PIPERACILLIN AND TAZOBACTAM FOR INJECTION, USP

PHARMACY BULK PACKAGE
NOT FOR DIRECT INFUSION

℞only

RECONSTITUTED STOCK SOLUTION MUST BE TRANSFERRED AND FURTHER DILUTED FOR I.V. INFUSION

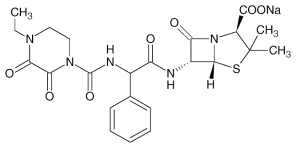
To reduce the development of drug-resistant bacteria and maintain the effectiveness of Piperacillin and Tazobactam for Injection, USP and other antibacterial drugs, Piperacillin and Tazobactam for Injection, USP should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

DESCRIPTION

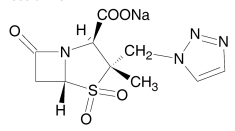
Package
The PHARMACY BULK PACKAGE BOTTLE is a container of sterile preparation which contains many single doses for parenteral use. The contents are intended for use in a pharmacy admixture program and are restricted to the preparation of admixtures for intravenous infusion.

Product
Piperacillin and Tazobactam for Injection, USP is an injectable antibacterial combination, product consisting of the semisynthetic antibiotic piperacillin sodium and the β-lactamase inhibitor tazobactam sodium for intravenous administration.

Piperacillin sodium is derived from D(-)-α-aminobenzyl-penicillin. The chemical name of piperacillin sodium is sodium (2*S*,5*R*,6*R*)-6-[(*R*)-2-(4-ethyl-2,3-dioxo-1-piperazine-carboxamido)-2-phenylacetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate. The chemical formula is $C_{23}H_{26}N_5NaO_7S$ and the molecular weight is 539.5. The chemical structure of piperacillin sodium is:



Tazobactam sodium, a derivative of the penicillin nucleus, is a penicillanic acid sulfone. Its chemical name is 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. The chemical formula is $C_{10}H_{11}N_4NaO_5S$ and the molecular weight is 322.3. The chemical structure of tazobactam sodium is:



Piperacillin and Tazobactam for Injection, USP parenteral combination is a white to off-white sterile, cryodesiccated powder consisting of piperacillin and tazobactam as their sodium salts packaged in glass vials. The product does not contain excipients or preservatives.

Each Piperacillin and Tazobactam for Injection USP, 40.5 g pharmacy bulk package bottle contains piperacillin sodium equivalent to 36 grams of piperacillin and tazobactam sodium equivalent to 4.5 g of tazobactam sufficient for delivery of multiple doses.

Piperacillin and Tazobactam for Injection, USP is a monosodium salt of piperacillin and a monosodium salt of tazobactam containing a total of 2.36 mEq (54.28 mg) of Na^+ per gram of piperacillin in the combination product.

CLINICAL PHARMACOLOGY

Adults
Peak plasma concentrations of piperacillin and tazobactam are attained immediately after completion of an intravenous infusion of Piperacillin and Tazobactam for Injection. Piperacillin plasma concentrations, following a 30 minute infusion of Piperacillin and Tazobactam for Injection, were similar to those attained when equivalent doses of piperacillin were administered alone, with mean peak plasma concentrations of approximately 134 mcg/mL, 242 mcg/mL and 298 mcg/mL for the 2.25 g, 3.375 g and 4.5 g Piperacillin and Tazobactam for Injection doses, respectively. The corresponding mean peak plasma concentrations of tazobactam were 15 mcg/mL, 24 mcg/mL and 34 mcg/mL, respectively.

Following a 30 minute I.V. infusion of 3.375 g Piperacillin and Tazobactam for Injection every 6 hours, steady-state plasma concentrations of piperacillin and tazobactam were similar to those attained after the first dose. In like manner, steady-state plasma concentrations were not different from those attained after the first dose when 2.25 g or 4.5 g doses of Piperacillin and Tazobactam for Injection were administered via 30 minute infusions every 6 hours. Steady-state plasma concentrations after 30 minute infusions every 6 hours are provided in **Table 1.**

Following single or multiple Piperacillin and Tazobactam for Injection doses to healthy subjects, the plasma half-life of piperacillin and of tazobactam ranged from 0.7 to 1.2 hours and was unaffected by dose or duration of infusion.

Piperacillin is metabolized to a minor microbiologically active desethyl metabolite. Tazobactam is metabolized to a single metabolite that lacks pharmacological and antibacterial activities. Both piperacillin and tazobactam are eliminated via the kidney by glomerular filtration and tubular secretion. Piperacillin is excreted rapidly as unchanged drug with 68% of the administered dose excreted in the urine. Tazobactam and its metabolite are eliminated primarily by renal excretion with 80% of the administered dose excreted as unchanged drug and the remainder as the single metabolite. Piperacillin, tazobactam, and desethyl piperacillin are also secreted into the bile.

Both piperacillin and tazobactam are approximately 30% bound to plasma proteins. The protein binding of either piperacillin or tazobactam is unaffected by the presence of the other compound. Protein binding of the tazobactam metabolite is negligible.

Piperacillin and tazobactam are widely distributed into tissues and body fluids including intestinal mucosa, gallbladder, lung, female reproductive tissues (uterus, ovary, and fallopian tube), interstitial fluid, and bile. Mean tissue concentrations are generally 50% to 100% of those in plasma. Distribution of piperacillin and tazobactam into cerebrospinal fluid is low in subjects with non-inflamed meninges, as with other penicillins.

After the administration of single doses of piperacillin/tazobactam to subjects with renal impairment, the half-life of piperacillin and of tazobactam increases with decreasing creatinine clearance. At creatinine clearance below 20 mL/min, the increase in half-life is twofold for piperacillin and fourfold for tazobactam 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 usual recommended daily dose of Piperacillin and Tazobactam for Injection. (See **DOSAGE AND ADMINISTRATION** section for specific recommendations for the treatment of patients with 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 6% and 21% of the piperacillin and tazobactam 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** section.

The half-life of piperacillin and of tazobactam increases by approximately 25% and 18%, respectively, in patients with hepatic cirrhosis compared to healthy subjects. However, this difference does not warrant dosage adjustment of Piperacillin and Tazobactam for Injection due to hepatic cirrhosis.

TABLE 1 STEADY STATE MEAN PLASMA CONCENTRATIONS IN ADULTS AFTER 30 MINUTE INTRAVENOUS INFUSION OF PIPERACILLIN/ TAZOBACTAM EVERY 6 HOURS

PIPERACILLIN

		Plasma Concentrations** (mcg/mL)						AUC** (mcg•hr/mL)
Piperacillin/ Tazobactam Dose[a]	No. of Evaluable Subjects	30 min	1 hr	2 hr	3 hr	4 hr	6 hr	AUC_{0-6}
2.25 g	8	134 (14)	57 (14)	17.1 (23)	5.2 (32)	2.5 (35)	0.9 (14)[b]	131 (14)
3.375 g	6	242 (12)	106 (8)	34.6 (20)	11.5 (19)	5.1 (22)	1 (10)	242 (10)
4.5 g	8	298 (14)	141 (19)	46.6 (28)	16.4 (29)	6.9 (29)	1.4 (30)	322 (16)

TAZOBACTAM

		Plasma Concentrations** (mcg/mL)						AUC** (mcg•hr/mL)
Piperacillin/ Tazobactam Dose[a]	No. of Evaluable Subjects	30 min	1 hr	2 hr	3 hr	4 hr	6 hr	AUC_{0-6}
2.25 g	8	14.8 (14)	7.2 (22)	2.6 (30)	1.1 (35)	0.7 (6)[c]	<0.5	16 (21)
3.375 g	6	24.2 (14)	10.7 (7)	4 (18)	1.4 (21)	0.7 (16)[b]	<0.5	25 (8)
4.5 g	8	33.8 (15)	17.3 (16)	6.8 (24)	2.8 (25)	1.3 (30)	<0.5	39.8 (15)

** Numbers in parentheses are coefficients of variation (CV%).
a: Piperacillin and tazobactam were given in combination.
b: N = 4
c: N = 3

Pediatrics
Piperacillin and tazobactam pharmacokinetics were studied in pediatric patients 2 months of age and older. The clearance of both compounds is slower in the younger patients compared to older children and adults.

In a population PK analysis, estimated clearance for 9 month-old to 12 year-old patients was comparable to adults, with a population mean (SE) value of 5.64 (0.34) mL/min/kg. The piperacillin clearance estimate is 80% of this value for pediatric patients 2 - 9 months old. In patients younger than 2 months of age, clearance of piperacillin is slower compared to older children; however, it is not adequately characterized for dosing recommendations. The population mean (SE) for piperacillin distribution volume is 0.243 (0.011) L/kg and is independent of age.

Microbiology
Piperacillin sodium exerts bactericidal activity by inhibiting septum formation and cell wall synthesis of susceptible bacteria. *In vitro,* piperacillin is active against a variety of gram-positive and gram-negative aerobic and anaerobic bacteria. 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.

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 USAGE** section.

Aerobic and facultative Gram-positive microorganisms:
Staphylococcus aureus (excluding methicillin and oxacillin-resistant isolates)

Aerobic and facultative Gram-negative microorganisms:
Acinetobacter baumanii

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 *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 (excluding methicillin and oxacillin resistant isolates)
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.[1,2] MIC values should be determined using serial dilutions of piperacillin combined with a fixed concentration of 4 mcg/mL tazobactam. The MIC values obtained should be interpreted according to criteria provided in **Table 2**.

Diffusion Technique:
Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[1,3] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 100 mcg of piperacillin and 10 mcg of tazobactam to test the susceptibility of microorganisms to piperacillin/tazobactam. The disk diffusion interpreted criteria are provided in **Table 2**.

Anaerobic Techniques
For anaerobic bacteria, the susceptibility to piperacillin/tazobactam can be determined by the reference agar dilution method.[4]

TABLE 2 SUSCEPTIBILITY INTERPRETIVE CRITERIA FOR PIPERACILLIN/TAZOBACTAM

	Susceptibility Test Result Interpretive Criteria					
	Minimal Inhibitory Concentration (MIC in mcg/mL)			Disk Diffusion (Zone Diameter in mm)		
Pathogen	S	I	R	S	I	R
Enterobacteriaceae and *Acinetobacter baumanii*	≤ 16	32 - 64	≥ 128	≥ 21	18 - 20	≤ 17
Haemophilus influenzae[a]	≤ 1	-	≥ 2	-	-	-
Pseudomonas aeruginosa	≤ 64	-	≥ 128	≥ 18	-	≤ 17
Staphylococcus aureus	≤ 8	-	≥ 16	≥ 20	-	≤ 19
Bacteroides fragilis group	≤ 32	64	≥ 128	-	-	-

a: 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.

A report of S ("Susceptible") indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of I ("Intermediate") indicates that the results 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 possible 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, which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of R ("Resistant") indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be considered.

Quality Control
Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the test procedures.[1,2,3,4] Standard piperacillin/tazobactam powder should provide the following ranges of values noted in **Table 3**. Quality control microorganisms are specific strains of microorganisms with intrinsic biological properties relating to resistance mechanisms and their genetic expression within the microorganism; the specific strains used for microbiological quality control are not clinically significant.

TABLE 3 ACCEPTABLE QUALITY CONTROL RANGES FOR PIPERACILLIN/TAZOBACTAM TO BE USED IN VALIDATION OF SUSCEPTIBILITY TEST RESULTS

	Acceptable Quality Control Ranges	
QC Strain	Minimum Inhibitory Concentration Range (MIC in mcg/mL)	Disk Diffusion Zone Diameter Ranges in mm
Escherichia coli ATCC 25922	1 - 4	24 – 30
Escherichia coli ATCC 35218	0.5 - 2	24 – 30
Pseudomonas aeruginosa ATCC 27853	1 - 8	25 – 33
Haemophilus influenzae[a] ATCC 49247	0.06 - 0.5	-
Staphylococcus aureus ATCC 29213	0.25 - 2	-
Staphylococcus aureus ATCC 25923	-	27 – 36
Bacteroides fragilis ATCC 25285	0.12 - 0.5	-
Bacteroides thetaiotaomicron ATCC 29741	4 - 16	-

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.

INDICATIONS AND USAGE

Piperacillin and Tazobactam for Injection is indicated for the treatment of patients with moderate to severe infections caused by piperacillin-resistant, piperacillin/tazobactam-susceptible, β-lactamase producing strains of the designated microorganisms in the specified conditions listed below:

Appendicitis (complicated by rupture or abscess) and peritonitis caused by piperacillin-resistant, β-lactamase producing strains of *Escherichia coli* or the following members of the *Bacteroides fragilis* group: *B. fragilis, B. ovatus, B. thetaiotaomicron,* or *B. vulgatus*. The individual members of this group were studied in less than 10 cases.

Uncomplicated and complicated skin and skin structure infections, including cellulitis, cutaneous abscesses and ischemic/diabetic foot infections caused by piperacillin-resistant, β-lactamase producing strains of *Staphylococcus aureus.*

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

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

Nosocomial pneumonia (moderate to severe) caused by piperacillin-resistant, β-lactamase producing strains of *Staphylococcus aureus* and by piperacillin/tazobactam-susceptible *Acinetobacter baumanii, 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**.)

Piperacillin and Tazobactam for Injection is indicated only for the specified conditions listed above. Infections caused by piperacillin-susceptible organisms, for which piperacillin has been shown to be effective, 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 mixed infections caused by piperacillin-susceptible organisms and piperacillin-resistant, β-lactamase producing organisms susceptible to Piperacillin and Tazobactam for Injection should not require the addition of another antibiotic. (See **DOSAGE AND ADMINISTRATION**.)

Piperacillin and Tazobactam for Injection is useful as presumptive therapy in the indicated conditions prior to the 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 the results of culture(s) and antimicrobial susceptibility testing are known.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Piperacillin and Tazobactam for Injection and other antibacterial drugs, Piperacillin and Tazobactam for Injection should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

CONTRAINDICATIONS

Piperacillin and Tazobactam for Injection is contraindicated in patients with a history of allergic reactions to any of the penicillins, cephalosporins, or β-lactamase inhibitors.

WARNINGS

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC/ANAPHYLACTOID) REACTIONS (INCLUDING SHOCK) HAVE BEEN REPORTED IN PATIENTS RECEIVING THERAPY WITH PENICILLINS INCLUDING PIPERACILLIN AND TAZOBACTAM FOR INJECTION. THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY OR A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE INITIATING THERAPY WITH PIPERACILLIN AND TAZOBACTAM FOR INJECTION, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, OR OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, PIPERACILLIN AND TAZOBACTAM FOR INJECTION SHOULD BE DISCONTINUED AND APPROPRIATE THERAPY INSTITUTED. **SERIOUS ANAPHYLACTIC/ANAPHYLACTOID REACTIONS (INCLUDING SHOCK) REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.**

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including Piperacillin and Tazobactam for Injection, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile.*

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile,* and surgical evaluation should be instituted as clinically indicated.

PRECAUTIONS

General
Bleeding manifestations 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, Piperacillin and Tazobactam for Injection should be discontinued and appropriate therapy instituted.

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.

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).

Piperacillin and Tazobactam for Injection is a monosodium salt of piperacillin and a monosodium salt of tazobactam and contains a total of 2.36 mEq (54.28 mg) of 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.

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

In patients with creatinine clearance ≤ 40 mL/min and dialysis patients (hemodialysis and CAPD), the intravenous dose should be adjusted to the degree of renal function impairment. (See **DOSAGE AND ADMINISTRATION**.)

Prescribing Piperacillin and Tazobactam for Injection in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of development of drug-resistant bacteria.

Information for Patients
Patients should be counseled that antibacterial drugs including Piperacillin and Tazobactam for Injection should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When Piperacillin and Tazobactam for Injection is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by Piperacillin and Tazobactam for Injection or other antibacterial drugs in the future.

Diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.

Laboratory Tests
Periodic assessment of hematopoietic function should be performed, especially with prolonged therapy, i.e., ≥ 21 days. (See **ADVERSE REACTIONS, Adverse Laboratory Events**.)

Drug Interactions
Aminoglycosides
The mixing of beta-lactam antibiotics with aminoglycosides *in vitro* can result in substantial inactivation of the aminoglycoside. However, amikacin and gentamicin have been shown to be compatible *in vitro* with piperacillin and tazobactam in certain diluents at specific concentrations for a simultaneous Y-site infusion. (See **DOSAGE AND ADMINISRATION.**)

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 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
Probenecid administered concomitantly with Piperacillin and Tazobactam for Injection prolongs the half-life of piperacillin by 21% and of tazobactam by 71%.

Vancomycin
No pharmacokinetic interactions have been noted 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, or other drugs that may affect the blood coagulation system or the thrombocyte function.

Vecuronium
Piperacillin when 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
Limited data suggests that co-administration of methotrexate and piperacillin may reduce the clearance of methotrexate due to competition for renal secretion. The impact of tazobactam on the elimination of methotrexate has not been evaluated. If concurrent therapy is necessary, serum concentrations of methotrexate as well as the signs and symptoms of methotrexate toxicity should be frequently monitored.

Drug/Laboratory Test 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 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 the 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.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term carcinogenicity studies in animals have not been conducted 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 concentrations 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 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 mcg/plate. There was no DNA damage in bacteria (Rec assay) exposed to piperacillin at concentrations up to 200 mcg/disk. Piperacillin was negative in the UDS test at concentrations up to 10,000 mcg/mL. In a mammalian point mutation (mouse lymphoma cells) assay, piperacillin was positive at concentrations ≥2500 mcg/mL. Piperacillin was negative in a cell (BALB/c-3T3) transformation assay at concentrations up to 3000 mcg/mL. *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 half (mice) or similar (rats) to the maximum recommended human daily dose based on body-surface area (mg/m^2). In another *in vivo* test, there was no dominant lethal effect when piperacillin was administered to rats at I.V. doses up to 2000 mg/kg/day, which is similar to the maximum recommended human daily dose based on body-surface area (mg/m^2). When mice were administered piperacillin at I.V. doses up to 2000 mg/kg/day, which is half the maximum recommended human daily 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 administered 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 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 I.V. doses up to 5000 mg/kg, which is 23 times the maximum recommended human daily dose based on body-surface area (mg/m^2).

Pregnancy

Teratogenic effects—Pregnancy Category B

Piperacillin/tazobactam

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 administered up to a dose which is 1 to 2 times and 2 to 3 times the human dose of piperacillin and tazobactam, respectively, based on body-surface area (mg/m^2).

Piperacillin and tazobactam cross the placenta in humans.

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 maximum recommended human daily 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 at doses up to 3 times 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 tazobactam administered at doses up to 6 and 14 times, respectively, 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 those found in maternal plasma.

There are, however, no adequate and well-controlled studies with the piperacillin/tazobactam combination or with piperacillin or tazobactam alone in pregnant women. Because animal reproduction studies are not always predictive of the human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

Piperacillin is excreted in low concentrations in human milk; tazobactam concentrations in human milk have not been studied. Caution should be exercised when Piperacillin and Tazobactam for Injection is administered to a nursing woman.

Pediatric Use

Use of Piperacillin and Tazobactam for Injection in pediatric patients 2 months of age or older with appendicitis and/or peritonitis is supported by evidence from well-controlled studies and pharmacokinetic studies in adults and in pediatric patients. This includes a prospective, randomized, comparative, open-label clinical trial with 542 pediatric patients 2-12 years of age with complicated intra-abdominal infections, in which 273 pediatric patients received piperacillin/tazobactam. Safety and efficacy in pediatric patients less than 2 months of age have not been established (see **CLINICAL PHARMACOLOGY** and **DOSAGE AND ADMINISTRATION**).

There are no dosage recommendations for Piperacillin and Tazobactam for Injection in pediatric patients with impaired renal function.

Geriatric Use

Patients over 65 years 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**.)

In general, dose selection for an elderly patient should be cautious, 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 such diseases 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. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

ADVERSE REACTIONS

Adverse Events From Clinical Trials

During the initial 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%).

Additional adverse systemic clinical events reported in 1% or less of the patients in the initial North American trials are listed below within each body system.

Autonomic nervous system —hypotension, ileus, syncope

Body as a whole —rigors, back pain, malaise

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

Pseudomembranous colitis was reported in one patient during the clinical trials. The onset of pseudomembranous colitis symptoms may occur during or after antibacterial treatment. (See **WARNINGS**.)

Hearing and Vestibular System —tinnitus

Hypersensitivity —anaphylaxis

Metabolic and Nutritional —symptomatic hypoglycemia, thirst

Musculoskeletal —myalgia, arthralgia

Platelets, Bleeding, Clotting —mesenteric embolism, purpura, epistaxis, pulmonary embolism (See **PRECAUTIONS, General**.)

Psychiatric —confusion, hallucination, depression

Reproductive, Female —leukorrhea, vaginitis

Respiratory —pharyngitis, pulmonary edema, bronchospasm, coughing

Skin and Appendages —genital pruritus, diaphoresis

Special senses —taste perversion

Urinary —retention, dysuria, oliguria, hematuria, incontinence

Vision —photophobia

Vascular (extracardiac) —flushing

Nosocomial Pneumonia Trials

In a completed study of nosocomial lower respiratory tract infections, 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 imipenem/cilastatin (500 mg/500 mg q6h) 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 imipenem/cilastatin group. Twenty-five (11%) patients in the piperacillin/tazobactam group and 14 (6.5%) in the imipenem/cilastatin 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%), excoriations (1.4%), and sweating (1.4%).

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, SGOT increased, SGPT increased, sinus bradycardia, somnolence, stomatitis, stupor, tremor, tachycardia, ventricular extrasystoles, and ventricular tachycardia.

In a previous nosocomial pneumonia study conducted with a dosing regimen of 3.375 g given every 4 hours with an aminoglycoside, the following adverse events, irrespective of drug relationship, were observed: diarrhea (20%); constipation (8.4%); agitation (7.1%); nausea (5.8%); headache (4.5%); insomnia (4.5%); oral thrush (3.9%); erythematous rash (3.9%); anxiety (3.2%); fever (3.2%); pain (3.2%); pruritus (3.2%); hiccough (2.6%); vomiting (2.6%); dyspepsia (1.9%); edema (1.9%); fluid overload (1.9%); stool changes (1.9%); anorexia (1.3%); cardiac arrest (1.3%); confusion (1.3%); diaphoresis (1.3%); duodenal ulcer (1.3%); flatulence (1.3%); hypertension (1.3%); hypotension (1.3%); inflammation at injection site (1.3%); pleural effusion (1.3%); pneumothorax (1.3%); rash, not otherwise specified (1.3%); supraventricular tachycardia (1.3%); thrombophlebitis (1.3%); and urinary incontinence (1.3%).

Adverse events irrespective of drug relationship observed in 1% or less of patients in the above study with Piperacillin and Tazobactam for Injection and an aminoglycoside included: aggressive reaction (combative), angina, asthenia, atelectasis, balanoposthitis, cerebrovascular accident, chest pain, conjunctivitis, deafness, dyspnea, earache, ecchymosis, fecal incontinence, gastric ulcer, gout, hemoptysis, hypoxia, pancreatitis, perineal irritation/pain, urinary tract infection with trichomonas, vitamin B_{12} deficiency anemia, xerosis, and yeast in urine.

Pediatrics

Studies of Piperacillin and Tazobactam for Injection in pediatric patients suggest a similar safety profile to that seen in adults. In a prospective, randomized, comparative, open-label clinical trial of pediatric patients with severe intra-abdominal infections (including appendicitis and/or peritonitis), 273 patients were treated with Piperacillin and Tazobactam for Injection (112.5 mg/kg every 8 hours) and 269 patients were treated with cefotaxime (50 mg/kg) plus metronidazole (7.5 mg/kg) every 8 hours. In this trial, treatment-emergent adverse events were reported by 146 patients, 73 (26.7%) in the Piperacillin and Tazobactam for Injection group and 73 (27.1%) in the cefotaxime/metronidazole group. Six patients (2.2%) in the Piperacillin and Tazobactam for Injection group and 5 patients (1.9%) in the cefotaxime/metronidazole group discontinued due to an adverse event.

In this study, adverse events that were reported in more than 1% of patients, irrespective of relationship to therapy with Piperacillin and Tazobactam for Injection were: diarrhea (7%), fever (4.8%), vomiting (3.7%), local reaction (3.3%), abscess (2.2%), sepsis (2.2%), abdominal pain (1.8%), infection (1.8%), bloody diarrhea (1.1%), pharyngitis (1.5%), constipation (1.1%) and SGOT increase (1.1%).

Adverse events reported in 1% or less of pediatric patients receiving Piperacillin and Tazobactam for Injection are consistent with adverse events reported in adults.

Additional controlled studies in pediatric patients showed a similar safety profile as that described above.

Post-Marketing Experience

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:

Gastrointestinal —hepatitis, cholestatic jaundice

Hematologic —hemolytic anemia, anemia, thrombocytosis, agranulocytosis, pancytopenia

Immune —hypersensitivity reactions, anaphylactic/anaphylactoid reactions (including shock)

Infections —candidal superinfections

Renal —interstitial nephritis, renal failure

Skin and Appendages —erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis

Post-marketing experience with Piperacillin and Tazobactam for Injection in pediatric patients suggests a similar safety profile to that seen in adults.

Adverse Laboratory Events (Seen During Clinical Trials)

Of the studies reported, including that of nosocomial lower respiratory tract infections in which a higher dose of Piperacillin and Tazobactam for Injection was used in combination with an aminoglycoside, changes in laboratory parameters, without regard to drug relationship, include:

Hematologic —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, prolonged partial thromboplastin time

Hepatic —transient elevations of AST (SGOT), ALT (SGPT), alkaline phosphatase, bilirubin

Renal —increases in serum creatinine, blood urea nitrogen

Urinalysis —proteinuria, hematuria, pyuria

Additional laboratory events include abnormalities in electrolytes (i.e., increases and decreases in sodium, potassium, and calcium), hyperglycemia, decreases in total protein or albumin, blood glucose decreased, gamma-glutamyltransferase increased, hypokalemia, and bleeding time prolonged.

The following adverse reaction has also been reported for Piperacillin for Injection:

Skeletal —prolonged muscle relaxation (See **PRECAUTIONS, Drug Interactions**.)

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

To report SUSPECTED ADVERSE REACTIONS, contact the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

OVERDOSAGE

There have been postmarketing reports of overdose with piperacillin/tazobactam. 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 concentrations of either piperacillin or tazobactam may be reduced by hemodialysis. Following a single 3.375 g dose of piperacillin/tazobactam, the percentage of piperacillin and tazobactam dose removed by hemodialysis was approximately 31% and 39%, respectively. (See **CLINICAL PHARMACOLOGY**.)

DOSAGE AND ADMINISTRATION

Piperacillin and Tazobactam for Injection should be administered by intravenous infusion over 30 minutes.

The usual daily dose of Piperacillin and Tazobactam for Injection for adults is 3.375 g every six hours totaling 13.5 g (12 g piperacillin/1.5 g tazobactam).

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 every six hours plus an aminoglycoside, totaling 18 g (16 g piperacillin/ 2 g tazobactam). 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 and the aminoglycoside are recommended for separate administration. Piperacillin and tazobactam and the aminoglycoside should be reconstituted, diluted, and administered separately when concomitant therapy with aminoglycosides is indicated. (See **PRECAUTIONS, Drug Interactions.**)

In circumstances where co-administration via Y-site is necessary, piperacillin and tazobactam is compatible for simultaneous coadministration via Y-site infusion only with the following aminoglycosides under the following conditions:

TABLE 4

Aminoglycoside	Piperacillin and Tazobactam Dose (grams)	Piperacillin and Tazobactam Diluent Volume (mL)	Aminoglycoside Concentration Range* (mg/mL)	Acceptable Diluents
Amikacin	2.25, 3.375, 4.5	50, 100, 150	1.75 - 7.5	0.9% Sodium Chloride or 5% Dextrose
Gentamicin	2.25, 3.375, 4.5	100, 150	0.7 - 3.32	0.9% Sodium Chloride

*The concentration ranges in Table 4 are based on administration of the aminoglycoside in divided doses (10-15 mg/kg/day in two daily doses for amikacin and 3-5 mg/kg/day in three daily doses for gentamicin). Administration of amikacin or gentamicin in a single daily dose or in doses exceeding those stated above via Y-site with piperacillin and tazobactam has not been evaluated. See package insert for each aminoglycoside for complete Dosage and Administration instructions.

Piperacillin and tazobactam is not compatible with tobramycin for simultaneous coadministration via Y-site infusion. Compatibility of piperacillin and tazobactam with other aminoglycosides has not been established. Only the concentration and diluents for amikacin or gentamicin with the dosages of piperacillin and tazobactam listed above have been established as compatible for coadministration via Y-site infusion. Simultaneous coadministration via Y-site infusion in any manner other than listed above may result in inactivation of the aminoglycoside by piperacillin and tazobactam.

Renal Insufficiency

In patients with renal insufficiency (Creatinine Clearance ≤ 40 mL/min), the intravenous dose of Piperacillin and Tazobactam for Injection 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 manufacturer. 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 q 6 h	4.5 q 6 h
20-40 mL/min*	2.25 q 6 h	3.375 q 6 h
<20 mL/min*	2.25 q 8 h	2.25 q 6 h
Hemodialysis**	2.25 q 12 h	2.25 q 8 h
CAPD	2.25 q 12 h	2.25 q 8 h

* 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 every twelve hours for all indications other than nosocomial pneumonia and 2.25 g every eight hours for nosocomial pneumonia. Since hemodialysis removes 30% to 40% of the administered dose, an additional dose of 0.75 g Piperacillin and Tazobactam for Injection should be administered following each dialysis period on hemodialysis days. No additional dosage of Piperacillin and Tazobactam for Injection is necessary for CAPD patients.

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.

Pediatric Patients

For children with appendicitis and/or peritonitis 9 months of age or older, weighing up to 40 kg, and with normal renal function, the recommended Piperacillin and Tazobactam for Injection dosage is 100 mg piperacillin/12.5 mg tazobactam per kilogram of body weight, every 8 hours. For pediatric patients between 2 months and 9 months of age, the recommended Piperacillin and Tazobactam for Injection dosage based on pharmacokinetic modeling, is 80 mg piperacillin/10 mg tazobactam per kilogram of body weight, every 8 hours, (see **PRECAUTIONS, General**, **Pediatric Use** and **CLINICAL PHARMACOLOGY**). Pediatric patients weighing over 40 kg and with normal renal function should receive the adult dose. There are no dosage recommendations for Piperacillin and Tazobactam for Injection in pediatric patients with impaired renal function.

Directions for Reconstitution and Dilution for Use

Intravenous Administration

Pharmacy Bulk Package
Not for Direct Infusion

RECONSTITUTED STOCK SOLUTION MUST BE TRANSFERRED AND FURTHER DILUTED FOR I.V. INFUSION

The pharmacy bulk package bottle is for use in a hospital pharmacy admixture service only under a laminar flow hood. After reconstitution, entry into the bottle must be made one time with a sterile transfer set or other sterile dispensing device, and contents should be dispensed as aliquots into intravenous solution using aseptic technique. Use entire contents of pharmacy bulk package bottle promptly. Discard unused portion after **4 hours** at room temperature (20°C to 25°C [68°F to 77°F]). This time period should begin with the introduction of solvent or diluents into the pharmacy bulk package bottle.

Reconstitute the pharmacy bulk package with exactly 152 mL of a compatible reconstitution diluent, listed below, to a concentration of 200 mg/mL of piperacillin and 25 mg/mL of tazobactam. Shake well until dissolved. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to and during administration, whenever solution and container permit.

Compatible Reconstitution Diluents

0.9% Sodium Chloride for Injection
Sterile Water for Injection‡
Dextrose 5%
Bacteriostatic Saline/Parabens
Bacteriostatic Water/Parabens
Bacteriostatic Saline/Benzyl Alcohol
Bacteriostatic Water/Benzyl Alcohol

Reconstituted Piperacillin and Tazobactam for Injection solution should be further diluted (recommended volume per dose of 50 mL to 150 mL) in a compatible intravenous solution listed below. Administer by infusion over a period of at least 30 minutes. During the infusion it is desirable to discontinue the primary infusion solution.

Compatible Intravenous Solutions

0.9% Sodium Chloride for Injection
Sterile Water for Injection‡
Dextran 6% in Saline
Dextrose 5%

LACTATED RINGER'S SOLUTION IS NOT COMPATIBLE WITH PIPERACILLIN AND TAZOBACTAM FOR INJECTION.

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

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

Piperacillin and Tazobactam for Injection is not chemically stable in solutions that contain only sodium bicarbonate and solutions that significantly alter the pH.

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

Piperacillin and Tazobactam for Injection can be used in ambulatory intravenous infusion pumps.

Stability of Piperacillin and Tazobactam for Injection Following Reconstitution

Piperacillin and Tazobactam for Injection is stable in glass and plastic containers (plastic syringes, I.V. bags and tubing) when used with compatible diluents.

The pharmacy bulk package bottle should **NOT** be frozen after reconstitution. Discard unused portions after storage for **4 hours** at room temperature. This time period should begin with the introduction of solvent or diluent into the pharmacy bulk package bottle.

Stability studies in the I.V. bags have demonstrated chemical stability (potency, pH of reconstituted solution and clarity of solution) for up to 24 hours at room temperature and up to one week at refrigerated temperature. Piperacillin and Tazobactam for Injection contains no preservatives. Appropriate consideration of aseptic technique should be used.

Stability of Piperacillin and Tazobactam for Injection in an ambulatory intravenous infusion pump has been demonstrated for a period of 12 hours at room temperature. Each dose was reconstituted and diluted to a volume of 37.5 mL or 25 mL. One-day supplies of dosing solution were aseptically transferred into the medication reservoir (I.V. bags or cartridge). The reservoir was fitted to a preprogrammed ambulatory intravenous infusion pump per the manufacturer's instructions. Stability of Piperacillin and Tazobactam for Injection is not affected when administered using an ambulatory intravenous infusion pump.

Parenteral drug products should be inspected visually for particulate matter or discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED

Piperacillin and Tazobactam for Injection, USP is supplied as a powder in the pharmacy bulk package bottle as follows:

Each Piperacillin and Tazobactam for Injection USP, 40.5 g pharmacy bulk package bottle contains piperacillin sodium equivalent to 36 grams of piperacillin and tazobactam sodium equivalent to 4.5 g of tazobactam and 54.28 mg/g piperacillin of sodium. Each pharmacy bulk package bottle contains 84.96 mEq (1,954 mg) of sodium.

NDC 60505-0773-0.

Prior to reconstitution: Store at 20 to 25°C (68 to 77°F). [See USP Controlled Room Temperature].

Also Available

Piperacillin and Tazobactam for Injection, USP is also supplied as follows:

Each Piperacillin and Tazobactam for Injection USP, 2.25 g vial provides piperacillin sodium equivalent to 2 grams of piperacillin and tazobactam sodium equivalent to 0.25 g of tazobactam. Each vial contains 4.72 mEq (109 mg) of sodium. Supplied 10 per box—NDC 60505-0686-4.

Each Piperacillin and Tazobactam for Injection USP, 3.375 g vial provides piperacillin sodium equivalent to 3 grams of piperacillin and tazobactam sodium equivalent to 0.375 g of tazobactam. Each vial contains 7.08 mEq (163 mg) of sodium. Supplied 10 per box— NDC 60505-0687-4.

Each Piperacillin and Tazobactam for Injection USP, 4.5 g vial provides piperacillin sodium equivalent to 4 grams of piperacillin and tazobactam sodium equivalent to 0.5 g of tazobactam. Each vial contains 9.44 mEq (217 mg) of sodium. Supplied 10 per box— NDC 60505-0688-4.

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