Tazopen®

Piperacillin Sodium BP +Tazobactam Sodium
2.25g & 4.5g IV infusion

Presentation:
Tazopen®4.5 g IV infusion: Each Tazopen® vial contains sterile powder Piperacillin Sodium BP equivalent to 4 g Piperacillin and Tazobactam Sodium equivalent to 0.5 g Tazobactam.
Tazopen®2.25 g IV infusion: Each Tazopen® vial contains sterile powder Piperacillin Sodium BP equivalent to 2 g Piperacillin and Tazobactam Sodium equivalent to 0.25 g Tazobactam.

Description:
Tazopen®4.5 g IV infusion: Piperacillin 4 g and tazobactam 0.5 g is a sterile mixture of Piperacillin Sodium (a semisynthetic antibiotic) and Tazobactam Sodium (the ß-lactamase inhibitor) powder for intravenous administration.
Tazopen®2.25 g IV infusion: Piperacillin 2 g and tazobactam 0.25 g is a sterile mixture of Piperacillin Sodium (a semisynthetic antibiotic) and Tazobactam Sodium (the ß-lactamase inhibitor) powder for intravenous administration.

Indications:
Appendicitis (complicated by rupture or abscess) and peritonitis caused by piperacillin-resistant, beta-lactamase producing strains of *Escherichia coli* or the following members of the Bacteroides fragilis group: *B. tragilis, B. ovatus, B. thetaiotaomicron,* or *B. vulgatus.*

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

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

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

Nosocomial pneumonia (moderate to severe) caused by piperacillin-resistant, /ß-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).

Microbiology
Piperacillin/tazobactam has been shown to be active against most strains of the following microorganisms both in vitro and in clinical infections.

Aerobic gram-negative bacilli
Acinetobacter baumannii (calcoaceticus)*, Aeromonas hydrophila, Alcaligenes xylosoxidans, Burkholderia* (Pseudomonas) *cepacia, Burkholderia* (Pseudomonas) *pseudomallei, Burkholderia cepacia , Capnocytophaga ochracea* (DF-1), *Citrobacter diversus, Citrobacter freundii, Eikenella corrodens, Enterobacter aerogenes, Enterobacter cloacae, Escherichia coli , Haemophilus influenzae , Hafnia alvei, Klebsiella oxytoca, Klebsiella pneumonia, Klebsiella spp., Morganella morganii, Proteus mirabilis, Proteus vulgaris, Providencia rettgeri, Providencia stuartii, Pseudomonas aeruginos*a

Aerobic gram-negative cocci
Moraxella catarrhalis (Branhamella)

Aerobic gram-positive cocci
Enterococcus, Staphylococcus aureus (methicillin-sensitive)

Anaerobic gram-negative bacilli
Bacteroides distasonis, Bacteroides fragilis, Bacteroides ovatus, Bacteroides thetaiotamicron, Bacteroides vulgates, Fusobacterium necrophorum, Prevotella bivia (Bacteroides), *Prevotella intermedius, Prevotella melaninogenicus.*

Anaerobic gram-positive bacilli
Clostridium sp.

Dosage and Administration:
Piperacillin and tazobactam should be administered by intravenous infusion over 30 minutes. The usual total daily dose of Piperacillin and tazobactam for adults is 3.375 g every six hours totaling 13.5 g (12.0 g piperacillin/1.5 g tazobactam).

Nosocomial Pneumonia:
Initial presumptive treatment of 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/2.0 g tazobactam). Treatment with the aminoglycoside should be continued in patients from whom *Pseudomonas aeruginosa* is isolated. If *Pseudomonas aeruginosa* is not isolated, the aminoglycoside may be discontinued at the discretion of the treating physician. Due to the in vitro inactivation of the aminoglycoside by beta-lactam antibiotics, piperacillin and tazobactam and the aminoglycoside are recommended for separate administration. piperacillin and tazobactam and the aminoglycoside should be reconstituted, diluted, and administered separately when concomitant therapy with aminoglycosides is indicated.

Renal Insufficiency :
In patients with renal insufficiency (Creatinine Clearance > 40 mL/min), the intravenous dose of Tazopen (piperacillin and tazobactam for IV infusion) should be adjusted to the degree of actual renal function impairment. In patients with nosocomial pneumonia receiving concomitant aminoglycoside therapy, the aminoglycoside dosage should be adjusted according to the recommendations of the manufacturer. The recommended daily doses of Piperacillin and tazobactam for patients with renal
insufficiency are as follows:

Renal Function (Creatinine Clearance mL/min)	All Indications (except nosocomial)	Nosocomial
>40 ml/min	3.375 gm 6 h	4.5 gm 6 h
20-40 mL/min*	2.25 gm 6 h	3.375 gm 6 h
<20 mL/min*	2.25 gm 8 h	2.25 gm 6 h
Hemodialysis**	2.25 gm 12 h	2.25 gm 8 h
Continuous ambulatory peritoneal dialysis	2.25 gm 12 h	2.25 gm 8 h

*Creatinine clearance for patients not receiving hemodialysis.
**0.75 g should be administered following each hemodialysis session on hemodialysis days for patients on hemodialysis, the maximum dose is 2.25 g every twelve hours for all indications other than nosocomial pneumonia and 2.25 g every eight hours for nosocomial pneumonia. Since hemodialysis removes 30% to 40% of the administered dose, an additional dose of 0.75 g piperacillin and tazobactam should be administered following each dialysis period on hemodialysis days. No additional dosage of piperacillin and tazobactam 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 (total 112.5mg) 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 (total 90mg) per kilogram of body weight, every 8 hours. Pediatric patients weighing over 40 kg and with normal renal function should receive the adult dose.

Duration of Therapy:
The usual duration of piperacillin and tazobactam treatment is from seven to ten days. However, the recommended duration 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.

Hepatic Insufficiency:
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 warran dosage adjustment of piperacillin and tazobactam due to hepatic cirrhosis.

Contraindication:
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 anaphylactic/anaphylactoid reactions (including shock) require immediate emergency treatment with epinephrine. Oxygen, intravenous steroids, and airway management, including intubation, should also be administered as indicated.

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including piperacillin and tazobactam 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.* 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.

Precaution:
Bleeding manifestations have occurred in some patients receiving j3-lactam antibiotics, including piperacillin. These reactions have sometimes been associated with abnormalities of coagulation tests such as clotting time, platelet aggregation and prothrombin time, and are more likely to occur in patients with renal failure. If bleeding manifestations occur, piperacillin and tazobactam for IV infusion 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 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 cteatinine clearance> 40 mL/min and dialysis patients (hemodialysis and CAPO), the intravenous dose should be adjusted to the degree of renal function impairment.

Pediatric Use:
Use 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. 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 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.

Use in Pregnancy:
Pregnancy Category B. Piperacillin and tazobactam cross the placenta in humans.

Use in Lactation:
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 IV infusion is administered to a nursing woman.

Adverse events:
Adverse events primarily involving the skin, including rash and pruritus; the gastrointestinal system, including diarrhea, nausea, and vomiting; and allergic reactions. Adverse local reactions that were reported, irrespective of relationship to therapy with piperacillin and tazobactam were phlebitis, IV infusion site reaction, pain, infiammation, thrombophlebitis, and edema. Gastrointestinal-hepatitis, cholestatic jaundice. Hematologic-hemolytic anemia, anemia, thrombocytosis, agranulocytosis, pancytopenia. Immune-hypersensitivity reactions, anaphylactic/anaphylactoid reactions (including shock). Infections-candidal superinfections. Renal-interstitial nephritis, renal failure. Skin and Appendages-erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis.

Drug Interactions:
Aminoglycosides :
The mixing of beta-lactam antibiotics with aminoglycosides in vitro can result in substantial inactivation of the aminoglycoside. The inactivation of aminoglycosides in the presence of penicillin-class drugs has been recognized. It has been postulated that penicillin-aminoglycoside complexes form; these complexes are microbiologically inactive and of unknown toxicity. Sequential administration of piperacillin and tazobactam with tobramycin to patients with normal renal function and mild to moderate renal impairment has been shown to modestly decrease serum concentrations of tobramycin but does not significantly affect tobramycin pharmacokinetics. When aminoglycosides are administered in combination with piperacillin to patients with end-stage renal disease requiring hemodialysis, the concentrations of the aminoglycosides (especially tobramycin) may be significantly altered and should be monitored. Since aminoglycosides are not equally susceptible to inactivation by piperacillin, consideration should be given to the choice of the aminoglycoside when administered in combination with piperacillin to these patients.

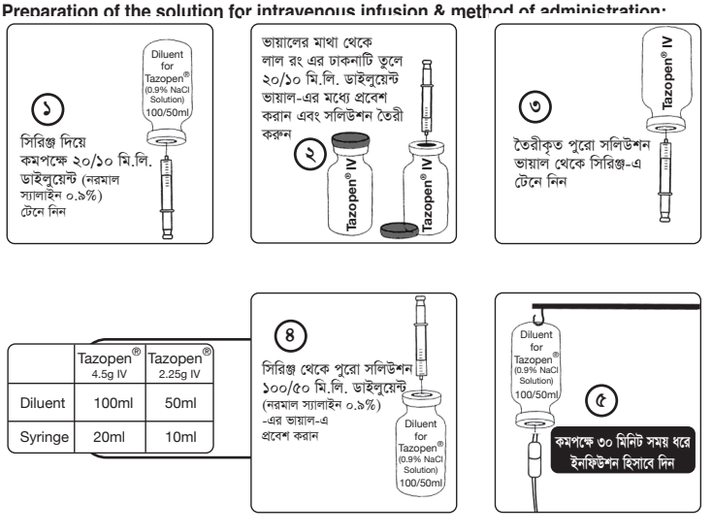
Probenecid:
Probenecid administered concomitantly with piperacillin and tazobactam prolongs the half-life of piperacillin by 21% and that of tazobactam by 71 %.

Vancomycin:
No pharmacokinetic interactions have been noted between piperacillin & tazobactam and vancomycin.
Heparin:
Coagulation parameters should be tested more frequently and monitored regularly during simultaneous administration of high doses of heparin, oral anticoagulants, or other drugs that may affect the blood coagulation system or the thrombocyte function.
Vecuronium .
Piperacillin when used concomitantly with vecuronium has been implicated in the prolongation of the neuromuscular blockade of vecuronium. piperacillin and tazobactam could produce the same phenomenon if given along with vecuronium. Due to their similar mechanism of action, it is expected that the neuromuscular blockade produced by any of the non-depolarizing muscle relaxants could be prolonged in the presence of piperacillin.

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

Over-dosage:
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 and tazobactam, the percentage of the piperacillin & tazobactam dose removed by hemodialysis was approximately 31% and 39%, respectively.

Preparation of the solution for intravenous infusion & method of administration:



	Tazopen® 4.5g IV	Tazopen® 2.25g IV
Diluent	100ml	50ml
Syringe	20ml	10ml

Piperacillin and tazobactam should not be mixed with other drugs in a syringe or infusion bottle since compatibility has not been established. It is not chemically stable in solutions that contain only sodium bicarbonate and solutions that significantly alter the pH. It should not be added to blood products or albumin hydrolysates. Piperacillin and tazobactam can be used in ambulatory intravenous infusion pumps.

Stability of piperacillin and tazobactam :
Piperacillin and tazobactam is stable in glass and plastic containers (plastic syringes, IV bags and tubing) when used with compatible diluents. Vials should be used immediately after reconstitution. Discard any 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]). Vials should not be frozen after reconstitution. Stability studies in the IV bags have demonstrated chemical stability (potency, pH of reconstituted solution and clarity of solution) for up to 24 hours at room temperature and up to one week at refrigerated temperature. piperacillin and tazobactam contains no preservatives. Appropriate consideration of aseptic technique should be used. Stability of piperacillin and tazobactam in an ambulatory intravenous infusion pump has been demonstrated for a period of 12 hours at room temperature.

Pharmaceutical precaution:
Prior to reconstitution, store piperacillin and tazobactam powder for intravenous injection at controlled room temperature below (30°C). Keep out of the reach of children.

Pack size:
Tazopen® 4.5 g IV infusion: Each combipack contains one vial of piperacillin sodium BP equivalent to 4 g of piperacillin and tazobactam sodium equivalent to 0.5 g of tazobactam, 1 (20ml) disposable syringe, 1 infusion set, 1 vial of 100ml diluent for Tazopen® (0.9% NaCl Solution), plastic hanger, first aid band & alcohol pad.
Tazopen® 2.25 g IV infusion: Each combipack contains one vial of piperacillin sodium BP equivalent to 2 g of piperacillin and tazobactam sodium equivalent to 0.25 g of tazobactam, 1 (10ml) disposable syringe, 1 infusion set with baby needle, 1 vial of 50ml diluent for Tazopen® (0.9% NaCl Solution), plastic hanger, first aid band & alcohol pad.

Manufactured by
RENATA LIMITED
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