PIPERACILLIN AND TAZOBACTAM FOR INJECTION: pharmacy bulk package bottles

Initial U.S. approval: 1993

PHARMACY BULK PACKAGE-NOT FOR DIRECT INFUSION • Reconstituted stock solution must be transferred and further diluted for I.V. infusion

To reduce the development of drug-resistant bacteria and main-

tain the effectiveness of Piperacillin and Tazobactam for Injection and other antibacterial drugs, Piperacillin and Tazobactam for Injection should be used only to treat infections that are proven or strongly suspected to be caused by bacteria. -- INDICATIONS AND USAGE-

Piperacillin and Tazobactam for Injection is a combination peni-cillin-class antibacterial and 8-lactamase inhibitor indicated for treatment of: Intra-abdominal infections (1.1) Skin and skin structure infections (1.2)

- Female pelvic infections (1.2) Community-acquired pneumonia (1.4) Nosocomial pneumonia (1.5)
- -----DOSAGE AND ADMINISTRATION -

- The usual daily dose of Piperacillin and Tazobactam for Injection for adults is 3.375 g every six hours totaling 13.5 g (12.0 g piperacillin'1.5 g tazobactam (2.1) 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 18.0 g (16.0 g piperacillin/2.0 g tazobactam), (2.2)
 Dosage in patients with renal impairment (≤40 mL/min of CRCL) and dialysis patients should be reduced, based on the degree of actual renal function impairment (2.3)
 For children with appendicitis and/or peritonitis the recomended Piperacillin and Tazobactam for Injection dosage is 100 mg piperacillin/12.5 mg tazobactam per kilogram of body weight, every 8 hours in pediatric patients 2 b months of ag, the recommended dosage is 80 mg piperacillin/10 mg tazobactam per kilogram of body weight, every 8 hours. (2.4)
 Piperacillin and Tazobactam for Injection and aminoglycosides should be reconstituted, diluted, and administered separately. Co-administration via Y-site can be done under certain conditions. (2.6)
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inted, consupation, madese, ineadance and insolations, contact Fresenius To report SUSPECTED ADVERSE REACTIONS, contact Fresenius Kabi USA, LLC, Vigilance and Medical Affairs at 1-800-551-7176 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. -DRUG INTERACTIONS-

-DOSAGE FORMS AND STRENGTHS-

Serious hypersensitivity reactions (anaphylactic/anaphylacticid) reactions have been reported in patients receiving Piperacillin and Tazobactam for Injection. Discontinue Piper-

repetation and razobactam for injection if a reaction cours. (5.1) Serious skin reactions, such as Stevens-Johnson syndrome and toxic epidermal necrolysis, have been reported (5.2). Discontinue Piperacillin and Tazobactam for Injection for progressive rashes.

Clostridium difficile associated diarrhea: evaluate patients if diarrhea ceven. (5.2)

diarrhea occurs. (5.3) Hematological effects (including bleeding, leukopenia and neutropenia) have occurred. Monitor hematologic tests dur-ing prolonged therapy. (5.4)

Piperacillin and Tazobactam for Injection: 40.5 g lyophilized powder for reconstitution in pharmacy bulk package bottles (3) -CONTRAINDICATIONS Patients with a history of allergic reactions to any of the penicil-

lins, cephalosporins, or B-lactamase inhibitors. (4

- Piperacillin and Tazobactam for Injection administration can significantly reduce tobramycin concentrations in hemodialysis patients. Monitor tobramycin concentrations in these patients. (7.1) Probeneid prolongs the half-lives of piperacillin and tazo-bactam and should not be co-administered with Piperacillin and Tazobactam for Injection unless the benefit outweighs
- Monitor coagulation parameters in patients receiving Piper-acillin and Tazobactam for Injection and heparin or oral anti-
- coagulants, (7.3)
 Piperacillin and Tazobactam for Injection may prolong the neuromuscular blockade of vecuronium and other non-depolarizing muscle relaxants. Monitor for adverse reactions related to neuromuscular blockade. (7.4)
- -- USE IN SPECIFIC POPULATIONS -Dosage in patients with renal impairment (<40 mL/min of CRCL) should be reduced to the degree of actual renal function impairment. (2.3, 8.6)

Revised: 1/2014

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discontinue the primary infusion solution

Dextrose 5%

Reconstituted piperacillin and tazobactam for injection solution should be further diluted (recommended volume per dose of 50 m.L 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

NOT FOR DIRECT INFUSION Reconstituted stock solution must be transferred and further diluted for I.V. infusion FULL PRESCRIBING INFORMATION

2.1 Adult Patients
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FOLL PRESCRIBING INFORMATION.

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 bacteria. INDICATIONS AND USAGE
Piperacillin and tazobactam for injection is a combination product consisting of a penicillin-class antibacterial, piperacillin, and a 8-lactamase inhibitor, tazobactam, indicated for the treatment of patients with moderate to severe infections caused by susceptible isolates of the designated bacteria in the conditions listed below.

Intra-abdominal Infections
Appendicitis (complicated by rupture or abscess) and peritonitis caused by B-lactamase producing isolates 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 fewer than 10 cases.

Skin and Skin Structure Infections Uncomplicated and complicated skin and skin structure infections, including cellulitis, cutaneous abscesses and ischemic/diabetic foot infections caused by \(\theta\)-lactamase producing isolates of \(Staphylococcus\) aureus.

1.3 Female Pelvic Infections Postpartum endometritis or pelvic inflammatory disease caused by β-lactamase producing isolates of *Escherichia coli*.

Community-acquired Pneumonia Community-acquired pneumonia (moderate severity only) caused by ß-lactamase producing isolates of *Haemophilus*

Nosocomial Pneumonia Nosocomial pneumonia (moderate to severe) caused by 8-lactamase producing isolates of *Staphylococcus aureus* and by piperacillin/tazobactam-susceptible *Acinetobacter bau-*

of pupersalimit accusation susceptible from the framework of a mannii, Haemophilius influenzae, Klebsiella pneumoniae, and Pseudomonas aeruginosa (Nosocomial pneumonia caused by P. aeruginosa should be treated in combination with an aminoglycoside) [see Dosage and Administration (2]].

To reduce the development of drug-resistant bacteria and

no reduce the development of unique resistant vaccine 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 infections that are proven or strongly suspected to be caused by bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the phesone of eight data local in a subscription of the phesone of eight data local ing antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy. **DOSAGE AND ADMINISTRATION**Piperacillin and tazobactam for injection should be administered by intravenous infusion over 30 minutes.

Adult Patients
The usual total daily dose of piperacillin and tazobactam for injection for adults is 3.375 g every six hours totaling 13.5 g (12.0 g piperacillin/1.5 g tazobactam). The usual duration of piperacillin and tazobactam for injection treatment is from 7 to 10 days.
Piperacillin and tazobactam for injection should be administered by intravenous infusion over 30 minutes. Nosocomial Pneumonia

Initial presumptive treatment of patients with nosocomial initial presumptive treatment of presents with insosconial preumonia should start with piperacillin and tazobactam for injection at a dosage of 4.5 g every six hours plus an amino-glycoside, totaling 18.0 g (16.0 g piperacillin/2.0 g tazobactam). The recommended duration of piperacillin and tazobactam for injection treatment for nosocomial pneumonia is

Adult Patients

continued in patients from whom P. aeruginosa is isolated. Renal Impairment In patients with renal impairment (creatinine clearance ≤ 40 mL/min) and dialysis patients (hemodialysis and CAPD), the intravenous dose of piperacillin and tazobactam for injection should be reduced to the degree of actual renal function impairment. The recommended daily doses of piperacillin and tazobactam for injection for patients with renal impair-ment are as follows:

7 to 14 days. Treatment with the aminoglycoside should be

Table 1: Recommended Dosing of Piperacillin and Tazobac-tam for Injection in Patients with Normal Renal Function and Renal Impairment (As total grams piperacillin/ tazobactam) **All Indications** Renal Function (creatinine clearance, (except nosocomial Nosocomial Pneumonia mL/min) 3.375 q6h >40 mL/min 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 *10.75 g (0.67 g piperacillin/0.08 g tazobactam) should be administered following each hemodialysis session on hemodialy-sis days

For patients on hemodialysis, the maximum dose is 2.25 g every twelve hours for all indications other than nosocomia 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 (0.67 g piperacillin/0.08 g tazobactam) should be administered following each di-alysis period on hemodialysis days. No additional dosage of piperacillin and tazobactam for injection is necessary for CAPD patients.

Pediatric Patients

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 Jese in Specific Populations (8.4) and Clinical Pharmacology (12.3)]. Pediatric patients weighing over 40 kg and with normal renal function should receive the adult dose. It has not been determined how to adjust piperacilling. dose. It has not been determined how to adjust piperacillin and tazobactam for injection dosage in pediatric patients with renal impairment.

Reconstitution and Dilution of Powder Formulations Pharmacy Bulk Package Bottles

Reconstituted stock solution must be transferred and further diluted for intravenous 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 vial must be made with a sterile transfer set or other sterile dispensing device,

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 24 hours if stored at room temperature 20°C to 25°C (68°F to 77°F), or after 48 hours if stored at refrigerated temperature 2°C to 8°C (36°F to 46°F). Reconstitute the pharmacy bulk package bottle 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 for Pharmacy Bulk

Bottles 0.9% Sodium chloride for injection Sterile water for injection[‡]
Dextrose 5%
Bacteriosatic saline/parabens Bacteriostatic water/parabens Bacteriostatic saline/benzyl alcohol Bacteriostatic water/benzyl alcohol

17 PATIENT COUNSELING INFORMATION *Sections or subsections omitted from the full prescribing information are not listed.

Compatible Intravenous Solutions for Pharmacy Bulk Package Bottles and Single Dose Vials.
0.9% Sodium chloride for injection
Sterlie water for injection¹
Dextran 6% in saline

LACTATED RINGER'S SOLUTION IS NOT COMPATIBILE 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.

Parenteral drug products should be inspected visually for particulate matter or discoloration prior to administration, whenever solution and container permit. Stability of Piperacillin and Tazobactam for Injection Powder

Formulations Following Reconstitution

Piperacillin and tazobactam for injection reconstituted from pharmacy bulk package bottles 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. Discourage and the provided provided the provided provided the provided that the provi

Pharmacy bulk package bottles should be used immedates and reconstitution. Discard any discosporation after 24 hours if stored at room temperature 20°C to 25°C (68°F to 77°F), or after 48 hours if stored at refrigerated temperature 2°C to 8°C (36°F to 46°F). Pharmacy bulk package bottles should not be frozen after reconstitution.

Stability studies in the I.V. bags have demonstrated chemi-

Stability studies in the I.V. Dags have demonstrated chemi-cal stability (botency, 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. Appro-priate consideration of aseptic technique should be used. Piperacillin and tazobactam for injection reconstituted from bulk package bottles can be used in ambulatory intravenous infusion pumps. 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 adminis-

and tazobactam for injection is not affected when administered using an ambulatory intravenous infusion pump. **Compatibility with Aminoglycosides**Due to the *in vitro* inactivation of aminoglycosides by piperacillin, piperacillin and tazobactam for injection and aminoadmin, piperachimi and azulouzamin injection and animo-glycosides are recommended for separate administration. Piperacillin and tazobactam for injection and aminoglyco-sides should be reconstituted, diluted, and administered separately when concomitant therapy with aminoglycosides is indicated [see Drug Interactions (7.1)].

In circumstances where co-administration via Y-site is nec-

Table 2: Compatibility with Aminoglycosides

Piperacillin and Tazo-bactam Dilu-ent Volume

(mL)

essary, piperacillin and tazobactam is compatible for simul-taneous coadministration via Y-site infusion only with the following aminoglycosides under the following conditions:

Piperacillin and Tazo-

bactam

Dose

(grams)

0.9% sodium chloride 2.25, 3.375 4.5 50, 100, 150 1.75 - 7.5or 5% 0.9% sodium Gentamicin 2.25, 3.375 50. 100 150 | 0.7 - 3.32 chloride or 5% *The concentration ranges in Table 2 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 Dos-age and Administration instructions.

with tobramycin for simultaneous coadministration via Y-site infusion. Compatibility of piperacillin and tazobactam with other aminoglycosides has not been established. Parenteral drug products should be inspected visually for

Piperacillin and tazobactam for injection is not compatible

macy bulk bottle contains piperacillin sodium equivalent to 36 grams of piperacillin and tazobactam sodium equivalent to 1.5 grams tazobactam.

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 AND PRECAUTIONS

Hypersensitivity Reactions
Serious and occasionally fatal hypersensitivity (anaphylactic/anaphylactoid) reactions (including shock) have been reported in patients receiving therapy with piperacillin and tazobactam for injection. These reactions are more likely to occur in individuals with a history of penicillin, cephalospones occasionate processors in the processor of the processors in the processor of the processors of t

rin, or carbapenem hypersensitivity or a history of sensitivity to multiple allergens. Before initiating therapy with piperacillin and tazobactam for injection, careful inquiry should be made concerning previous hypersensitivity reactions. If an allergic reaction occurs, piperacillin and tazobactam for injection should be discontinued and appropriate therapy incitivated.

instituted. Serious Skin Reactions Serious Skin reactions. Serious skin reactions, such as Stevens-Johnson syndrome and toxic epidermal necrolysis, have been reported in pa-tients receiving piperacillin and tazobactam for injection.

If patients develop a skin rash they should be monitored closely and piperacillin and tazobactam for injection discontinued if lesions progress. Clostridium difficile Associated Diarrhea 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

dextrose

Accept-able

Aminoglycoside Concentra-

(mg/mL)

Only the concentration and diluents for amikacin or gentamicin with the dosages of piperacillin and tazobactam for injection listed above have been established as compatible for coadministration via Y-site infusion. Simultaneous co-administration via Y-site infusion in any manner other than listed above may result in inactivation of the aminoglycoside by piperacillin and tazobactam.

particulate matter and discoloration prior to administration, whenever solution and container permit. **DOSAGE FORMS AND STRENGTHS**Piperacillin and tazobactam for injection is supplied as a white to off-white powder in bottles of the following sizes: Each Piperacillin and Tazobactam for Injection 40.5 g phar-

CONTRAINDICATIONS

Adverse Laboratory Events (Seen During Clinical Trials)
Of the trials reported, including that of nosocomial lower re-spiratory tract infections in which a higher dose of piperacil-lin and tazobactam for injection was used in combination

Renal-increases in serum creatinine, blood urea nitrogen Additional laboratory events include abnormalities in

time prolonged

Post-Marketing Experience
In addition to the adverse drug reactions identified in clinical
trials in Table 3 and Table 4, the following adverse reactions
have been identified during postapproval use of piperacillin

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish causal relationship to drug exposure. Gastrointestinal-hepatitis, jaundice

Renal—interstitial nephritis

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

The following adverse reaction has also been reported for piperacillin for injection:

-hypersensitivity reactions, anaphylactic/anaphy-

Additional Experience with Piperacillin

Diarrhea (11.3%)
Constipation (7.7%)
Nausea (6.9%)
Vomiting (3.3%)
Dyspepsia (3.3%)
Abdominal pain (1.3%) Pseudomembranous colitis (≤1%) General disorders and administration site conditions Fever (2.4%)

Injection site reaction (≤1%) Rigors (≤1%) Immune system disorders Anaphylaxis (≤1%) Infections and infestations Candidiasis (1.6%)

Metabolism and nutrition disorders Hypoglycemia (≤1%)

Myalgia(≤1%) Arthralgia (≤1%)

Nervous system disorders Headache (7.7%) Insomnia (6.6%) Skin and subcutaneous tissue disorders
Rash (4.2%, including maculopapular, bullous, and
urticarial)
Pruritus (3.1%)

Musculoskeletal and connective tissue disorders

Vascular disorders
Phlebitis (1.3%)
Thrombophlebitis (≤1%)
Hypotension (≤1%)
Purpura (≤1%)
Epistaxis (≤1%)
Flushing (≤1%)

Nosocomial Pneumonia Trials

Nosocomial Pneumonia Trials Two trials of nosocomial lower respiratory tract infections were conducted. In one study, 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 imipenent/cliastatin (500 mg/500 mg (6h) 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 imipenent/cliastatin group. Twenty-five (11.0%) patients in the piperacillin/tazobactam group and 14 (6.5%) in the imipenent/cliastatin group (pp. 0.0.5) discontinued treatment due to an adverse event. to an adverse event. The second trial used a dosing regimen of 3.375 g given every 4 hours with an aminoglycoside. Table 4: Adverse Reactions from Piperacillin and Tazobactam for Injection Plus Aminoglycoside Clinical Trials^a System Organ Class Adverse Reaction

Blood and lymphatic system disorders Thrombocythemia (1.4%) Anemia (≤1%) Thrombocytopenia (≤1%) Eosinophilia (≤1%) Gastrointestinal disorders
Diarrhea (20%)
Constipation (8.4%)
Nausea (5.8%)

General disorders and administration site conditions Fever (3.2%) Injection site reaction (≤1%)

Vomiting (2.7%)

Dyspensia (1.9%) Abdominal pain (1.8%)

Stomatitis (≤1%)

Infections and infestations

Oral candidiasis (3.9%) Candidiasis (1.8%) Investigations
BUN increased (1.8%)
Blood creatinine increased (1.8%)
Liver function test abnormal (1.4%)

Alkaline phosphatase increased (≤1%)
Aspartate aminotransferase increased (≤1%) Alanine aminotransferase increased (≤1%) Metabolism and nutrition disorders

Nervous system disorders Headache (4.5%) Insomnia (4.5%) lenal and urinary disorders Renal failure (≤1%)

Hypoglycemia (≤1%) Hypokalemia (≤1%)

Skin and subcutaneous tissue disorders Rash (3.9%) Pruritus (3.2%) Vascular disorders
Thrombophlebitis
(1.3%)

For adverse drug reactions that appeared in both studies the higher frequency is presented. Pediatrics

Hypotension (1.3%)

seen in adults. In a prospective, rainformer, by 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, technol. plus meutinidazue (7.3 ing/kg) events were reported by 146 patients, 73 (26.7%) in the piperacillin and tazobactam for injection group and 73 (27.1%) in the eefotaxime/metronidazole group. Six patients (2.2%) in the piperacillin and tazobactam for injection group and 5 patients (1.9%) in the eefotaxime/metronidazole group discontinued due to an electron exercise.

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,

adverse event.

with an aminoglycoside, changes in laboratory parameters Hematologic—decreases in hemoglobin and hematocrit, thrombocytopenia, increases in platelet count, eosinophilia, leukopenia, neutropenia. 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),

electrolytes (i.e., increases and decreases in sodium, po-tassium, and calcium), hyperglycemia, decreases in total protein or albumin, blood glucose decreased, gamma-glutamyltransferase increased, hypokalemia, and bleeding

alkaline phosphatase, bilirubin

and tazobactam for injection

Hematologic-hemolytic anemia, agranulocytosis, pancy-

lactoid reactions (including shock)

Skeletal-prolonged muscle relaxation [see Drug Interac-

may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibacterial drug 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 antibacterial drug use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibacterial treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

Hematologic Effects
Bleeding manifestations have occurred in some patients receiving B-lactam drugs, 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 beelding manifestations occur, piperacillin and tazobactam for injection should be discontinued and appropriate therapy instituted.

The leukopenia/neutropenia associated with piperacillin and tazobactam for injection administration appears to be reversible and most frequently associated with prolonged Periodic assessment of hematopoietic function should be performed, especially with prolonged therapy, ie, \geq 21 days [see Adverse Reactions (6.1)].

Central Nervous System Effects
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).

Electrolyte Effects
Piperacillin and tazobactam for injection contains a total of 2.35 mEq (54 mg) of Nar 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.

therapy or diuretics.

Development of Drug-Resistant Bacteria
Prescribing piperacillin and tazobactam for injection in
the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient
and increases the risk of development of drug-resistant
bacteria. ADVERSE REACTIONS
Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical

trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates

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 monotherapy 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%). Table 3: Adverse Reactions from Piperacillin and Tazobactam for Injection Monotherapy Clinical Trials

System Organ Class Adverse Reaction Gastrointestinal disorders

RUG INTERACTIONS

Aminoglycosides
Piperacillin may inactivate aminoglycosides by converting them to microbiologically inert amides

In vivo inactivation: When aminoglycosides are adminis-tered in conjunction with piperacillin to patients with end-stage renal disease requiring hemodialysis, the concentrations of the aminoglycosides (especially tobramycin) may be significantly reduced and should be monitored.

Sequential administration of piperacillin and tazobactam for injection and tobramycin to patients with either normal renal function or mild to moderate renal impairment has been shown to modestly decrease serum concentrations of tobramycin but no dosage adjustment is considered

In vitro inactivation:
Due to the in vitro inactivation of aminoglycosides by Due to the *in vitro* inactivation of aminoglycosides by piperacillin, piperacillin and tazobactam for injection and aminoglycosides are recommended for separate administration. Piperacillin and tazobactam for injection and aminoglycosides should be reconstituted, diluted, and administerate separately when concomitant therapy with aminoglycosides is indicated. Piperacillin and tazobactam for injection is compatible with amikacin and gentamicin for simultaneous Y-site infusion in certain diluents and at specific concentrations. Piperacillin and tazobactam for injection is not compatible with tobramycin for simultaneous Y-site infusion [see Dosage and Administration (2.6)].

Probenecid

Probenecial administered concomitantly with piperacillin and tazobactam prolongs the half-life of piperacillin by 21% and that of tazobactam by 71% because probenecid inhibits tubular renal secretion of both piperacillin and tazobactam. Probenecid should not be co-administered with piperacillin. and tazobactam for injection unless the benefit outweighs Anticoagulants

Coagulation parameters should be tested more frequently

and monitored regularly during simultaneous administra-tion of high doses of heparin, oral anticoagulants, or other drugs that may affect the blood coagulation system or the thrombocyte function. [see Warnings and Precautions (5.4)] Vecuronium

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 injenseracillin. Manitor for advances longed in the presence of piperacillin. Monitor for adverse reactions related to neuromuscular blockade (See package insert for vecuronium bromide). Methotrexate 7.5 Limited data suggests that co-administration of methotrex-Lamited udat suggests that co-administration of methotrex-ate and piperacillism may reduce the clearance of methotrex-ate 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.

Effects on Laboratory Tests
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 requiriously and confirmed by other diagnostic be interpreted cautiously and confirmed by other diagnostic

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 be used. USE IN SPECIFIC POPULATIONS **Pregnancy** Teratogenic effects—Pregnancy Category B

Piperacillin/Tazobactam

Puperaculini razooaccam Teratology studies have been performed in mice and rats and have revealed no evidence of harm to the fetus when piperacillin/tazobactam is administerid intravenously up to a dose of 3000/750 mg/kg piperacillin/zaobactam 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. There are, however, no adequate and well-controlled studies with the piperacillin/tazobactam combination or with

piperacillin or tazobactam alone in pregnant women. Be-cause 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

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 pedistudies and pirarmacokinetic studies in adultis 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 Commence of Comme

cal Pharmacology (12) and Dosage and Administration (2)].

It has not been determined how to adjust piperacillin and tazobactam for injection dosage in pediatric patients with

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 impairment [see Dosage and Administration (2)].

renal impairment.

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 dues these. drug therapy.

Piperacillin and tazobactam for injection contains 54 mg (2.35 mEq) 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 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. Renal Impairment Renal Impairment In patients with creatinine clearance ≤ 40 mL/min and dialysis patients (hemodialysis and CAPD), the intravenous dose of piperacillin and tazobactam for injection should be reduced to the degree of renal function impairment [see Dosage and Administration (2]].

Dosage adjustment of piperacillin and tazobactam for injection is not warranted in patients with hepatic cirrhosis [See Clinical Pharmacology (12.3)].

Hepatic Impairment

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

There have been postmarketing reports of overdose with piperacillin/tazobactam. The majority of those events ex-

piperaciminazooaciam. The majority of mose events ex-perienced, 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) [see Warnings and Precautions (5.5)]. Treatment should be supportive and symptomatic according 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 the piperacillin and tazobactam dose removed by hemodialysis was approximately 31% and 39%, respectively [see Clinical Pharmacology (12)].

Piperacillin and tazobactam for injection is an injectable antibacterial combination product consisting of the semisyn-thetic antibacterial piperacillin sodium and the ß-lactamase inhibitor tazobactam sodium for intravenous administration. Piperacillin sodium is derived from $D(-)-\alpha$ -aminobenzyl

bactam parenteral combination, is a white to off-white sterile, cryodesiccated powder consisting of piperacillin and tazobactam as their sodium salts packaged in glass bottles. The product does not contain excipients or preservatives. The pharmacy bulk package bottle is a container of sterile preparation which contains many single doses for paren-teral use. The contents are intended for use in a pharmacy

Piperacillin and tazobactam for injection, piperacillin/tazo-

admixture program and are restricted to the preparation of admixtures for intravenous infusion. Each piperacillin and tazobactam for injection 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 de-

livery of multiple doses Piperacillin and tazobactam for injection is a monosodium

salt of piperacillin and a monosodium salt of tazobactam containing a total of 2.35 mEq (54 mg) of sodium (Na*) per gram of piperacillin in the combination product.

CLINICAL PHARMACOLOGY 12. ULINIUAL FRANKAGO 12.1 Mechanism of Action

Piperacillin and tazobactam for injection is an antibacterial drug [see Microbiology (12.4)].

12.2 Pharmacodynamics The pharmacodynamic parameter for piperacillin/tazobactam that is most predictive of clinical and microbiological efficacy is time above MIC.

12.3 Pharmacokinetics
The mean and coefficients of variation (CV%) for the pharmacokinetic parameters of piperacillin and tazobactam after multiple intravenous doses are summarized in Table 5.

Toble E. M	oon (C)	/0/\ Dinoroo	illin and	Tozob	notom	DV
Table 5: Mean (CV%) Piperacillin and Tazobactam PK Parameters Piperacillin						rĸ
	Piperacillin					
Piperacillin/ Tazobactam	C _{max}	AUC _b	CL	٧	T _{1/2}	CL _R
Doseª	mcg/ mL	mcg•h/mL	mL/min	L	h	mL/ min
2.25 g	134	131 (14)	257	17.4	0.79	-
3.375 g	242	242 (10)	207	15.1	0.84	140
4.5 g	298	322 (16)	210	15.4	0.84	-
Tazobactam						
Piperacillin/ Tazobactam	C _{max}	AUC _b	CL	٧	T _{1/2}	CL _R
Doseª	mcg/ mL	mcg•h/mL	mL/min	L	h	mL/ min
2.25 g	15	16.0 (21)	258	17.0	0.77	-
3.375 g	24	25.0 (8)	251	14.8	0.68	166
4.5 g	34	39.8 (15)	206	14.7	0.82	-
Piperacillin and tazobactam were given in combination, infused over 30 minutes. Numbers in parentheses are coefficients of variation (CV%).						

Peak plasma concentrations of piperacillin and tazobactam are attained immediately after completion of an intravenue infusion of piperacillin and tazobactam for injection. Piperacillin plasma concentrations, following a 30-minute infusion of piperacillin and tazobactam for injection, were considered to the control of th

similar to those attained when equivalent doses of piper-acillin were administered alone. Steady-state plasma con-centrations of piperacillin and tazobactam were similar to those attained after the first dose due to the short half-lives of piperacillin and tazobactam. Distribution Distribution

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 (see Table 6). Table 6: Piperacillin/Tazobactam Concentrations in Selected Tissues and Fluids after Single 4 g/0.5 g 30-min IV Infusion of Piperacillin and Tazobactam for Injection

Tazo Mean PIP Sam-Tazo Con-Tissue: pling Concentra-period^b tion Range Range Tissue Tissue centration N^{a} or Fluid Range

		(h)	(mg/L)	riango	(mg/L)	Range
Skin	35	0.5 – 4.5	34.8 – 94.2	0.60 - 1.1	4.0 – 7.7	0.49 - 0.93
Fatty Tissue	37	0.5 – 4.5	4.0 – 10.1	0.097 – 0.115	0.7 – 1.5	0.10 - 0.13
Muscle	36	0.5 – 4.5	9.4 – 23.3	0.29 - 0.18	1.4 – 2.7	0.18 - 0.30
Proxi- mal Intes- tinal Mucosa	7	1.5 – 2.5	31.4	0.55	10.3	1.15
Distal Intes- tinal Mucosa	7	1.5 – 2.5	31.2	0.59	14.5	2.1
Appen- dix	22	0.5 – 2.5	26.5 – 64.1	0.43 - 0.53	9.1 – 18.6	0.80 - 1.35
			ed a single sa of the infusio			
Met	aboli	sm				

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

Excretion

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 Both piperacillin and tazobactam are eliminated via the kid-

Bout piperachini and azooaccian are eliminated via the kid-ney by glomerular filtration and tubular secretion. Piperacii-lin 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. Piperaciilin, tazobactam and desethyl piperacillin are also secreted into the bile. Specific Populations Renal impairment
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

specific recommendations for the treatment of patients with

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 (2) for

renal impairment.

Hemodialysis removes 30% to 40% of a piperacillin/tazo-bactam 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 tazo-bactam dose removed as the tazobactam metabolite. For dosage recommendations for patients undergoing hemodi-alysis [see Dosage and Administration (2).] Hepatic Impairment Hepatic impairment.

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 circhesia.

Piperacillin and tazobactam pharmacokinetics were stud-ied 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 adults, with a population mean (cy Vatile of 3.94 (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.

Geriatrics Geriatrics
The impact of age on the pharmacokinetics of piperacillin and tazobactam was evaluated in healthy male subjects, aged 18-35 years (n=6) and aged 65 to 80 years (n=12). Mean half-life for piperacilln and tazobactam was 32% and 55% higher, respectively, in the elderly compared to the younger subjects. This difference may be due to age-related changes in creatinine clearance. Hace
The effect of race on piperacillin and tazobactam was evaluated in healthy male volunteers. No difference in piperacillin or tazobactam pharmacokinetics was observed between Asian (n=9) and Caucasian (n=9) healthy volunteers who received single 4/0.5 g doses.

Drug Interactions The potential for pharmacokinetic drug interactions between piperacillin and tazobactam for injection and amino-glycosides, probenecid, vancomycin, heparin, vecuronium, and methotrexate has been evaluated [see Drug Interactions (7)].

12.4 Microbiology Mechanism of Action
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 ß-lactamase inhibitor of the Molecular class A enzymes, including Richmond-Sykes class III (Bush class 2b & 2b') penicillin-

ases 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 Spectrum of Activity Piperacillin/tazobactam has been shown to be active against most isolates of the following microorganisms both in vitro and in clinical infections [see Indications and Us-Gram-positive bacteria:

Staphylococcus aureus (methicillin susceptible isolates

Gram-negative bacteria

Acinetobacter baumannii Escherichia coli Haemophilus influenzae (excluding B-lactamase negative, ampicillin-resistant isolates)
Klebsiella pneumoniae
Pseudomonas aeruginosa (given in combination with an aminoglycoside to which the isolate is susceptible)

The following in vitro data are available, but their clinical

controlled clinical trials. Gram-positive bacteria: Enterococcus faecalis (ampicillin or penicillin-susceptible isolates only)

isolates only)

Streptococcus agalactiae[†] Streptococcus pneumoniae[†] (penicillin-susceptible isolates only) Streptococcus pyogenes† Viridans group streptococci†

Gram-negative bacteria: Citrobacter koseri Moraxella catarrhalis Morganella morganii Neisseria gonorrhoeae Proteus mirabilis Proteus vulgaris Serratia marcescens Providencia stuartii Providencia rettgeri

Salmonella enterica

Anaerobic bacteria:

Aniartonic Datcieria:
Clostridium perfringens
Bacterioles distasonis
Prevotella melaninogenica
'These are not 8-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 se-lecting 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 agan) or equivalent with standardized inoculum concentrations and standardized concentrations of pioneracilian and taxopactam now. ized 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 7.

Diffusion Technique:
Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. The zone size provides an estimate of the susceptibility of bacteria to antimicrobial compounds. The zone size should be determined using a standardized test method^{1,2} and requires the use of standardized inculum concentrations. This ternimeru using a standardizeti test method." and 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 7. Anaerobic Techniques
For anaerobic bacteria, the susceptibility to piperacillin/

tazobactam can be determined by the reference agai dilution method.⁴

Table 7: Susceptibility Interpretive Criteria for Piperacillin/ Tazobactam

Susceptibility Test Result Interpretive Criteria						
Minimal Inhibitory Concentration (MIC in mcg/mL)			Disk Diffusion (Zone Diameter in mm)			
S	- 1	R	S	ı	R	
≤ 16	32 – 64	≥ 128	≥ 21	18 – 20	≤ 17	
≤ 16	32 – 64	≥ 128	≥ 21	18 – 20	≤ 17	
≤ 1	-	≥ 2	≥ 21	-	-	
≤ 16	32 – 64	≥ 128	≥ 21	15 – 20	≤ 14	
≤ 32	64	≥ 128	-		-	
	M ((1 S ≤ 16 ≤ 16 ≤ 1 6 ≤ 16	Minimal Inh Concentre (MIC in me) S I ≤ 16 32 - 64 ≤ 16 32 - 64 ≤ 1 - ≤ 16 32 - 64	Minimal Inhibitory Concentration (MIC in meg/ml) S	Criteria Minimal Inhibitory Concentration (MIC in mcg/mL) Discontration (Zo \$ 1 R S \$ 16 32 - 64 ≥ 128 ≥ 21 \$ 16 32 - 64 ≥ 128 ≥ 21 \$ 1 - ≥ 2 ≥ 21 \$ 1 - ≥ 2 ≥ 21 \$ 16 32 - 64 ≥ 128 ≥ 21	Minimal Inhibitory Concentration (MIC in mcg/mL) Disk Diffusit (Zone Diame in mm)	

incoulated with a direct colony suspension and incubated at 35°C in ambient air for 20 to 24 hours. Note: Susceptibility of staphylococci to piperacillin/tazobactam may be deduced from testing only penicillin and either cefoxitin or oxacillin.

A report of S ("Susceptible") indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentration at the infection site necessary to inhibit growth of the pathogen. 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 even if the antimicrobial compound in the blood reaches the concentration usually achievable at the infection site; other therapy should be considered. therapy should be considered.

Quality Control
Standardized susceptibility test procedures require the use of quality controls to monitor and ensure the accuracy and precision of supplies and reagents used in the assay, and the techniques of the individuals performing the test procedures. 1234 Standard piperacillin/tazobactam powder should provide the following ranges of values noted in Table 8. Quality control bacteria are specific strains of bacteria 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. quality control are not clinically significant. Table 8: Acceptable Quality Control Ranges for Piperacil-lin/Tazobactam to Be Used in Validation of Susceptibility Test

	Acceptable Quality Control Ranges				
	Minimum Inhibitory				
	Concentration	Disk Diffusion			
QC Strain	Range (MIC in mcg/mL)	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 influenzaeª ATCC 49247	0.06 – 0.5	33 – 38			
Staphylococ- cus aureus ATCC 29213	0.25 – 2	-			
Staphylococ- cus aureus ATCC 25923	-	27 – 36			
Bacteroides fragilis ^b ATCC 25285	0.12 – 0.5	-			
Bacteroides thetaiotaomi- cron ^o ATCC 29741	4 – 16	-			
Clostridium difficile ^b ATCC 700057	4 – 16	-			
Eubacterium lentum ATCC 43055	4 – 16	-			
plicable only to noculated with 35°C in ambier ^b The quality co roides thetaiota	ontrol range for Haemophili tests performed using Hae a direct colony suspension it air for 20 to 24 hours. ontrol ranges for Bacteroid nomicron are applicable on dilution method.	emophilus Test Medium on and incubated at the ses fragilis and Bacte-			

 13 NONCLINICAL TOXICOLOGY
 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
 Long-term carcinogenicity studies in animals have not
 been conducted with piperacillin/tazobactam, piperacillin, or tazobactam Piperacillin/Tazobactam

Priperacillin/fazobactam was negative in microbial muta-genicity assays, the unscheduled DNA synthesis (UDS) test, a mammalian point mutation (Chinese hamster ovary cell HPRT) assay, and a mammalian cell (BALB/c-3T3) trans-formation assay. In vivo, piperacillin/fazobactam did not induce chromosomal aberrations in rats. Pineracillin/Tazobactam

Reproduction studies have been performed in rats and have revealed no evidence of impaired fertility when piperacillin/ tazobactam is administered intravenously up to a dose of 1280/320 mg/kg piperacillin/tazobactam, which is similar to the maximum recommended human daily dose based on body-surface area (mg/m²). REFERENCES Clinical and Laboratory Standards Institute (CLSI). Performance Standards for Antimicrobial Susceptibility Testing; Twenty-third Informational Supplement. CLSI document M100-S23, Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2013.

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USA, 2013.
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sylvarian 19047, USA, 2012. Clinical and Laboratory Standards Institute (CLSI), Methods for Antimicrobial Susceptibility Testing of Anaerobic Bac-teria; Approved Standard — Eight Edition. CLSI document M11-48. Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, PA 19087 USA, 2012. CLINITEST® is a registered trademark of Siemens Health-care Diagnostics Inc. HOW SUPPLIED/STORAGE AND HANDLING Piperacillin and Tazobactam for Injection is supplied in the

pharmacy bullk package bottle provides piperacillin sodium equivalent to 36 grams of piperacillin and tazobactam sodium equivalent to 4.5 g of tazobactam. Each pharmacy bulk package bottle contains 84.6 mEq (1,945 mg) of sodium. Product Code 304074, NDC 63323-304-74 Piperacillin and Tazobactam for Injection pharmacy bulk package bottles should be stored at 20°C to 25°C (68°F to 77°F) [see USP Controlled Room Temperature] prior to reconstitution.

Each Piperacillin and Tazobactam for Injection 40.5 g

PATIENT COUNSELING INFORMATION
Patients should be counseled that antibacterial drugs in-

This container closure is not made with natural rubber latex.

Patients should be counseled that antibacterial drugs in-cluding 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 consolidation the full course of therapy may (1) decrease the should be taken exactly as directed. Suppling observed in for 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 antibacterial drugs which usually ends when the drug is discontinued. Sometimes after starting treatment with antibacterial drugs, patients can develop watery and bloody stools (with or with-

out stomach cramps and fever) even as late as two or more months after having taken the last dose of the drug. If this occurs, patients should contact their physician as soon as possible. For all questions concerning adverse reactions associated with the use of this product or for inquiries concerning our products, please contact us at 1-800-551-7176 or

www.fresenius-kabi.us.

FRESENIUS KABI

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855943/02

Anaerobic bacteria: Bacteroides fragilis group (B. fragilis, B. ovatus, B. thetaio-taomicron, and B. vulgatus)

significance is unknown.

At least 90% of the following microorganisms exhibit an in At least 90% of the incoming introdugatisms extinct all mytro 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-

Staphylococcus epidermidis (methicillin susceptible