Only for the use of Medical Professionals

Tazosyn®

Piperacillin and Tazobactam

Description

Tazosyn® is the combination preparation of Piperacillin sodium (a semisynthetic antibiotic) and Tazobactam sodium (the β-lactamase inhibitor) powder for intravenous administration. 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, a triazolylmethyl penicillanic acid sulfone, is a potent inhibitor of many beta-lactamases, including the plasmid and chromosomally mediated enzymes that commonly cause resistance to penicillins. The presence of tazobactam in the piperacillin / tazobactam formulation enhances and extends the antibiotic spectrum of piperacillin to include many beta-lactamase producing bacteria normally resistant to it.

Indications

Tazosyn® is indicated for the treatment of patients with:

• Nosocomial pneumonia (moderate to severe)

• Community-acquired pneumonia (moderate severity only)

• Uncomplicated and complicated skin and skin structure infections, including cellulitis, cutaneous abscesses and
Ischemic / diabetic foot infections

• Post partum endometritis or pelvic inflammatory disease

• Appendicitis (complicated by rupture or abscess) and peritonitis

• Bacterial infections in neutropenic infection patients in combination with an aminoglycoside

Dosage and administration

Tazosyn® may be given by slow intravenous infusion (20 to 30 minutes).

Adults, children 12 years and older

The usual intravenous dosage for adults and children with normal renal function is piperacillin 4 g / tazobactam 0.5 g given every eight hours.

The total daily dose depends on the severity and localization of the infection and can vary from piperacillin 2 g / tazobactam 0.25 g to piperacillin 4 g / tazobactam 0.5 g (piperacillin / tazobactam) administered every six or eight hours.

Children under the age of 12 years

Recommended intravenous dosage for hospitalized children with intra-abdominal infection. For children aged 2 to 12 years, weighing up to 40 kg, and with normal renal function, the recommended dosage is piperacillin 100 mg / tazobactam 12.5 mg per kg every eight hours.

For children aged 2 to 12 years, weighing over 40 kg, and with normal renal function, follow the adult dose guidance, i.e. piperacillin 4 g / tazobactam 0.5 g every eight hours.

Duration of Therapy
The duration of therapy should be guided by the severity of the infection and the patient's clinical and bacteriological progress. Therapy is recommended to be a minimum of five days and a maximum of 14 days, considering that dose administration should continue at least 48 hours after the resolution of clinical signs and symptoms.

Renal Insufficiency

In patients with renal insufficiency (Creatinine Clearance ≤ 40 mL / min), the intravenous dose of piperacillin / tazobactam 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 of tazobactam for patients with renal insufficiency are as follows:

Adults
Recommended dosing of Tazosyn® in patients with normal renal function and renal insufficiency
(As total grams piperacillin / tazobactam)

Renal Function (Creatinine Clearance, mL/min)	All Indications (except nosocomial pneumonia)	Nosocomial Pneumonia
>40 mL/min	3.375 g 6 h	4.5 g 6 h
20-40 mL/min*	2.25 g 6 h	3.375 g 6 h
<20 mL/min*	2.25 g 8 h	2.25 g 6 h
Hemodialysis**	2.25 g 12 h	2.25 g 8 h
CAPD	2.25 g 12 h	2.25 g 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 of tazobactam should be administered following each dialysis period on hemodialysis days. No additional dosage of piperacillin and of tazobactam is necessary for CAPD patients.

Pediatrics
Use of piperacillin and of tazobactam in pediatric patients 2 months of age or older with appendicitis and / or peritonitis. Safety and efficacy in pediatric patients less than 2 months of age have not been established. There are no dosage recommendations for piperacillin / tazobactam in pediatric patients with impaired renal function.

Hepatic impairment:

Measurement of serum level of piperacillin / tazobactam will provide additional guidance for adjunctive dosage. However, this difference does not warrant dosage adjustment of piperacillin and of tazobactam due to hepatic cirrhosis.

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.

Use in pregnancy and lactation

Piperacillin and Tazobactam is a drug of pregnancy category B.

Adequate human studies on the use of Piperacillin / tazobactam during pregnancy are not available. Pregnant women should be treated only if the expected benefit outweighs the possible risks to the pregnant woman and fetus.
Piperacillin is excreted in low concentrations in human milk. Tazobactam concentrations in human milk have not been studied. Women who are breast feeding should be treated only if the expected benefit outweighs the possible risks to the woman and child.

Side effects

The common side effects 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, injection site reaction, pain, inflammation, thrombophlebitis, and edema.

The other side effects are hepatitis, cholestatic jaundice, hemolytic anemia, anemia, thrombocytosis, agranulocytosis, pancytopenia, hypersensitivity reactions, anaphylactic / anaphylactoid reactions (including shock), candidal superinfections, interstitial nephritis, renal failure, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis

Contraindication

Piperacillin and tazobactam is contraindicated in patients with a history of hypersensitivity to any of the penicillins, cephalosporins, or β-lactamase inhibitors.

Precautions

Bleeding manifestations have occurred in some patients receiving β-lactam antibiotics, including piperacillin. If bleeding manifestations occur, piperacillin and tazobactam should be discontinued and appropriate therapy instituted. 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 2.35 mEq (54 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.

Drug Interactions

Aminoglycosides

Sequential administration of piperacillin and tazobactam with tobramycin (aminoglycoside) 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.

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 and tazobactam (piperacillin / 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

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.

Overdosage

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.

Directions for Reconstitution and Dilution for Use

Prior to use, Piperacillin and Tazobactam 2.25 g and 4.5 g Infusion must be reconstituted with sterile water for injection or sodium chloride BP 0.9 % w/v injection as per table below:.
Piperacillin / Tazobactam infusion

Vial size (piperacillin / tazobactam)	Minimum volume of diluent to be added to vial
2.25 g (2 g / 0.25 g)	10 mL
4.5 g (4 g / 0.5 g)	20 mL

The reconstituted solution may be further diluted to 100 mL with Normal Saline (Sodium Chloride BP 0.9 % w/v), Dextrose 5 %, Dextran 6 % in saline. To reduce microbiological hazard, use as soon as practicable after reconstitution. Discard any unused portion after 24 hours if stored at room temperature (20°C to 25°C) or after 48 hours if storage at refrigerated temperature (2°C to 8°C).

Pharmaceutical precautions

Store piperacillin and tazobactam powder for intravenous infusion at controlled room temperature (20°C to 25°C) prior to reconstitution. Keep away from the reach of children.

Presentation

Tazosyn® 2.25 gm IV infusion: Each **Tazosyn**® vial contains sterile lyophilized Piperacillin 2 gm as Sodium USP and Tazobactam 0.25 gm as Sodium USP.

Tazosyn® 4.5 gm IV infusion: Each **Tazosyn**® vial contains sterile lyophilized Piperacillin 4 gm as Sodium USP and Tazobactam 0.5 gm as Sodium USP.

Package quantities

Tazosyn® 2.25 gm IV infusion: Each combipack contains 1 vial of sterile lyophilized Piperacillin 2 gm as Sodium USP and Tazobactam 0.25 gm as Sodium USP, 1 vial of 100 ml Salinor® (Sodium Chloride BP 0.9 % w/v).

Tazosyn® 4.5 gm IV infusion: Each combipack contains 1 vial of sterile lyophilized Piperacillin 4 gm as Sodium USP and Tazobactam 0.5 gm as Sodium USP, 1 vial of 100 ml Salinor® (Sodium Chloride BP 0.9 % w/v).

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