# PIPERACILLIN SODIUM
# TAZOBACTAM SODIUM

## PIPTAZ®

2 g / 250 mg Powder for Injection
4 g / 500 mg Powder for Injection
**(For Intravenous Infusion)**
**ANTIBACTERIALS (PENICILLINS)**

**FORMULATIONS**

Each 2.25 g vial contains:
Piperacillin (as sodium), USP ..... 2 g
Tazobactam (as sodium) ..... 250 mg

Each 4.5 g vial contains:
Piperacillin (as sodium), USP ..... 4 g
Tazobactam (as sodium) ..... 500 mg

**PRODUCT DESCRIPTIONS**

**Piperacillin/Tazobactam 2.25 g powder for injection:** white to off-white powder filled in a clear transparent 20 mL USP type I glass vial, capped with 20 mm grey bromobutyl rubber closure and sealed with 20 mm colored flip off seal

**Piperacillin/Tazobactam 4.5 g powder for injection:** white to off-white powder filled in a clear transparent 30 mL USP type I glass vial, capped with 20 mm grey bromobutyl rubber closure and sealed with 20 mm colored flip off seal

Piperacillin/Tazobactam contains a total of 2.23 mEq (51 mg) sodium ($Na^+$) per gram of piperacillin in the combination product.

After reconstitution with a compatible diluent, piperacillin/tazobactam powder for injection dissolves completely into a clear, colorless to light yellow solution, free from foreign particles.

**PHARMACODYNAMICS**

Piperacillin, an extended-spectrum penicillin, exerts its antimicrobial action in growing and dividing bacteria by interfering with septum formation and cell wall synthesis of susceptible bacteria. It binds to penicillin-binding proteins on the bacterial cell wall and blocks peptidoglycan synthesis. Peptidoglycan is a heteropolymeric structure that gives the cell wall its mechanical stability. The final stage of the peptidoglycan synthesis involves the completion of the cross-linking with the terminal glycine residue of the pentaglycine bridge linking to the fourth residue of the pentapeptide. The transpeptidase that performs this step is inhibited by piperacillin. The bacterial cell wall weakens leading to swelling and rupture of the microorganism.

Tazobactam, a penicillinic acid sulfone with $\beta$-lactamase inhibitory properties, is similar to sulbactam although it is regarded as more potent. It irreversibly inactivates many plasmid-mediated and some chromosome-mediated $\beta$-lactamases. Tazobactam can inhibit staphylococcal $\beta$-lactamases and $\beta$-lactamases classified as Richmond-Sykes types II, III, IV and V. Unlike clavulanic acid, tazobactam generally does not induce production of type I chromosomally mediated cephalosporinases in *Pseudomonas* or Enterobacteriaceae.

**ANTIMICROBIAL SPECTRUM OF ACTIVITY**

Piperacillin/Tazobactam combines a bactericidal antibiotic with a $\beta$-lactamase inhibitor. *In vitro*, piperacillin is active against a variety of Gram-positive and Gram-negative aerobic and anaerobic bacteria. Tazobactam has little clinically relevant *in vitro* antibacterial activity due to its low affinity to penicillin-binding proteins.

Piperacillin/Tazobactam is active *in vitro* and in clinical infections against most strains of the following microorganisms:

| Aerobic and Facultative Gram-positive | Aerobic and Facultative Gram-negative |
|---|---|
| *Staphylococcus aureus* (excluding methicillin and oxacillin-resistant isolates | *Acinetobacter baumanni*<br>*Escherichia coli*<br>*Haemophilus influenzae* (excluding beta-lactamase negative, ampicillin-resistant isolates) |
| **Gram-negative Anaerobes** | *Klebsiella pneumoniae*<br>*Pseudomonas aeruginosa* (given in combination with an aminoglycoside to which the isolate is susceptible) |
| *Bacteroides fragilis group (B. fragilis, B. ovatus, B. thetaiotaomicron, and B. vulgaris)* | |

Piperacillin/Tazobactam demonstrated *in vitro* activity against strains of the following microorganisms; however, clinical significance is unknown:

| Aerobic and Facultative Gram-positive | Aerobic and Facultative Gram-negative |
|---|---|
| *Enterococcus faecalis* (ampicillin or penicillin-susceptible isolates only)<br>*Staphylococcus epidermidis* (excluding methicillin and oxacillin-resistant isolates)<br>*Streptococcus agalactiae**<br>*Streptococcus pneumoniae* *(*penicillin-susceptible isolates only*)<br>*Streptococcus pyogenes**<br>*Viridans group streptococci** | *Citrobacter koseri*<br>*Moraxella catarrhalis*<br>*Morganella morganii*<br>*Neisseria gonorrhoeae*<br>*Proteus mirabilis*<br>*Proteus vulgaris*<br>*Serratia marcescens*<br>*Providencia stuartii*<br>*Providencia rettgeri*<br>*Salmonella enterica* |
| **Gram-positive Anaerobe** | **Gram-negative Anaerobes** |
| *Clostridium perfringens* | *Bacteroides distasonis*<br>*Prevotella melaninogenica* |

*These are not beta-lactamase producing bacteria and, therefore, are susceptible to piperacillin alone.

It is suggested to carry out susceptibility tests.

**PHARMACOKINETICS**

Peak plasma concentrations of piperacillin and tazobactam are attained immediately after completion of intravenous infusion. After a 30-minute infusion of piperacillin/tazobactam, piperacillin plasma concentration is similar to that attained when piperacillin is given alone, with mean peak plasma concentrations of about 134 and 298 mcg/mL for the 2.25 and 4.5 g doses, respectively. The corresponding mean peak plasma concentrations of tazobactam were 15 and 34 mcg/mL, respectively.

Piperacillin/tazobactam is widely distributed into body fluids including pleural, peritoneal, synovial, interstitial, and wound fluids. It is also distributed into tissues including kidneys, gall bladder, intestinal mucosa, lung, female reproductive tissues (uterus, ovary and fallopian tubes), adipose, and bile. Mean tissue concentrations are generally 5% to 100% of those in plasma. However, distribution of piperacillin/tazobactam into the cerebrospinal fluid is low in adults with non-inflamed meninges. Piperacillin and tazobactam cross the placenta. Piperacillin is distributed into milk; it is not known whether tazobactam is distributed into milk.

Both piperacillin and tazobactam are approximately 30% bound to plasma proteins in adults.

The plasma half-life ($t_{1/2}$) of piperacillin and plasma $(t_{1/2})$ of tazobactam range from 0.7 to 1.2 hours in adults. In adults with cirrhosis, the $t_{1/2}$ of piperacillin and tazobactam are increased by about 25% and 185%, respectively, compared with adults with normal hepatic function. In adults with creatinine clearances less than 20 mL/minute, the $t_{1/2}$ of piperacillin is two times higher and the $t_{1/2}$ of tazobactam is four times higher compared with adults with normal renal function.

In adults, about 68% of a piperacillin dose and 80% of a tazobactam dose is eliminated unchanged in the urine. Clearance of piperacillin and tazobactam in children 9 months to 12 years old is comparable to that of adults, with a population mean value of 5.64 mL/min/kg. Piperacillin clearance in children 2 to 9 months old is estimated to be 80% of that value; clearance is slower in patients below 2 months old compared with older children.

**INDICATIONS**

For the treatment of the following moderate to severe infections caused by piperacillin-resistant, piperacillin/tazobactam-susceptible, and $\beta$-lactamase producing strains of susceptible microorganisms:

**Adults and Adolescents**

- Lower respiratory tract infections including severe community-acquired pneumonia and healthcare-associated pneumonia
  ***(Note:** Healthcare-associated pneumonia caused by Pseudomonas aeruginosa should be treated in combination with an aminoglycoside)*
  - Uncomplicated and complicated skin and skin structure infections including cellulitis, cutaneous abscesses, and acute ischemic/diabetic foot infections
  - Intra-abdominal infections including appendicitis (complicated by rupture and abscess) and peritonitis
  - Complicated and uncomplicated urinary tract infections
  - Gynecologic infections including postpartum endometritis or pelvic inflammatory disease
  - Bone and joint infections
  - Bacterial sepsis
  - Bacterial infections in neutropenic patients
    ***(Note:** Full therapeutic doses of piperacillin/tazobactam plus an aminoglycoside should be used)*
  - Polymicrobic infections including those where aerobic and anaerobic organisms are suspected (intra-abdominal, skin and skin structure, upper and lower respiratory tract, gynecological).

**Children**

- Complicated intra-abdominal infections in children ≥ 2 months old
- Bacterial infections in febrile neutropenic children 2 to 12 years old

**DOSAGE AND ADMINISTRATION**

Piperacillin/tazobactam is administered by intravenous (IV) infusion over 30 minutes.

Due to the *in vitro* inactivation of the aminoglycosides by beta-lactam antibiotics, piperacillin/tazobactam and the aminoglycoside should be reconstituted, diluted and administered separately when concomitant treatment is indicated.

**Usual Adult Dose**

- **For most infections:** 4 g piperacillin/500 mg tazobactam administered every 8 hours
  The total daily dose depends on the site and severity of infection and can vary from 2 g piperacillin/250 mg tazobactam to 4 g piperacillin/500 mg tazobactam administered every 6, 8 or 12 hours.
- **For healthcare-associated pneumonia:** 4 g piperacillin/500 mg tazobactam administered every 6 hours, in conjunction with an aminoglycoside (see **INTERACTIONS WITH OTHER MEDICAMENTS**)
- **For bacterial infections in neutropenic patients:** 4 g piperacillin/500 mg tazobactam administered every 8 hours, in conjunction with an aminoglycoside (see **INTERACTIONS WITH OTHER MEDICAMENTS**). The total daily dose depends on the severity and localization of the infection and can vary from 2 g piperacillin/250 mg tazobactam to 4 g piperacillin/500 mg tazobactam administered every 6 or 8 hours.

**Dose in Adults with Renal Impairment:**

| | Recommended Piperacillin/Tazobactam Dose | |
|---|---|---|
| **Renal Function (Creatinine Clearance)** | **All Indications (except healthcare-associated pneumonia)** | **Healthcare-associated pneumonia*** |
| 20 to 40 mL/min** | 2 g piperacillin/250 mg tazobactam every 6 hours | 3 g piperacillin/375 mg tazobactam every 6 hours |
| < 20 mL/min** | 2 g piperacillin/250 mg tazobactam every 8 hours | 2 g piperacillin/250 mg tazobactam every 6 hours |
| Hemodialysis*** | 2 g piperacillin/250 mg tazobactam every 12 hours | 2 g piperacillin/250 mg tazobactam every 8 hours |
| Continuous Ambulatory Peritoneal Dialysis (CAPD) | 2 g piperacillin/250 mg tazobactam every 12 hours | 2 g piperacillin/250 mg tazobactam every 8 hours |

* In patients with healthcare-associated pneumonia receiving concomitant aminoglycoside therapy, the aminoglycoside dosage should be adjusted according to the recommendations of the aminoglycoside used.

**Creatinine clearance for patients not receiving hemodialysis

***Since hemodialysis removes 30% to 40% of the administered dose, one additional dose of 750 mg (670 mg piperacillin/80mg tazobactam) should be administered following each dialysis period.
No additional dosage of piperacillin/tazobactam dose is needed for CAPD patients.

**Pediatric Dose**

- **Hospitalized children (≥ 2 months old) with complicated intra-abdominal infections**

| Age Group/ Body Weight | Recommended Piperacillin/Tazobactam Dose in Children with Normal Renal Function* |
|---|---|
| Children 2 to 9 months old | 80 mg piperacillin/10 mg tazobactam per kg body weight per dose administered every 8 hours** |
| Children ≥ 9 months old, weighing less than or equal to 40 kg | 100 mg piperacillin/12.5 mg tazobactam per kg body weight per dose administered every 8 hours |
| Children ≥ 9 months old, weighing more than 40 kg | Follow adult dosing recommendations |

*There are no dosage recommendations for children with renal impairment. Each patient must be closely monitored for signs of drug toxicity. Dose and interval should be adjusted accordingly.
**Dose based on pharmacokinetic modeling

- **Neutropenic children (2 to 12 years old) with fever suspected to be due to bacterial infections:** 80 mg piperacillin/10 mg tazobactam per kg body weight per dose administered every 6 hours

***NOTE: Dose in children should not exceed 4 g piperacillin/500 mg tazobactam per dose administered over 30 minutes***

**Duration of Treatment:**

The duration of treatment will depend on the type and severity of infection and on the patient's clinical and bacteriological progress. It should be continued for a maximum of 48 to 72 hours after fever has subsided or after evidence of bacterial eradication has been obtained.

- **For most infections:** 5 to 14 days
- **For healthcare-associated pneumonia:** 7 to 14 days
- **For group A/B-hemolytic streptococci infections:** Minimum of 10 days to minimize the risk of rheumatic fever or glomerulonephritis.
- **Concomitant treatment with an aminoglycoside:** Treatment with the aminoglycoside should be continued in patients from whom *Pseudomonas aeruginosa* is isolated. If *Pseudomonas aeruginosa* is not isolated, the aminoglycoside maybe discontinued at the discretion of the attending physician.

***Or, as prescribed by a physician.***

**Directions for Use, Compatibility and Stability:**

To reconstitute, dissolve piperacillin/tazobactam powder for injection (as shown in the table below) with compatible diluent and shake thoroughly until all contents are dissolved.

| Piperacillin/Tazobactam | Volume of Compatible Diluent (mL) |
|---|---|
| 2.25 g vial (2 g piperacillin/250 mg tazobactam) | 10 mL |
| 4.5 g vial (4 g piperacillin/500 mg tazobactam) | 20 mL |

The reconstituted solution is stable for 24 hours if stored at 25°C or for 48 hours if stored at 2°C to 8°C. Vials should not be frozen.

**Compatible Diluents for Reconstitution**

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

Reconstituted piperacillin/tazobactam should be further diluted to desired volume (50 to 150 mL) with 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.

**Compatible Intravenous Solutions for Infusion**

- Sterile Water for Injection*
- 0.9% Sodium Chloride for Injection
- 5% Dextrose Injection
- 5% Dextrose and 0.9% Sodium Chloride for Injection

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

**Incompatibilities**

- Lactated Ringer's Solution is **not** compatible with piperacillin/tazobactam.
- Whenever piperacillin/tazobactam is used concomitantly with another antibiotic, the drugs must be administered separately.
- Piperacillin/Tazobactam should not be mixed with other drugs in a syringe or infusion bottle due to possible problems with compatibility.
- Piperacillin/Tazobactam should not be added to blood products or albumin hydrolysates.
- Piperacillin/Tazobactam is not chemically stable in solutions that contain only sodium bicarbonate and solutions that significantly alter pH.
  - *Prior to administration, parenteral drug products should be inspected visually for particulate matter and discoloration whenever solution and container permit.*
  - *Shake the reconstituted solution before use.*
  - *Observe strict aseptic technique when drawing up the contents of the vial. If contaminated, it has the potential to become a source of infection to patients.*

**CONTRAINDICATIONS**

Patients with a history of allergic reactions to any of the penicillins, cephalosporins, or $\beta$-lactamase inhibitors, or to any component of the product

**WARNINGS AND PRECAUTIONS**

- **HYPERSENSITIVITY REACTIONS:** SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC/ANAPHYLACTOID) REACTIONS (INCLUDING SHOCK) HAVE BEEN REPORTED IN PATIENTS RECEIVING TREATMENT WITH PENICILLINS INCLUDING PIPERACILLIN/TAZOBACTAM. THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF HYPERSENSITIVITY TO PENICILLIN 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. CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, OR OTHER ALLERGENS BEFORE INITIATING TREATMENT WITH PIPERACILLIN/TAZOBACTAM. IN CASE OF AN ALLERGIC REACTION, PIPERACILLIN/TAZOBACTAM SHOULD BE DISCONTINUED AND APPROPRIATE AND 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.**

As with other semi-synthetic penicillins, piperacillin treatment has been associated with an increased incidence of fever and rash in patients with cystic fibrosis.

- *Clostridium difficile-associated diarrhea:* This has been observed with the use of nearly all antibacterial agents, including piperacillin/tazobactam, and may range in severity from mild diarrhea to fatal colitis. It is important to consider this diagnosis in patients who present with diarrhea following administration of antibacterial agents.
- *Bleeding Manifestations:* Piperacillin/tazobactam is reported to cause abnormalities in clotting time, platelet aggregation and prothrombin time, particularly in patients with renal failure. In case of bleeding manifestations, piperacillin/tazobactam should be discontinued and appropriate treatment instituted.
- *Convulsions:* As with other penicillins, patients may experience neuromuscular excitability or convulsions if higher than recommended doses are administered intravenously, especially in patients with renal impairment.
- *Sodium Content:* Piperacillin/Tazobactam contains a total of 2.23 mEq (51 mg) sodium ($Na^+$) per gram of piperacillin in the combination product. This should be considered when treating patients requiring restricted salt intake.
- *Hypokalemia:* This may occur in patients with low potassium reserves or those receiving concomitant medicinal products that may lower potassium levels; periodic electrolyte determinations may be advisable in such patients.

**Other Precautions**

- In patients with creatinine clearance of ≤ 40 mL/min, the dose should be adjusted according to the degree of renal impairment (see **DOSAGE AND ADMINISTRATION**).
- Periodic assessment of organ system functions including renal, hepatic and hematopoietic should be performed, particularly during prolonged therapy, i.e., ≥ 21 days (see **UNDESIRABLE EFFECTS**).
- Piperacillin is not recommended in the treatment of meningitis and brain abscess because of its poor penetration into the CSF.
- The selection of piperacillin/tazobactam for an individual patient should take into account the appropriateness of using a broad-spectrum semi-synthetic penicillin based on factors such as the severity of the infection and the prevalence of resistance to other suitable antibacterial agents.
- Prescribing piperacillin/tazobactam in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to be beneficial to the patient and increases the risk of the development of drug-resistant microorganisms.
- As with other antibacterial drugs, long term or repeated use may result in overgrowth of non-susceptible organisms, including fungi.

**INTERACTIONS WITH OTHER MEDICAMENTS**

| DRUGS | NATURE OF INTERACTION |
|---|---|
| **Aminoglycosides** | The mixing of beta-lactam antibiotics (piperacillin/tazobactam) with aminoglycosides *in vitro* can result in substantial inactivation of the aminoglycoside.<br>It has been postulated that penicillin-aminoglycoside complexes form and these complexes are microbiologically inactive and of unknown toxicity. Sequential administration of piperacillin/tazobactam with tobramycin to patients with normal renal function and mild to moderate renal impairment has been shown to modestly decrease serum concentrations of tobramycin but does not significantly affect tobramycin pharmacokinetics. When aminoglycosides are administered in combination with piperacillin to patients with end-stage renal disease requiring hemodialysis, aminoglycosides (especially tobramycin) concentrations may be significantly altered and should be closely monitored. |
| **Heparin, Anticoagulants and Drugs Affecting the Blood** | Coagulation parameters should be tested more frequently and monitored regularly during simultaneous administration of piperacillin/tazobactam with high doses of heparin, oral anti-coagulants, or other drugs that may affect the blood coagulation system and/or the thrombocyte function. |
| **Methotrexate** | Piperacillin may reduce the excretion of methotrexate; therefore, serum concentrations of methotrexate should be closely monitored in patients to avoid toxicity. |
| **Neuromuscular Blocking Agents** | Prolonged neuromuscular blockade has been reported when vecuronium was used concomitantly with piperacillin, and this also could occur if piperacillin/tazobactam is used with vecuronium. Since other non-depolarizing muscle relaxants have similar mechanisms of action, a similar effect could occur if piperacillin/tazobactam is used concomitantly with any of these drugs. |
| **Probenecid** | Concomitant administration of probenecid and piperacillin/tazobactam produced a longer half-life and lower renal clearance of both piperacillin and tazobactam. However, peak plasma concentrations of either drug are not affected. |
| **Vancomycin** | No pharmacokinetic interactions have been noted between piperacillin/tazobactam and vancomycin. |

**Interference with Laboratory Tests:**

Positive test results for the assays listed below in patients receiving piperacillin/tazobactam should be confirmed by other diagnostic methods:

- As with other penicillins, the administration of piperacillin/tazobactam may result in a false positive reaction of glucose in the urine using a copper-reduction method (Clinitest®). It is recommended that glucose tests based on enzymatic glucose-oxidase reactions (e.g., Diastix® or Tes-Tape) be used.
- Positive test results using the Bio-Rad laboratories Platelia *Aspergillus* EIA test have been reported 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.
- Positive direct antiglobulin (Coombs') test results have been reported in patients receiving piperacillin. This reaction may interfere with hematologic studies or transfusion cross-matching procedures and should be considered in patients receiving the drug.

**STATEMENT ON USAGE FOR HIGH RISK GROUPS**

**Pregnancy:** (Pregnancy Category B) Reproduction studies in mice and rats using various combinations of piperacillin and tazobactam (up to 1 to 2 times the human dosage of piperacillin and 2 to 3 times the human dosage of tazobactam based on body surface area) have not revealed evidence of harm to the fetus.

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

**Lactation:** Piperacillin is excreted at low concentrations in human milk while tazobactam concentrations in human milk have not been studied. Piperacillin/tazobactam should be used with caution in breastfeeding women.

**Children:** The safety and efficacy of piperacillin/tazobactam in children younger than 2 months old have not been established.

**Elderly:** In general, dose selection in elderly patients usually starts at the low end of the dosing range, considering the greater frequency of decreased cardiac, hepatic, or renal function, and of concomitant disease or other drug therapy.

**Renal Impairment:** Piperacillin/tazobactam is known to be substantially excreted by the kidneys, and the risk of toxic reactions to this drug may be greater in patients with renal impairment. Careful dose selection and monitoring of renal function are recommended.

**Hepatic Impairment:** In individuals with liver disease or those receiving cytotoxic therapy or diuretics, piperacillin/tazobactam has been reported rarely to produce a decrease in serum potassium levels at high doses of piperacillin.

**UNDESIRABLE EFFECTS**

Adverse drug reactions reported with piperacillin/tazobactam are similar to those reported with piperacillin alone and generally are transient and mild to moderate in severity.

The most frequently reported adverse reactions include allergic reactions, erythema, pruritus, rash (including maculopapular, bullous, urticarial, and eczematoid), urticaria, dyspepsia, diarrhea, nausea, vomiting, superinfection, phlebitis, thrombophlebitis, and insomnia.

**Body as a Whole:** Back pain, chills, fatigue, fever/pyrexia, malaise, rigors, tiredness

**Injection Site/Local Reactions:** Edema, inflammation, pain

**Cardiovascular:** Arrhythmia, including atrial fibrillation, ventricular fibrillation, cardiac arrest, cardiac failure, circulatory failure, myocardial infarction; bradycardia, chest pain, flushing, hypotension, hypertension, tachycardia, including supraventricular and ventricular

**Dermatologic/Hypersensitivity Reactions:** Anaphylaxis, anaphylactic/anaphylactoid reactions (including shock), angioedema (particularly in cystic fibrosis patients), bullous dermatitis, candidal superinfections, eczema, erythema multiforme, exanthema, increased sweating, Stevens-Johnson syndrome, toxic epidermal necrolysis

**Gastrointestinal:** Abdominal pain, bloody diarrhea, *Clostridium difficile*-associated diarrhea, colitis, constipation, dry mouth, flatulence, gastritis, hemorrhage, hiccups, ileus, melena, stool changes/loose stools, ulcerative stomatitis

**Genitourinary:** Increased serum creatinine and blood urea nitrogen (BUN); dysuria, hematuria, incontinence, interstitial nephritis/tubulointerstitial nephritis, oliguria, proteinuria, pyuria, renal failure, urinary retention; genital pruritis, leukorrhea, moniliasis, vaginitis

**Hepatic:** Hepatitis/cholestatic hepatitis, cholestatic jaundice; transient increases in aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, and bilirubin; increased gamma-glutamyltransferase (GGT)

**Hematologic:** Anemia/hemolytic anemia, agranulocytosis, transient leukopenia, neutropenia and thrombocytopenia have been reported in patients receiving piperacillin/tazobactam for a prolonged period of time (e.g., after 21 days or more) and generally were reversible; thrombocytosis, pancytopenia, transient eosinophilia, positive direct Coombs' test, epistaxis, granulocytopenia, decreases in hemoglobin and hematocrit; mesenteric embolism, prolonged prothrombin, purpura, platelet aggregation/increases in platelet count, prolongations in bleeding time, prothrombin time and partial thromboplastin time, disturbed thrombocyte function

**Metabolic/Nutritional:** Abnormalities in electrolytes (i.e., increase/decrease in sodium, potassium and calcium), symptomatic hypoglycemia, hypokalemia (sometimes associated with metabolic alkalosis), thirst, decreases in total protein or albumin

**Musculoskeletal:** Arthralgia, muscular weakness, myalgia, prolonged muscle relaxation

**Nervous System:** Agitation, anxiety, confusion, depression, dizziness, hallucination, headache, tremors, seizures/convulsions (neuromuscular excitability or seizures could occur if higher than recommended doses are given IV, especially in patients with kidney failure), syncope, vertigo

**Respiratory:** Bronchospasm, coughing, dyspnea, pharyngitis, pulmonary edema, rhinitis

**Other Adverse Effects:** Tinnitus, taste perversion, photophobia

- The following adverse events were reported in patients with nosocomial pneumonia receiving piperacillin/tazobactam with an aminoglycoside:
  - *Drug-related adverse events:* Acidosis, abdomen enlarged, acute kidney failure, asthenia, chest pain, CNS depression, confusion, cough increased, dehydration, diplopia, drug level decreased, dysphagia, generalized edema/peripheral edema, excoriations, fungal dermatitis, glossitis, grand mal convulsion, hyperglycemia, hypertonia, hypoventilation, hypochromic anemia, hyponatremia, hypophosphatemia, hypoxia, kidney function abnormal, leukocytosis, local reaction to procedure, oral moniliasis, prothrombin decreased, respiratory disorder, sinus bradycardia, somnolence, stomatitis, stupor, sweating, thrombocythemia, urinary tract infection, ventricular extrasystoles
  - *Irrespective of drug relationship:* Aggressive reaction (combative), angina, anorexia, atelectasis, balanoposthitis, cerebrovascular accident, conjunctivitis, deafness, duodenal ulcer, earache, ecchymosis, erythematous rash, fecal incontinence, fluid overload, gastric ulcer, gout, hemoptysis, oral thrush, pancreatitis, perineal irritation/pain, pleural effusion, pneumothorax, urinary incontinence, urinary tract infection with *Trichomonas*, vitamin B12 deficiency anemia, xerosis, yeast in urine
- Adverse events reported in children with severe intra-abdominal infections, irrespective of relationship to piperacillin/tazobactam include abscess and sepsis.
- Other adverse effects reported with parenteral piperacillin (alone) include cylindruria, vein irritation, deep vein thrombosis, and hematoma.

**OVERDOSE AND TREATMENT**

Nausea, vomiting and diarrhea have been reported in cases of overdose. Neuromuscular excitability or convulsions have also been reported when higher than usual recommended doses are given intravenously, especially in patients with renal failure.

In case of an overdose, piperacillin/tazobactam treatment should be discontinued and supportive and symptomatic treatment be initiated as needed. Piperacillin or tazobactam may be removed by hemodialysis.

**STORAGE CONDITIONS**

Store at temperatures not exceeding 25°C.
Keep the product out of sight and reach of children.

**AVAILABILITY:** 4 g / 500 mg Powder for Injection (I.V.) - in box of 1 vial - DR - XR03668
2 g / 250 mg Powder for Injection (I.V.) - in box of 1 vial - DR - XR03669

**CAUTION:** Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

**ADVERSE DRUG REACTION REPORTING STATEMENT**

For suspected adverse drug reaction, seek medical attention immediately and report to the FDA at www.fda.gov.ph **AND** Unilab at (+632) 858-1000 or productsafety@unilab.com.ph. By reporting undesirable effects, you can help provide more information on the safety of this medicine.

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