Front Page

Brodactam™

Piperacillin and Tazobactam for Injection, USP

50060

Presentation
Each vial for IV infusion contains sterile, dry mixture of Piperacillin Sodium USP equivalent to 4.0g Piperacillin and Tazobactam Sodium USP equivalent to 0.5g Tazobactam.

Indications
Piperacillin and Tazobactam is indicated for the treatment of patients with moderate to severe infections caused by piperacillin-resistant, piperacillin/tazobactam susceptible, ß-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, ß-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 cellulites, cutaneous abscesses and ischemic/diabetic foot infections caused by piperacillin-resistant,
ß-lactamase producing strains of Staphylococcus aureus.
Postpartum endometritis or pelvic inflammatory disease caused by piperacillin-resistant,
ß-lactamase producing strains of Escherichia coli.
Community-acquired pneumonia (moderate severity only) caused by piperacillin-resistant,
ß-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).
Piperacillin and tazobactam for IV infusion is indicated only for the specified conditions listed above. Infections caused by piperacillin-susceptible organisms, for which piperacillin has been shown to be effective, are also amenable to treatment due to its piperacillin content. The tazobactam component of this combination product does not decrease the active of the piperacillin component against piperacillin-susceptible organisms. Therefore, the treatment of mixed infections caused by piperacillin-susceptible organisms and piperacillin-resistant,
ß-lactamase producing organisms susceptible to pipercillin and tazobactam should not require the addition of another antibiotic. This combination product 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 gram-positive and gram-negative aerobic and anaerobic organisms.

Microbiology:
Piperacillin 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 a little clinically relevant in vitro activity against bacteria due to its reduced affinity to penicillin binding proteins.
It is, however, a ß-lactamase inhibitor of the Richmond-Sykes class III (Bush class 2b & 2b[1]) penicillinases and cephalosporinases. It varies in its ability to inhibit class II and IV (2a & 4) penicillinases. Tazobactam does not induce chromosomally-mediated ß-lactamases 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 ß-lactamase negative, ampicillin-resistant 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 (ampicilliin or penicillin-susceptible isolates only), Staphylococcus epidermidis (excluding methicillin and oxacillin-resistant isolates), Streptococcus agalactie, Streptococcus pneumoniae (penicillin-susceptible isolates only), Streptococcus pyogenes, Viridans group streptococci.

Aerobic and facultive Gram-negative microorganisms:
Citrobacter koseri, Moraxella catarrhlis, Morganella morganii, Neisseria gonorrhoeae, Proteus mirabilis, Proteus vulgaris, Serratia marcescens, Providencia stuartii, Providencia rettgri, Salmonella enterica

Gram-positive anaerobes: Clostridium perfringens

Gram-negative anaerobes: Bacteroides distasonis, Prevetella melaninogenca

Contra-Indication: Piperacillin and tazobactam is contraindicated in patients with a history of allergic reactions to any of the penicillins, cephalosporins, or b-lactamase inhibitors.

Side-Effects:
Sensitivity reaction including urticaria, fever, joint pain, angioedema, anaphylactic shock in hypersensitive patient. Also nausea, vomiting, diarrhoea; less commonly stomatitis, dyspepsia, constipation, jaundice, hypotension, headache, insomnia, and injection-site reactions; rarely abdominal pain, hepatitis, oedema, fatigue, and eosinophilia; very rarely hypoglycaemia, hypokalaemia, pancytopenia, Stevens-Johnson syndrome, and toxic epidermal necrolysis.

Precautions:
Bleeding manifestations have occurred in some patients receiving b-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 super infections should be kept in mind. If this occurs, appropriate measures should be taken. As with other penicillins, patients may experience neuromuscular exitability 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 who have potentially low potassium reserves and who are receiving cytotoxic therapy or diuretics. As with other semi synthetic penicillins, piperacillin therapy has been associated with an increased incidence of fever and rash in cystic fibrosis patients. In patients with creatinine clearance
> 40mL/min and daily sis patients (hemodialysis and CAPD), 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. In general, dose selection for an elderly patient should be cautions, 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.

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.

Dosage & 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 aeroginosa is isolated. If Pseudomononas aeroginosa 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, pipercillin 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.

Back Page

Renal Insufficiency:
In patients with renal insufficiency (Creatinine Clearance > 40 ml/min), the intravenous dose of (piperacillin andtazobactam for IV infusion) should be adjusted to the degree of actual renal function impairment. 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 nosocominal pneumonia)	Nosocomial Pneumonia
>40 ml/min	3.375 g 6h	4.5 g 6h
20-40 ml/min*	2.25 g 6h	3.375g 6h
<20ml/min*	2.25 g 8h	2.25 g 6h
Hemodialysis**	2.25 g 12h	2.25 g 8h
CAPD	2.25 g 12h	2.25 g 8h

*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 every eight hours for nosocomial pneumonia. Since hemodialysis removes 30% to 40% of the administered dose, and additional 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.

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 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.

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%.

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 vacuronium, 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 concentractions of methotrexate as well as the signs and symptoms of methotrexate toxicity should be frequently monitored

Overdose:
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 3.375g dose of piperacillin and tazobactam, the percentage of the piperacillin & tazobactam dose removed by hemodialysis was approximately 31% and 39% respectively.

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, inflammation, thrombophlebitis, and edema, gastrointestinal-hepatitis, cholestatic jaundice. Hematologtic-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.

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, surgical evaluation should be instituted as clinically indicated

Preparation of solution for IV infusion and method of administration:
Administration by intravenous infusion should be continued over 30 minutes. Withdraw 20 ml diluent (0.9% w/v Sodium Chloride solution) by the disposable syringe and push into the vial containing Piperacillin and Tazobactam powder. Mix to become the vial contents a complete solution. Withdraw the total solution by the syringe and push into the bottle of 0.9% w/v Sodium Chloride solution.
Vials should be used immediately after reconstitution. Discard any unused portion of solution. Vials should not be frozen after reconstitution.

Storage Condition:
Prior to reconstitution, store piperacillin and tazobactam powder for intravenous infusion at cool (below 25°C) and dry place, protected from light and keep out of children's reach.

Commercial Pack:
Brodactam 4.5gm IV Infusion:
Each pack contains:
1 vial of dry powder of Piperacillin and Tazobactam
1 bottle of 100ml Synovia Normal Saline (0.9% Sodium Chloride BP) as diluent.
1 sterile disposable syringe (20ml)
1 infusion set, 1 plastic hanger
1 first aid band and 1 alcohol pad

Manufactured by:
synovia
Synovia Pharma PLC., Station Road, Tongi, Gazipur.
A Subsidiary of BEXIMCO PHARMACEUTICALS LTD.

524163/1

Direction Slip artwork legend

Product Name	:	Broductum
Code number	:	524163/1
Dimension	:	L 13.78 x W 3.9 inches
Min. size of text	:	8 pt
Used Colors	:	Black C ■ Pantone 186 C ■