For the use of a Registered Medical Practitioner or a hospital or a laboratory only.

TAZOLIN 2.25 g & 4.5 g DPI

Piperacillin and Tazobactam for Injection USP (I.V. USE ONLY / SINGLE DOSE)

FOR HEALTHCARE PROFESSIONALS

COMPOSITION :

Tazolin 2.25 g

Each vial contains :
Piperacillin Sodium USP
equivalent to Piperacillin 2 g
Tazobactam Sodium
equivalent to Tazobactam USP 250 mg

Tazolin 4.5 g

Each vial contains :
Piperacillin Sodium USP
equivalent to Piperacillin 4 g
Tazobactam Sodium
equivalent to Tazobactam USP 500 mg

DESCRIPTION:

The combination of Piperacillin and Tazobactam is an injection antibacterial combination product consisting of the semisynthetic antibiotic Piperacillin sodium and the beta-lactamase inhibitor Tazobactam sodium for intravenous administration.

PHARMACOLOGICAL PROPERTIES

PHARMACODYNAMIC PROPERTIES:

Pharmacotherapeutic group: Penicillin (Beta-lactam) antibiotics and Beta-lactamase inhibitors

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 beta-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 beta-lactamases at Tazobactam concentrations achieved with the recommended dosage regimens.
The combination of Piperacillin and Tazobactam has been shown to be active against most strains of the following microorganisms both *in vitro* and in clinical infections.

AEROBIC AND FACULTATIVE GRAM-POSITIVE MICROORGANISMS :

- *Staphylococcus aureus* (excluding methicillin and oxacillin-resistant isolates), *Enterococcus faecalis* (ampicillin or penicillin-susceptible isolates only), *staphylococcus epidermidis* (excluding methicillin and oxacillin-resistant isolates), *Streptococcus agalactiae*, *Streptococcus pnemoniae* (penicillin-susceptible isolates only), *Streptococcus pyogenes*, *Viridans* group *Streptococci*.

AEROBIC AND FACULTATIVE GRAM-NEGATIVE MICROORGANISMS :

- *Acinetobacter baumanii*, *Escherichia coli*, *Haemophilus influenzae* (excluding beta-lactamase negative, ampicillin-resistant isolates), *klebsiella pneumoniae*, *pseudomonas aeruginosa* (given in combination with an aminoglycoside to which the isolates is susceptible), *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 fragilis* group (*B. fragilis*, *B. ovatus*, *B. thetaiotaomicron*, and *B. vulgates*), *Bacteroides distasonis*, *Prevotella melaninogenica*

PHARMACOKINETICS:

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

Steady-state plasma concentrations were not different from those attained after the first dose when 2.25g or 4.5g doses of Piperacillin and Tazobactam were administered via 30-minutes infusions every 6 hours. Steady-state plasma concentrations after 30-minute infusion every 6 hours are provided in Table 1.

TABLE 1: STEADY STATE MEAN PLASMA CONCENTRATIONS IN ADULTS AFTER 30-MINUTE INTRAVENOUS INFUSION OF PIPERACILLIN AND TAZOBAC TAM 6 HOURS

					PIPERACILLIN			
		Plasma Concentrations(µg/mL)**						**AUC**(µg-hr/mL)**
Piperacillin and 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)**
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 (µg/ mL)**						**AUC**(µg-hr/ mL)**
Piperacillin and Tazobactam Dose [a]	**No. of Evaluable Subjects**	**30 min**	**1 hr**	**2 hr**	**3hr**	**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**	**16.0 (21)**
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

Following single or multiple Piperacillin and Tazobactam doses to healthy subjects, the plasma half-life of Piperacillin and 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 a 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 tissue and body fluids including intestinal mucosa, gall bladder, lungs, female reproductive tissues (uterus, ovary, fallopian tubes), interstitial fluid and bile. Mean tissue concentrations are generally 50-100% of those in the 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 dose of Piperacillin and Tazobactam to subjects with renal impairment, the half-life of Piperacillin and Tazobactam increases with decreasing creatinine clearance. At creatinine clearance below 20 mL/min, the increase in half-life is two fold for

Piperacillin and fourfold for Tazobactam compared to subjects with normal renal function. Dosage adjustments for Piperacillin and Tazobactam are recommended when creatinine clearance is below 40 mL/min in patients receiving the usual recommended daily dose of Piperacillin and Tazobactam. (See **DOSAGE AND ADMINISTRATION** section for specific recommendations for the treatment of patients with renal insufficiency.) Hemodialysis removes 30% to 40% of a Piperacillin and 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 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 due to hepatic cirrhosis.

PEDIATRICS: The combination of 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.

CLINICAL PARTICULARS

INDICATIONS AND USAGE:

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

Intra-abdominal Infections

Piperacillin and tazobactam is indicated in adults and pediatric patients (2 months of age and older) for the treatment of appendicitis (complicated by rupture or abscess) and peritonitis caused by beta-lactamase producing isolates of Escherichia coli or the following members of the Bacteroides fragilis group: B. fragilis, B. ovatus, B. thetaiotaomicron, or B. vulgatus.

Nosocomial Pneumonia

Piperacillin and tazobactam is indicated in adults and pediatric patients (2 months of age and older) for the treatment of nosocomial pneumonia (moderate to severe) caused by beta-lactamase producing isolates of Staphylococcus aureus and by piperacillin and tazobactam-susceptible Acinetobacter baumannii, Haemophilus influenzae, Klebsiella pneumoniae, and Pseudomonas aeruginosa (Nosocomial pneumonia caused by P. aeruginosa should be treated in combination with an aminoglycoside) [see Dosage and Administration (2)].

Skin and Skin Structure Infections

Piperacillin and tazobactam is indicated in adults for the treatment of uncomplicated and complicated skin and skin structure infections, including cellulitis, cutaneous abscesses and ischemic/diabetic foot infections caused by beta-lactamase producing isolates of Staphylococcus aureus.

Female Pelvic Infections

Piperacillin and tazobactam is indicated in adults for the treatment of postpartum endometritis or pelvic inflammatory disease caused by beta-lactamase producing isolates of Escherichia coli. 1.5 Community-acquired Pneumonia Piperacillin and tazobactam is indicated in adults for the

treatment of community-acquired pneumonia (moderate severity only) caused by beta-lactamase producing isolates of Haemophilus influenzae.

Usage

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Piperacillin and tazobactam and other antibacterial drugs, Piperacillin and tazobactam should be used only to treat or prevent 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 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. The usual total daily dose of the combination of Piperacillin and Tazobactam for adults is 13.5 given as 3.375 g every 6 hours.

Dosage in Adult Patients With Indications Other Than Nosocomial Pneumonia

The usual total daily dosage of Piperacillin and tazobactam for adult patients with indications other than nosocomial pneumonia is 3.375 g every six hours [totaling 13.5 g (12.0 g piperacillin and 1.5 g tazobactam)], to be administered by intravenous infusion over 30 minutes. The usual duration of Piperacillin and tazobactam treatment is from 7 to 10 days.

Dosage in Adult Patients With Nosocomial Pneumonia

Initial presumptive treatment of adult patients with nosocomial pneumonia should start with Piperacillin and tazobactam at a dosage of 4.5 g every six hours plus an aminoglycoside, [totaling 18.0 g (16.0 g piperacillin and 2.0 g tazobactam)], administered by intravenous infusion over 30 minutes. The recommended duration of Piperacillin and tazobactam treatment for nosocomial pneumonia is 7 to 14 days. Treatment with the aminoglycoside should be continued in patients from whom P. aeruginosa is isolated.

Dosage in Adult Patients With Renal Impairment:

In patients with renal insufficiency (creatine clearance≤ 40mL/min), the intravenous dose of the combination of Piperacillin & Tazobactam should be reduced based on the degree of renal impairment. The recommended daily dosage of Piperacillin and tazobactam for patients with renal impairment administered by intravenous infusion over 30 minutes is described below:

Recommended Dosing of the combination of Piperacillin and Tazobactam in Patients with Normal Renal Function and Renal Insufficiency (As total grams Piperacillin and 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
20-40mL/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		

HEMODIALYSIS: For patients on hemodialysis, the maximum dose is 2.25 g every twelve hours for all indications other than nosocomial pneumonia and 2.25g every eight hours for nosocomial pneumonia.

Since hemodialysis removes 30% to 40% of the administered dose, an additional dose of 0.75g of the combination of Piperacillin and Tazobactam should be administered following each dialysis period on hemodialysis days. No additional dosage of the combination of Piperacillin and Tazobactam is necessary for CAPD patients.

Dosage in Pediatric Patients With Appendicitis/Peritonitis or Nosocomial Pneumonia
The recommended dosage for pediatric patients with appendicitis and/or peritonitis or nosocomial pneumonia aged 2 months of age and older, weighing up to 40 kg, and with normal renal function, is described in Table 2

Table 2: Recommended Dosage of Piperacillin and tazobactam in Pediatric Patients 2 Months of Age and Older, Weighing Up to 40 kg, and With Normal Renal Function#		
Age	Appendicitis and/or Peritonitis	Nosocomial Pneumonia
2 months to 9 months	90 mg/kg (80 mg piperacillin and 10 mg tazobactam) every 8 (eight) hours	90 mg/kg (80 mg piperacillin and 10 mg tazobactam) every 6 (six) hours
Older than 9 months of age	112.5 mg/kg (100 mg piperacillin and 12.5 mg tazobactam) every 8 (eight) hours	112.5 mg/kg (100 mg piperacillin and 12.5 mg tazobactam) every 6 (six) hours

Administer Piperacillin and tazobactam by intravenous infusion over 30 minutes.

Pediatric patients weighing over 40 kg and with normal renal function should receive the adult dose.
Dosage of Piperacillin and tazobactam in pediatric patients with renal impairment has not been determined.

DURATION OF THERAPY:

The usual duration of the combination of Piperacillin and Tazobactam treatment is from seven to ten days. However, the recommended duration of the combination of Piperacillin and Tazobactam treatment is from seven to ten days. However, the recommended duration of the combination of Piperacillin and Tazobactam 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.

CONTRAINDICATIONS:

The combination of Piperacillin and Tazobactam is contraindicated in Patients with a history of allergic reactions to any of the Penicillins, cephalosporins or beta-lactamase inhibitors.

WARNINGS:

Serious and occasionally fatal hypersensitivity (anaphylactic/anaphylactoid) reactions including shock have been reported in patients receiving penicillin therapy. Severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pulstulosis (AGEP) have been reported. If progressive rash or hypersensitivity reactions occur, discontinue Piperacillin and Tazobactam immediately and initiate appropriate therapy.

Hemophagocytic lymphohistiocytosis (HLH) has been reported with Piperacillin and Tazobactam. If signs or symptoms suggestive of HLH occur, treatment should be discontinued immediately.

Nephrotoxicity has been observed in critically ill patients, particularly with concomitant vancomycin therapy. Renal function should be monitored during treatment.

Rhabdomyolysis has also been reported during post-marketing use. If signs or symptoms of rhabdomyolysis occur, discontinue therapy and initiate appropriate management.

Clostridioides difficile-associated diarrhea (CDAD) has been reported with nearly all antibacterial agents including Piperacillin and Tazobactam and may range from mild diarrhea to fatal colitis.

Clostridioides difficile-associated diarrhea (CDAD) has been reported with us of nearly all antibacterial agents, including Piperacillin and Tazobactam and may range in severity from mild diarrhoea 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 diarrhoea 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:

Additional monitoring of renal function is recommended in critically ill patients and in patients receiving concomitant vancomycin due to increased risk of acute kidney injury.

GENERAL: Bleeding manifestations have occurred in some patients receiving beta-lactam antibiotics, including Piperacillin. These reactions have sometimes been associated with abnormalities of coagulation tests such as clotting time, platelet aggregation and prothrombin time, and are more likely to occur in patients with renal failure. If bleeding manifestations occur, the combination of Piperacillin and Tazobactam 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 convulsion if higher than recommended doses are given intravenously (particularly in the presence of renal failure).

The combination of Piperacillin and Tazobactam is a monosodium salt of Piperacillin and a monosodium salt of Tazobactam and contains a total of 2.79 mEq (64 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 the combination of Piperacillin and Tazobactam 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.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: Long-term Carcinogenicity studies in animals have not been conducted with the combination of Piperacillin and Tazobactam, Piperacillin, or Tazobactam.

PREGNANCY:

TERATOGENIC EFFECTS-PREGNANCY CATEGORY B : Reproduction studies have been performed in rats and have revealed no evidence of impaired fertility due to the combination of Piperacillin and Tazobactam administered up to a dose which is similar to the maximum recommended human daily dose based on body-surface area (mg/m^2). There are, however, no adequate and well controlled studies with the combination of Piperacillin and Tazobactam 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 in 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 the combination of Piperacillin and Tazobactam is administered to a nursing woman.

PEDIATRIC USE:

Use of the combination of Piperacillin and Tazobactam 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 the combination of Piperacillin and Tazobactam. Safety and efficacy in pediatric patients less than 2 months of age have not been established

There are no dosage recommendations for the combination of Piperacillin and Tazobactam 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.
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.

The combination of Piperacillin and Tazobactam contains 64 mg (2.79 mEq) of sodium per gram of Piperacillin in the combination product. At the usual recommended doses, patient would receive between 768 and 1024 mg/day (33.5 and 44.6 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.

HEPATIC IMPAIRMENT

Dosage adjustment of Piperacillin and tazobactam is not warranted in patients with hepatic cirrhosis.

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.

DRUG INTERACTIONS:

Aminoglycosides: The mixing of the combination of Piperacillin and Tazobactam with an aminoglycoside *in vitro* can result in substantial inactivation of the aminoglycoside. The aminoglycosides should be reconstituted and administered separately.

Probenecid: Probenecid administered concomitantly with the combination of Piperacillin and Tazobactam prolongs the half-life of Piperacillin by 21% and that of Tazobactam by 71%.

Vancomycin: Concomitant administration of Piperacillin and Tazobactam with vancomycin may increase the incidence of acute kidney injury. Monitor renal function in patients receiving both therapies.

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

Heparin : Coagulation parameters should be tested more frequently and monitored regularly during simultaneus administration of high doses of heparin, oral anticoagulants or other drug that may affect the blood coagulation system or the thrombocyte function.

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 frequency monitored.

ADVERSE EFFECTS:

The most commonly reported adverse reactions (incidence >5%) include diarrhea, constipation, nausea, headache and insomnia. Additional post-marketing adverse reactions include severe cutaneous adverse reactions, hemophagocytic lymphohistiocytosis (HLH), nephrotoxicity and rhabdomyolysis.

Adverse events reported in 1% or less of patients are as follows:

Body as a whole-rigors, back pain, malaise.

Autonomic nervous system-hypotension, ileus, syncope

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.

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

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

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

DIRECTIONS FOR RECONSTITUTION AND DILUTION FOR USE:
Intravenous Administration: 2.25 g and 4.5 g of the combination of Piperacillin and Tazobactam should be reconstituted with 10 mL and 20 mL sterile water for Injection respectively.

Shake well until dissolved.

COMPATIBLE RECONSTITUTION DILUENTS: These include 0.9% Sodium Chloride for Injection, Sterile Water for Injection maximum recommended volume per dose of sterile water for Injection is 50 mL), Dextrose 5%, Bacteriostatic saline/ Parabens, Bacteriostatic water/Parabens , Bacteriostatic saline/ Benzyl Alcohol, Bacteriostatic Water/Benzyl Alcohol.

Reconstituted combination of Piperacillin and Tazobactam solution should be further diluted (recommended volume per dose of 50ml to 150 ml) in a compatible intravenous diluent 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: These include 0.9% Sodium Chloride for Injection, Sterile Water for Injection (maximum recommended volume per dose of Sterile Water for Injection is 50 mL.), Dextrose 5%, Dextran 6% in Saline, Lactate Ringer's solution is not compatible.

INSTRUCTIONS FOR USE: The combination of Piperacillin and Tazobactam should not be mixed with other drugs in a syringe or infusion bottle since compatibility has not been established.

The combination of Piperacillin and Tazobactam is not chemically stable in solutions that contain only sodium bicarbonate and solutions that significantly alter the pH.
The combination of Piperacillin and Tazobactam should not be added to blood products or albumin hydrolysates.

LACTATED RINGERS SOLUTION IS NOT COMPATIBLE WITH THE COMBINATION OF PIPERACILLIN AND TAZOBACTAM:
The combination of Piperacillin and Tazobactam should not be added to blood products or albumin hydrolysates. When concomitant therapy with aminoglycosides is indicated the combination of

Piperacillin and Tazobactam and the aminoglycoside should be reconstituted and administered separately, due to the *in vitro* inactivation of the aminoglycoside by the penicillin.

OVERDOSE:

There have been postmarketing reports of overdose with the combination of Piperacillin and Tazobactam. The majority of those events experienced, including nausea, vomiting and diarrhoea, have also been reported with the usual recommended dosage. 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 concentration of either Piperacillin or Tazobactam may be reduced by hemodialysis.

STORAGE AND STABILITY:

Prior to Reconstitution: Keep at controlled room temperature 15^0-30^0C. Reconstitute vials with 5 ml of compatible diluent per gram of Piperacillin. Shake well until dissolved. Use single dose vials immediately after reconstitution. Discard any unused portion after 24 hours if stored at room temperature or after 48 hours if stored at refrigerated temperature (2^0C to 8^0C[36^0F to 46^0F]). Stability in an ambulatory intravenous infusion pump has been demonstrated for a period of 12 hours at room temperature.

This document was last revised on May 2026.

National Healthcare