,4-dioxide

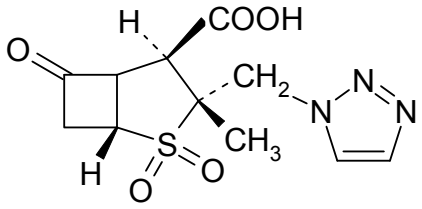
Tazobactam Sodium
Sodium (2*S*,3*S*,5*R*)-3-methyl-7-oxo-3-(1*H*-1,2,3-triazol-1-ylmethyl)-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate 4,4-dioxide

Molecular formula and molecular mass:

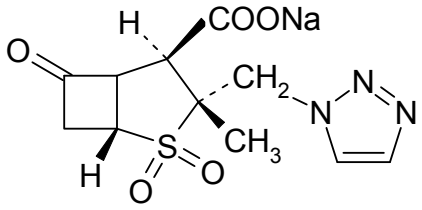
Tazobactam Acid:
$C_{10}H_{12}N_4O_5S$; 300.29

Tazobactam Sodium:
$C_{10}H_{11}N_4NaO_5S$; 322.29

Structural formula: Tazobactam Acid



Tazobactam Sodium



Physicochemical properties:

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

Proper name: Piperacillin Monohydrate
Piperacillin Sodium

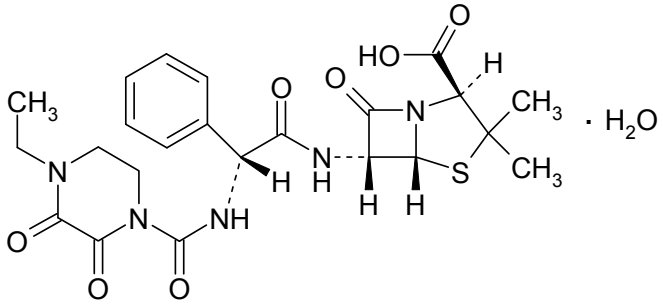
Chemical name: Piperacillin Monohydrate
(2*S*,5*R*,6*R*)-6-[(*R*)-2-(4-ethyl-2,3-dioxo-1-piperazincarboxamido)-2-phenylacetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptalic acid monohydrate

Piperacillin Sodium
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

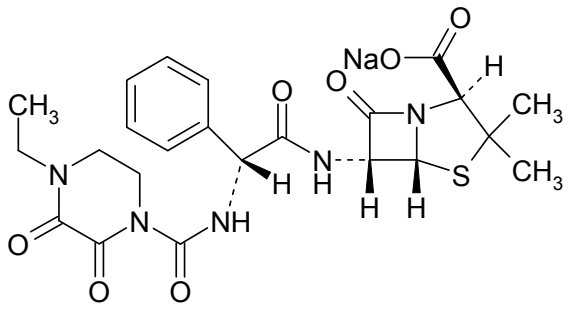
Molecular formula and molecular mass: Piperacillin Monohydrate
$C_{23}H_{27}N_5O_7S \cdot H_2O$; 537.57

Piperacillin Sodium
$C_{23}H_{26}N_5NaO_7S$; 539.54

Structural formula: Piperacillin Monohydrate



Piperacillin Sodium



Physicochemical properties:

Piperacillin monohydrate is a white to off-white crystalline powder. The aqueous solubility of its sodium salt is 1 g/1.4 mL 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.

Composition:

Sterile piperacillin sodium/tazobactam sodium is a white to off-white cryodesiccated powder or cake consisting of tazobactam and piperacillin as their sodium salts packaged in glass vials.

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 i.v. 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 to 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 ß-lactam antibiotics in combination with ß-lactamase inhibitors. Results of preclinical studies support the use of piperacillin/tazobactam in patients with infectious diseases.

Human Pharmacology

Bioavailability:
Twelve healthy male volunteers were given a single i.m. injection of 2 g piperacillin/0.25 g tazobactam to determine absolute bioavailability. Within one hour peak plasma concentrations of 125 µg/mL and 15.6 µg/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 a 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 i.v. 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 4 g/0.5 g or 2 g/0.5 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 i.v. infusion of 3 g piperacillin and 0.377 g ^{14}C-tazobactam (60 microcuries), tazobactam was excreted about 80% as unchanged drug and the remainder as M1. Up to 4 hours postdose, 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/tazobactam is eliminated by renal pathways, and recovery of piperacillin from piperacillin/tazobactam in bile is < 1% (HPLC assay) of the dose administered. About 50 to 70% of the dose is excreted unchanged by the kidney. The excretion is unaffected by coadministration of tazobactam. Urine concentrations of piperacillin from piperacillin/tazobactam generally exceeded 1500 µg/mL over the dosing interval following a 30 minute i.v. infusion of 3 g piperacillin/0.375 g 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 i.v. infusion of

3 g piperacillin/0.375 g tazobactam.

Following an i.v. 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 postdose. Fecal recovery of radioactivity was < 1% of the dose.

Protein Binding:
In humans, the protein binding of piperacillin was < 20% and tazobactam was < 5%. This was essentially constant over the therapeutic range. 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 $T_{½}$ 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 $T_{½}$ was unchanged, whereas an increase of about 18% in tazobactam $T_{½}$ was observed. Following an i.v. infusion of 3 g piperacillin and 0.375g ^{14}C-tazobactam (60 microcuries), the $T_{½}$ of total radioactivity in plasma was 3.2 hours reflecting the elimination of M1.

Renal/Hepatic Impairment:
Mean plasma concentrations of piperacillin and tazobactam in subjects with decreased renal impairment are shown in **Table 2 (A, B)**. While decreasing renal function from CL_{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 $T_{½}$ increased (up to 2- and 4-fold, respectively) as renal function decreased. Dosage regimen adjustments are recommended at CL_{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 (hour)								
	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 (hour)								
	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

Hemodialysis removed approximately 30 to 40% of the piperacillin and tazobactam doses; M1 was removed from the systemic circulation similarly to tazobactam. To maintain predialysis 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 $T_{½}$ (25%) for piperacillin. Similar changes in tazobactam CL_T (25%) and $T_{½}$ (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.

Coadministration of a 1 g oral dose of probenecid did not significantly change C_{max} but lowered CL_R (20 to 25%) and increased $T_{½}$ for piperacillin by 21% and tazobactam by 71%.

Coadministration 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 coadministered.

Neutropenic:
In neutropenic subjects, after 30 minute infusions of 3 g piperacillin/0.375 g tazobactam every 4 hours for 5 days, the elimination $T_{½}$ 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. *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 ß-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 ß-lactamases at tazobactam levels achieved with the recommended dosing regimen.

There are important variables affecting the therapeutic effectiveness or the results of the susceptibility testing of an antibiotic, i.e., concentration of the bacterial inoculum, pH of the medium or body site, serum binding or media supplementation with sera and the test methodology.

Effects of the Inoculum Size
The presence of tazobactam reduces the marked inoculum effect observed with piperacillin against *Enterobacteriaceae* and *Haemophilus influenzae*. Against strains of the *Bacteroides fragilis* group, piperacillin/tazobactam showed an intermediate inoculum effect. The effect was observed at inoculums of 10^8 cfu/mL and affected mostly the bactericidal activity of the ß-lactam/inhibitor combination.

Effect of pH
The activity of piperacillin/tazobactam against most microorganisms is not adversely affected by a pH down to 5.5. However, some strains will be less susceptible (approximately fourfold increase in the MIC) at pH of 5.5.

Effect of Serum

Both piperacillin and tazobactam bind to plasma proteins. However, this binding did not appear to affect the results of susceptibility testing (MIC) if the test media was supplemented with 5% human serum.

Effect of Test Methodology or the Test Medium

Zone sizes obtained on DST (Diagnostic Sensitivity Test) and Iso-Sensitest agars showed similar zone sizes for 1450 paired sets of assays (96.1% of the 1450 strains showed agreement within 3 mm).

MIC results of piperacillin/tazobactam tested by the NCCLS agar and broth dilution methods were not significantly different; the mean piperacillin/tazobactam MICs were 3.2 and 3.3 µg/mL for the agar broth microdilution test, respectively.

Table 3 provides a summary of the *in vitro* activities of piperacillin and piperacillin/tazobactam against a number of clinical isolates.

Table 3: The *In Vitro* Activities of Piperacillin and Piperacillin/Tazobactam Against Clinical Isolates[(a)] of Various Gram-positive and Gram-negative Aerobic and Anaerobic Species

Organism	No. Strains	Drug	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)	Distribution of Isolates at Indicated Concentration (µg/mL)											
					≤ 0.12	0.25	0.5	1	2	4	8	16	32	64	128	≥ 256
Gram-Negative																
Acinetobacter spp.	77 77	P PT4[(b)]	16 4	128 32	12	4	1 2	3	2 8	7 12	15 15	30 13	9 1	3 2	6 4	4 1
Branhamella catarrhalis	25 25	P PT4	0.25 ≤ 0.125	1 ≤ 0.125	12 23	3	1	9			1	1				
Citrobacter diversus	20 20	P PT4	8 2	16 4	1	1		3	8	4 6	9 1	4 1	1			1
Citrobacter freundii	43 43	P PT4	4 2	128 32	1			1 7	15 19	12 11	5	1	2 1	2	4 1	3 1
Enterobacter aerogenes	44 44	P PT4	4 4	64 32				2 3	15 14	17 16	1	2 3	2 6	3 1	3	
Enterobacter cloacae	140 140	P PT4	2 2	> 128 128	1		1 4	17 23	55 61	36 24	4 2	1 3	3 7	1 1	8 10	14 4
Enterobacter spp.	14 14	P PT4	2 2	16 8			1	3 3	5 4	2 3	2 3	1				1
Escherichia coli	797 797	P PT4	2 2	> 128 4	1 14	1 9	8 56	178 314	340 311	59 49	12 18	17 11	26 5	16 3	30 2	109 5
Haemophilus influenzae	139 138	P PT4	≤ 0.125 ≤ 0.125	16 ≤ 0.125	90 130	2 3	4 2	22	4 2	1	3	1	1	1	1	10
Haemophilus spp.	39 39	P PT4	≤ 0.125 ≤ 0.125	2 0.5	20 28	3 6	3 2	9 2	1 1	2			1			

Organism	No. Strains	Drug	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)	Distribution of Isolates at Indicated Concentration (µg/mL)											
					≤ 0.12	0.25	0.5	1	2	4	8	16	32	64	128	≥ 256
Klebsiella spp.	98 98	P PT4	8 2	32 4		4	2	2 22	11 51	24 12	34 5	15	4	4	1 1	3 1
Klebsiella pneumoniae	256 256	P PT4	8 2	128 8	3	2	5	4 27	16 97	81 86	87 11	24 12	11 5	2 2	7 1	24 5
Proteus indole negative	156 156	P PT4	1 0.25	4 0.5	5 20	37 73	27 49	65 8	4 1	3 4	6	2 1	2	1	1	3
Proteus indole positive	59 59	P PT4	1 0.25	32 0.5	2 17	5 25	8 12	28 3	4 2	4	1		2	4		1
Providencia spp.	13 13	P PT4	2 1	64 8		1 2	1 3	4 2	2 3	1 1	1	1	1 1	2		1
Pseudomonas aeruginosa	313 312	P PT4	4 4	64 32	2	2 5	3 6	7 3	34 46	129 143	55 50	33 24	16 14	13 5	10 5	11 9
Pseudomonas spp.	24 25	P PT4	2 2	16 16	8		2 1	6 3	6 2	6 7	1 1	2 2	1			1
Serratia spp.	53 53	P PT4	2 2	64 8		2	6	10 10	18 19	11 10	5 3	2 2	1	1 1	1	4
Other Gram-negative Rods	31 31	P PT4	1 0.25	2 1	9 15	3 4	3 6	12 3	1 1		1	3 1				
Xanthomonas maltophilia	43 43	P PT4	> 128 64	> 128 > 128				1	1	1	1	3 10	3 6	4 4	10 4	22 16
Gram-positive																
Corynebacterium spp.	19 19	P PT4	1 0.5	> 128 > 128	3 7	1 2	1 3	6	1 1	1 2	3 1		1	1		2 2
Enterococcus faecalis	277 258	P PT4	4 4	4 4	2 3	1 4	1 3	30 37	58 78	170 119	8 8	2 2	1 1	1 1	2	1 2
Enterococcus faecium	31 28	P PT4	8 8	> 128 > 128	2 2	1 1		2 1	1 1	7 6	5 5	3 3	2 1	1 2	3 2	4 4
Enterococcus spp.	65 27	P PT4	4 4	32 128	1 2		1	7 4	17 3	26 9	3 2	1 1	4 3		1 1	4 2
Other Gram-positive Rods	19 19	P PT4	1 1	2 2	1 2	2 4	5 3	7 8	3 1				1 1			
Staphylococcus aureus	487 475	P PT4	4 1	64 2	2 7	13	11 62	90 229	54 135	113 25	65 3	61	33	21 1	19	18
Staphylococcus coag. negative	203 201	P PT4	1 0.5	8 2	4 40	22 49	24 45	69 46	37 17	25 3	12 1	7	2			1
Streptococcus Group A	50 50	P PT4	0.25 ≤ 0.125	1 ≤ 0.125	22 48	4 1	1 1	23								
Streptococcus Group B	92 91	P PT4	0.5 0.25	1 0.5	16 28	27 34	16 21	32 8	1							
Streptococcus pneumoniae	149 149	P PT4	≤ 0.125 ≤ 0.125	1 ≤ 0.125	109 135	6 5	2 5	30 2	1	2		1				
Streptococcus spp.	256	P	0.25	2	111	27	6	85	12	8	2	2			1	2

Organism	No. Strains	Drug	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)	Distribution of Isolates at Indicated Concentration (µg/mL)											
					≤ 0.12	0.25	0.5	1	2	4	8	16	32	64	128	≥ 256
	256	PT4	≤ 0.125	1	175	35	15	10	9	3	4	1	1		1	2
Anaerobes																
Bacteroides fragilis group	338 339	P PT4	8 1	64 8	70	37	1 32	9 37	39 42	65 52	65 52	65 11	47 5	16	11 1	20
Bacteroides pigmented	36 36	P PT4	1 ≤ 0.125	16 2	6 28	3 1	2 1	8 2	2 4	5	4	4	2			
Bacteroides spp.	101 101	P PT4	4 ≤ 0.125	16 2	7 76	4 5	6 1	17 5	9 6	13 4	14 4	21	8	2		
Clostridium perfringens	36 36	P PT4	≤ 0.125 ≤ 0.125	1 ≤ 0.125	20 33	4 2		12 1								
Gram-positive																
Clostridium spp.	24 24	P PT4	1 1	8 8	6 8	1 2	2 2	6 3	2 4	4 2	1 2	1 1		1		
Fusobacterium spp.	25 25	P PT4	≤ 0.125 ≤ 0.125	4 4	15 20	2 1	1	3 1		3 2		1	1			
Miscellaneous Anaerobes	19 19	P PT4	0.5 ≤ 0.125	16 2	6 10	3 2	3 2	4 2	2		1	1 1			1	
Misc. Anaerobic Gram-positive Rods	37 37	P PT4	1 ≤ 0.125	16 16	11 22	3 3	2 3	12 4	2		1	6 3	1 1			
Peptostreptococcus	166 166	P PT4	≤ 0.125 ≤ 0.125	1 0.5	97 138	8 10	4 4	45 4	1 1	2 2	7 6	2 1				

[(a)] Isolates from patients enrolled in clinical evaluation studies of piperacillin/tazobactam in North America and Europe.
[(b)] MICs are expressed as concentration of piperacillin in the presence of the 4 µg/mL of tazobactam.

Susceptibility Tests

Measurement of MIC or MBC and achieved antimicrobial compound concentrations may be appropriate to guide therapy in some infections. (See **DETAILED PHARMACOLOGY** for further information on drug concentrations achieved in infected body sites and other pharmacokinetic properties of this antimicrobial drug product.)

Diffusion techniques

Quantitative methods that require measurement of zone diameters provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. The NCCLS standardized procedure has been recommended for use with disks to test the susceptibility of microorganisms to piperacillin/tazobactam using the 100 µg/10 µg piperacillin/tazobactam disk. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for piperacillin/tazobactam.

Reports from the laboratory giving results of the standard single-disk susceptibility test with a 100 µg/10 µg piperacillin/tazobactam disk should be interpreted according to the following criteria:

For *Enterobacteriaceae*:

Zone Diameter (mm)	Interpretation
≥ 21	Susceptible (S)
18 – 20	Intermediate (I)
≤ 17	Resistant (R)

For *Haemophilus* species:

Zone Diameter (mm)	Interpretation
≥ 27	Susceptible (S)
≤ 26	Resistant (R)

For *Pseudomonas aeruginosa* species:

Zone Diameter (mm)	Interpretation
≥ 18	Susceptible (S)
≤ 17	Resistant (R)

For *Staphylococcus* species:

Zone Diameter (mm)	Interpretation
≥ 20	Susceptible (S)
≤ 19	Resistant (R)

A report of "Susceptible" indicates that the pathogen is likely to be inhibited by usually achievable concentrations of the antimicrobial compound in the blood. A report of "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 "Resistant" indicates that usually achievable concentrations of the antimicrobial compound in the blood are unlikely to be inhibitory and other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control microorganisms. The 100 μg/10 μg piperacillin/tazobactam disk should give the following zone diameters in these laboratory test quality control strains:

Microorganism	Zone Diameter (mm)
Escherichia coli ATCC 25922	24 – 30
Escherichia coli ATCC 35218	25 – 31
Pseudomonas aeruginosa ATCC 27853	25 – 33
Haemophilus influenzae ATCC 49247	32 – 36

Dilution techniques

Quantitative methods that are used to determine minimum inhibitory concentrations provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure (NCCLS, Method for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically) uses a dilution method (broth, agar, or microdilution) or equivalent with piperacillin/tazobactam powder. The MIC values obtained should be interpreted according to the following criteria:

For *Enterobacteriaceae*:

MIC (µg/mL)	Interpretation
≤ 16	Susceptible (S)
32 – 64	Intermediate (I)
≥ 128	Resistant (R)

For *Pseudomonas aeruginosa*:

MIC (µg/mL)	Interpretation
≤ 64	Susceptible (S)
≥ 128	Resistant (R)

For *Haemophilus* species:

MIC (µg/mL)	Interpretation
≤ 1	Susceptible (S)
≥ 2	Resistant (R)

For *Staphylococcus* species:

MIC (µg/mL)	Interpretation
≤ 8	Susceptible (S)
≥ 16	Resistant (R)

Interpretation is as stated above for results using diffusion techniques.

As with standard diffusion techniques, dilution methods require the use of laboratory control microorganisms. Standard piperacillin/tazobactam (8:1) powder should provide the following MIC values:

Microorganism	MIC (µg/mL)
Eschericia coli ATCC 25922	1 – 4
Eschericia coli ATCC 35218	2 – 8
Pseudomonas aeruginosa ATCC 27853	1 – 8
Staphylococcus aureus ATCC 29213	1 – 4
Haemophilus influenzae ATCC 49247	0.06 – 0.25

Anaerobic techniques

For anaerobic bacteria, the susceptibility to piperacillin/tazobactam can be determined by the reference agar dilution method or by alternate standardized test methods.

For *Bacteroides* species, the dilution and zone diameters should be interpreted as follows:

MIC (µg/mL)	Zone Diameter (mm)	Interpretation
≤ 16	≥ 21	Susceptible (S)
≥ 32	≤ 20	Resistant (R)

As with standard diffusion techniques, dilution methods require the use of laboratory control microorganisms. Standard piperacillin/tazobactam lyophilized powder should provide the following MIC values:

Microorganism	MIC (µg/mL)
Bacteroides fragilis ATCC 25285	1 – 4

TOXICOLOGY

Acute Toxicity

In mice (10/sex), i.v. 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, i.v. 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 convulsion were observed. In mice (10/sex), i.v. doses of tazobactam up to 3500 mg/kg resulted in no mortality and no signs of toxicity or treatment-related effects while an i.v. 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, i.v. 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 i.v., shallow and frequent respiration, muscular hypertonia, staggering, and convulsions were observed. Following administration of i.p. doses of 4000:1000 mg/kg of piperacillin:tazobactam, there was no mortality. At this i.p. 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, i.v. doses of piperacillin resulted in death in 8 of 10 females at 1000 mg/kg (bid), 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 i.p. 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), i.v. 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, i.v. 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 i.v. 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 ß-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.

Reproductive Toxicology

Tazobactam alone or in combination with piperacillin did not affect fertility in rats. IP doses of tazobactam or piperacillin:tazobactam caused adverse changes in reproductive performance of F_0 generation only at doses greater than or equal to 160:40 mg/kg/day piperacillin:tazobactam that caused maternal toxicity (decreased food consumption and/or body weights). The F_1 and F_2 generations were unaffected.

Intravenous doses up to 3000 mg/kg/day of tazobactam and 3000:750 mg/kg/day piperacillin:tazobactam were not teratogenic in mice and rats. Postnatal growth and development, behaviour and reproductive performance of the F_1 generation were unaffected by *in utero* exposure of rats to tazobactam alone or in combination with piperacillin. Mortality in rats was caused by a rapid injection rate of piperacillin or piperacillin/tazobactam but is not relevant to clinical usage.

Perinatal and Postnatal Toxicity

In rats, i.p. doses of tazobactam and piperacillin/tazobactam caused effects on perinatal growth and postnatal growth and development at doses (320 mg/kg/day of tazobactam and 640:160 mg/kg/day of piperacillin/tazobactam) that caused maternal toxicity (decreased food consumption and/or body weight gain).

Carcinogenicity, Mutagenicity, Impairment of Fertility

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

Piperacillin/tazobactam:

Piperacillin/tazobactam was negative in microbial mutagenicity assays at concentrations up to 14.84/1.85 µg/plate. Piperacillin/tazobactam was negative in the unscheduled DNA synthesis (UDS) test at concentrations up to 5689/711 µg/mL. Piperacillin/tazobactam was negative in a mammalian point mutation (Chinese hamster ovary cell HPRT) assay at concentrations up to 8000/1000 µg/mL. Piperacillin/tazobactam was negative in a mammalian cell (BALB/c-3T3) transformation assay at concentrations up to 8/1 µg/mL. *In vivo*, piperacillin/tazobactam did not induce chromosomal aberrations in rats dosed i.v. 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 μg/plate. There was no DNA damage in bacteria (Rec assay) exposed to piperacillin at concentrations up to 200 μg/disc. Piperacillin was negative in the UDS test at concentrations up to 10,000 μg/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 μg/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 μg/mL, which is 8 times the human plasma concentration. *In vivo*, piperacillin did not induce chromosomal aberrations in mice at i.v. doses up to 2000 mg/kg/day or rats at i.v. 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 i.v. doses up to 2000 mg/kg/day, which is similar to the human dose based on body surface area. When mice were given piperacillin at i.v. doses up to 2000 mg/kg/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 i.v. doses up to 2000 mg/kg/day did not show increased mutation frequencies.

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

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PART III: CONSUMER INFORMATION
PrPIPERACILLIN/TAZOBACTAM FOR INJECTION
Sterile piperacillin sodium/tazobactam sodium
Lyophilized Powder for Injection
For Intravenous Use

This leaflet is part III of a three-part "Product Monograph" published when Piperacillin/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/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/Tazobactam for Injection is used for the treatment of bacterial infections.

What it does:
Piperacillin/Tazobactam for Injection is an antibiotic which helps stop the spread of infection by inhibiting the growth of bacteria.

When it should not be used:
Piperacillin/Tazobactam for Injection should not be used by patients who are allergic to:
- any ingredient in the drug;
- penicillin antibiotics (i.e., amoxicillin);
- cephalosporins antibiotics (i.e., cephalexin);
- ß-lactamase inhibitors (i.e., clavulanic acid).

What the medicinal ingredient is:
Piperacillin and tazobactam.

What the nonmedicinal ingredients are:
There are no nonmedicinal ingredients.

What dosage forms it comes in:
Piperacillin/Tazobactam for Injection is available as 2.25 g, 3.375 g, and 4.5 g of powder in glass vials. The powder is mixed with sterile liquid to give a solution for injection by your doctor.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions
- Severe and sometimes fatal allergic reactions may occur in people who are allergic to penicillins, cephalosporins, or other allergens.
- If an allergic reaction occurs during therapy with Piperacillin/Tazobactam for Injection, the medication should be stopped and immediate medical attention should be sought.

BEFORE you use Piperacillin/Tazobactam for Injection, talk to your doctor or pharmacist if:
- you are allergic to penicillins, cephalosporins, or other allergens;
- you are pregnant, planning to become pregnant, or are breast-feeding;
- you have cystic fibrosis, bowel inflammation, bleeding problems, or kidney problems;
- you are on dialysis, or if you have a history of severe diarrhea or bowel problems due to an antibiotic;
- you are on a salt-restricted diet or have low blood potassium levels.

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with Piperacillin/Tazobactam for Injection include:
- aminoglycosides (a type of antibiotic; i.e., tobramycin),
- probenecid (a drug used to treat gout),
- drugs used to thin blood (i.e., heparin),
- vecuronium (a muscle relaxant), and
- methotrexate (a drug used to treat cancer).

Lactated Ringer's solution is not compatible with Piperacillin/Tazobactam for Injection.

When piperacillin/tazobactam is administered concurrently with another antibiotic, the drugs should not be mixed in the same solution and must be administered separately.

PROPER USE OF THIS MEDICATION

Usual dose:
The usual total daily dose of Piperacillin/Tazobactam for Injection for adults is 3.375 g, administered by intravenous infusion, every six hours, for a total dose of 13.5 g per day.

For nosocomial pneumonia (hospital-acquired pneumonia), the daily dose of piperacillin/tazobactam for adults is 4.5 g plus an aminoglycoside (type of antibiotic) every six hours, for a total of 18.0 g per day.

If you have kidney problems, the doctor will adjust the dose to suit you.

Overdose:
Symptoms of overdose include: nausea, vomiting, diarrhea, neuromuscular excitability, and convulsions.

In the event of overdose, patients should receive medical attention immediately.

Missed Dose:
In order to get the best results from your treatment with Piperacillin/Tazobactam for Injection you should take it on a regular basis. If you miss one of your Piperacillin/Tazobactam for Injection doses, ask your doctor for further instructions. Do not take a double dose of this drug without your physician's consent.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The most common side effects in patients treated with Piperacillin/Tazobactam for Injection include: allergic reactions, diarrhea, headache, constipation, nausea, insomnia, rash, vomiting, heartburn, itching, stool changes, fever, agitation, pain, fungal infection, high blood pressure, dizziness, abdominal pain, chest pain, swelling, anxiety, rhinitis, and difficulty breathing.

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	Severe diarrhea, stomach pain/cramps, or bloody stools			✓
	Chest Pain			✓
	Difficulty breathing			✓
Uncommon	Severe allergic reactions (rash; hives; itching; difficulty breathing; tightness in the chest; swelling of the mouth, face, lips, or tongue)			✓
	Seizures			✓
	Fast, slow, or irregular heartbeat			✓
	Yellowing of the eyes or skin			✓

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

HOW TO STORE IT

Piperacillin/Tazobactam for Injection vials should be stored at controlled room temperature between 15 and 30°C.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada through the Canada Vigilance Program collects information on serious and unexpected side effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Canada Vigilance:

by toll-free telephone: 866-234-2345
by toll-free fax: 866-678-6789
Online: www.healthcanada.gc.ca/medeffect
by email: CanadaVigilance@hc-sc.gc.ca

By regular mail:
CanadaVigilance National Office
Marketed Health Products Safety and Effectiveness Information Division
Marketed Health Products Directorate
Health Products and Food Branch
Health Canada
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

NOTE: Should you require information related to the management of the side effect, please contact your health care provider before notifying Canada Vigilance. 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:

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This leaflet was prepared by *Pharma Strides Canada Corp.*

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