Front

Pipbacta™ IV

(Piperacillin + Tazobactam) Injection

پیپبیکٹا انجکشن

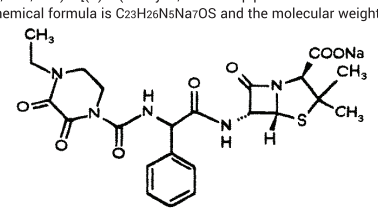
COMPOSITION:
Pipbacta Injection 4.5 gm:
Each vial contains:
Sterile Piperacillin Sodium equivalent to
Piperacillin ..... 4.0 gm.
Sterile Tazobactam Sodium equivalent to
Tazobactam ..... 0.5 gm.
Also contains 9.44 mmol (217 mg) of Sodium

Product Specs.: USP

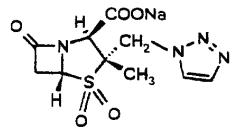
Pipbacta Injection 2.25 gm:
Each vial contains:
Sterile Piperacillin Sodium equivalent
to Piperacillin ..... 2.0 gm.
Sterile Tazobactam Sodium equivalent
to Tazobactam ..... 0.25 gm.
Also contains 4.72 mmol (109 mg) of Sodium

Product Specs.: USP

DESCRIPTION:
Piperacillin and Tazobactam for Injection is an injectable antibacterial combination product consisting of the semisynthetic antibiotic piperacillin sodium and the βlactamase inhibitor tazobactam sodium for intravenous administration. Piperacillin sodium is derived from D(-)-α aminobenzyl-penicillin. The chemical name of piperacillin sodium is sodium: (2S, 5R, 6R)-6-[(R)-2-(4-ethyl-2,3-dioxo-1-piperazinecarboxamido)-2phenylacetamido]-3,3-dimethyl-7-oxo-4thia-1azabicyclo[3.2.0]heptane-2- carboxylate. The chemical formula is $C_{23}H_{26}N_5Na_7OS$ 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(2S,3S,5R)-3methyl7oxo3(1H1,2,3triazol1ylmethyl)4thia1azabicyclo [3.2.0] zeptane2carboxylate4,4dioxide. 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:



Clinical Pharmacology:
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 β-lactamase inhibitor of the molecular class A enzymes, including 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.
Pharmacodynamics: The pharmacodynamic parameter for piperacillin/tazobactam that is most predictive of clinical and microbiological efficacy is time above MIC.
Pharmacokinetics: The mean and coefficients of variation (CV%) for the pharmacokinetic parameters of piperacillin and tazobactam after multiple intravenous doses are summarized in below table.

Mean (CV%) Piperacillin and Tazobactam PK Parameters

Piperazillin						
Piperacillin/ Tazobactan Dose*	C_{max} mcg/mL	AUC[b] mcg•h/mL	CL mL/min	V L	T½ h	CL_g 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/ Tazobactan Dose*	C_{max} mcg/mL	AUC[b] mcg•h/mL	CL mL/min	V L	T½ h	CL_g 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	–

[a] Piperacillin and tazobactam were given in combination, infused over 30 minutes.
[b] Numbers in parentheses are coefficients of variation (CV%).

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

MICROBIOLOGY:
Piperacillin sodium exerts bactericidal activity by inhibiting septum formation and cell wall synthesis of susceptible bacteria. Tazobactam sodium has little clinically relevant in vitro activity against bacteria due to its reduced affinity to penicillinbinding proteins. It is, however, a βlactamase 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 βlactamases 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.
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 βlactamase negative, ampicillin resistance 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).
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.

INDICATIONS AND USAGE:
Piperacillin and Tazobactam for injection is indicated for the treatment of patients with moderate to severe infections caused by piperacillinresistant, 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.
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). Piperacillin and Tazobactam for Injection is indicated only for the specified conditions listed above. Infections caused by piperacillinsusceptible 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 piperacillinsusceptible organisms and piperacillin resistant, β lactamase producing organisms susceptible to Piperacillin and Tazobactam for Injection should not require the addition of another antibiotic. 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 grampositive and gram negative aerobic and anaerobic organisms. 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.

DOSAGE AND ADMINISTRATION:
Piperacillin and Tazobactam for injection should be administered by intravenous infusion over 30 minutes. 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 g piperacillin/1.5 g tazobactam). 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.
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 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 (expect nosocominal Pneumonia)	Nosocominal 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 administrated follwoing 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.
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. 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.
Compatible reconstitution diluents: 0.9% Sodium Chloride for injection, Sterile Water for injection‡, Dextrose 5%, Bacteriostatic Saline/Parabens, Bacteriostatic

Back

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‡, Dextrose 5%, Dextran 6% in Saline. (‡Maximum recommended volume per dose of sterile water for injection is 50 mL.)

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: 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. 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 βlactam 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 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. 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.
Laboratory tests: Periodic assessment of hematopoietic function should be performed, especially with prolonged therapy, i.e., ≥ 21 days.

SPECIAL 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 renal function. Dosage adjustments are recommended when creatinine clearance is below 40 mL/min in patients receiving the usual recommended daily dose.
Administration for specific recommendations for the treatment of patients with renal-impairment: 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.
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 due to hepatic cirrhosis.
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 months old to 12 years 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.
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.
Race: 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.
Pregnancy - 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 bodysurface area(mg/m2). 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 bodysurface area (mg/m2) Piperacillin and tazobactam cross the placenta in humans. 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 bodysurface area (mg/m2). There are, however, no adequate and wellcontrolled 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 wellcontrolled studies and pharmacokinetic studies in adults and in pediatric patients. Safety and efficacy in pediatric patients less than 2 months of age have not been established. 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. 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. 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.

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.

DRUG INTERACTIONS:
Aminoglycosides: The mixing of betalactam antibiotics with aminoglycosides in vitro can result in substantial inactivation of the aminoglycoside. It has been postulated that penicillinaminoglycoside 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 endstage 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 that of tazobactam by 71%.
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. Neuromuscular blockade produced by any of the non¬depolarizing muscle relaxants could be prolonged in the presence of piperacillin.
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.
Carcinogenesis, Mutagenesis, Impairment of fertility: Long ¬term carcinogenicity studies in animals have not been conducted with piperacillin/tazobactam, piperacillin, or tazobactam.

ADVERSE REACTIONS:
Local reactions: Phlebitis (1.3%), injection site reaction (0.5%), pain (0.2%), inflammation (0.2%), thrombophlebitis (0.2%), and edema (0.1%).
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.
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 system — 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

OVERDOSAGE:
There have been post marketing 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 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.

INSTRUCTIONS:
- Store in a cool and dry place, below 30ºC.
- Protect from heat, sunlight & moisture.
- Keep out of the reach of children.
- Do not freeze.
- Always use freshly reconstituted solution.
- To be sold on the prescription of a registered medical practitioner only.

PRESENTATION:
Pipbacta IV Injection 4.5 gm : Pack of 4.5 gm IV injection vial with 20 ml water for injection ampoule.
Pipbacta IV Injection 2.25 gm : Pack of 2.25 gm IV injection vial with 10 ml water for injection ampoule.

ہدایات:
دوا کو خشک اور ٹھنڈی جگہ، ۳۰ درجہ سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔
گرمی، دھوپ اور نمی سے بچائیں۔
بچوں کی پہنچ سے دور رکھیں۔
منجمند ہونے سے بچائیں۔
انجکشن تیار کرنے کے فوراً بعد استعمال کریں۔
صرف مستند ڈاکٹر کے نسخہ پر فروخت کریں۔

Manufactured by:
Global Pharmaceuticals (Pvt) Ltd.
Plot No. 204-205, Industrial Triangle, Kahuta Road,
Islamabad - Pakistan.

FOR FURTHER INFORMATION PLEASE CONTACT:

CCL
Manufactured for:
CCL Pharmaceuticals (Pvt.) Ltd.
62 Industrial Estate, Kot Lakhpat, Lahore, Pakistan.