For use only of a Registered Medical Practitioner or Hospital or Laboratory

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Piperacillin and Tazobactam Injection IP

Biopiper TZ® / Biopiper TZ® 2.25G बायोपाइपर टी ज़ेड / बायोपाइपर टी जेड २.२५जी

Composition:
Biopiper TZ®4.5 g

Each Vial Contains:

Piperacillin Sodium I.P. (Sterile) Equivalent to Piperacillin	4 gm
Tazobactam Sodium I.P. (Sterile) Equivalent to Tazobactam	500 mg

Biopiper TZ® 2.25g

Each Vial Contains:

Piperacillin Sodium I.P. (Sterile) Equivalent to Piperacillin	2 gm
Tazobactam Sodium I.P. (Sterile) Equivalent to Tazobactam	250 mg

Piperacillin and Tazobactam injection IP complies with IP organic impurities test I.
Biopiper TZ®4.5g and Biopiper TZ®2.25g (Piperacillin and Tazobactam injection IP) is an injectable antibacterial combination product consisting of the semisynthetic antibiotic piperacillin sodium and the ß-lactamase 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-piperazine-carboxamido)-2-phenylacetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate. The chemical formula is $C_{23}H_{26}N_5NaO_7S$ and the molecular weight is 539.5
Tazobactam sodium, a derivative of the penicillin nucleus, is a penicillanic acid sulfone. Its chemical name is sodium (2S,3S,5R)-3-methyl-7-oxo-3-(1H-1,2,3-triazol-1-ylmethyl)- 4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate-4,4-dioxide. The chemical formula is $C_{10}H_{11}N_4NaO_5S$ and the molecular weight is 322.3.

Pharmacotherapeutic group Antibacterial for Systemic Use
ATC code J01CR05

CLINICAL PHARMACOLOGY

Piperacillin sodium exerts bactericidal activity by inhibiting septum formation and cell wall synthesis of susceptible bacteria.

Peak plasma concentrations of Piperacillin and Tazobactam are attained immediately after completion of an intravenous infusion. Following single or multiple Piperacillin and Tazobactam doses to healthy subjects, 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.

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

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.

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 two fold for piperacillin and four fold for tazobactam compared to subjects with normal renal function. Dosage adjustments for Piperacillin and Tazobactam are recommended when creatinine clearance is below 40 mL/min in patients receiving the usual recommended daily dose of Piperacillin and Tazobactam (Piperacillin and Tazobactam injection IP). 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.

CLINICAL PARTICULARS

Therapeutic Indications

- Biopiper TZ® (Piperacillin and Tazobactam injection IP) 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 cellulitis, 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 (Piperacillin and Tazobactam injection IP) 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 Piperacillin and tazobactam 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 piperacillin-susceptible organisms and piperacillin-resistant, ß-lactamase producing organisms susceptible to Piperacillin and tazobactam should not require the addition of another antibiotic.

Posology and Method of 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 g piperacillin sodium/1.5 g tazobactam sodium).

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 sodium/2.0 g tazobactam sodium). 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.

Renal Insufficiency
In patients with renal insufficiency (Creatinine Clearance ≤ 40 mL/min), the intravenous dose of Piperacillin and 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. The recommended daily doses of Piperacillin and Tazobactam for patients with renal insufficiency are as follows:

Recommended Dosing of Piperacillin and Tazobactam 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 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 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.

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.

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 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 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 in pediatric patients with impaired renal function.

CONTRAINDICATIONS
Piperacillin and Tazobactam is contraindicated in patients with a history of allergic reactions to any of the penicillins, cephalosporins, or ß-lactamase inhibitors.

SPECIAL WARNINGS

Serious and occasionally fatal hypersensitivity (anaphylactic/ anaphylactoid) reactions (including shock) have been reported in patients receiving therapy with penicillins including Piperacillin and Tazobactam. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity or a history of sensitivity to multiple allergens. Careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, or other allergens. If an allergic reaction occurs, Piperacillin and Tazobactam 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.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including piperacillin/tazobactam, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by Clostridium difficile is one primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against Clostridium difficile colitis.

PRECAUTIONS FOR USE
General
Bleeding manifestations have occurred in some patients receiving ß-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 (Piperacillin and Tazobactam injection IP) 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 is a monosodium salt of piperacillin and a monosodium salt of tazobactam and 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.

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.

Laboratory Tests
Periodic assessment of hematopoietic function should be performed, especially with prolonged therapy.

DRUG INTERACTIONS
Aminoglycosides
The mixing of Piperacillin and Tazobactam with an aminoglycoside in vitro can result in substantial inactivation of the aminoglycoside.

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 and 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.

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.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Long term carcinogenicity studies in animals have not been conducted with piperacillin/tazobactam, piperacillin, or tazobactam.

Piperacillin/Tazobactam
Piperacillin/tazobactam was negative in microbial mutagenicity assays at concentrations up to 14.84/1.86 µg/plate.

Pediatric Use
Use of Biopiper-TZ ® in Pediatric Patients 2 months of age or older with appendicitis and/or peritonitis is supported by evidence from well-controled 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 Biopiper -TZ® 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.

Pregnancy
Teratogenic effects-Pregnancy Category B

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 body-surface area (mg/m^2). Piperacillin and Tazobactam cross the placenta in humans.

There are, however, no adequate and well-controlled 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 is administered to a nursing woman.

ADVERSE REACTIONS
Swelling, redness, pain, or soreness at the injection site may occur. Dizziness, trouble sleeping, nausea, vomiting, diarrhea, or headache may also occur. Other unlikely but serious side effects occur: muscle cramps/spasms, swelling of the arms/legs/hands/feet, bruising/bleeding, chest pain, confusion, new signs of infection (e.g., fever, persistent sore throat), severe abdominal/stomach pain, slow/fast/irregular heartbeat, persistent nausea/vomiting, seizures, extreme tiredness, dark/cloudy urine, change in the amount of urine, yellowing eyes/skin.

It may also cause a severe intestinal condition Clostridium difficile-associated diarrhea due to resistant bacteria. This condition may occur during treatment or weeks to months after treatment has stopped. Inform your doctor immediately if you develop: persistent diarrhea, abdominal or stomach pain/cramping, blood/mucus in your stool. A very serious allergic reaction can occur and seek immediate medical attention if you notice rash, itching/swelling (especially of the face/tongue/throat), severe dizziness, hypokalaemia, bronchospasm.

OVERDOSAGE
There have been postmarketing 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.

Directions for Reconstitution and Dilution for Use
Intravenous Administration
For conventional vials, reconstitute Piperacillin and Tazobactam per gram of piperacillin with 5 mL of a compatible reconstitution diluent like 0.9% Sodium Chloride for Injection, Sterile Water for Injections IP,. Dextrose 5% and bacteriostatic water.

2.25g and 4.5g Piperacillin and Tazobactam should be reconstituted with 10 mL and 20 mL of Sterile Water for Injections IP respectively. Swirl until dissolved.

ADMINISTRATION
Reconstituted Piperacillin and Tazobactam Solution should be further diluted (recommended volume per dose of 50 mL to 150 mL) in a compatible intravenous diluent 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 Diluent Solutions
0.9% Sodium Chloride for Injection
Sterile Water for Injections IP
Dextrose 5%
Dextran 6% in saline

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

Piperacillin and Tazobactam should not be mixed with other drugs in a syringe or infusion bottle since compatibility has not been established.

Piperacillin and Tazobactam is not chemically stable in solutions that contain only sodium bicarbonate and solutions that significantly alter the pH.

LACTATED RINGER'S SOLUTION IS NOT COMPATIBLE WITH Piperacillin and Tazobactam. Piperacillin and Tazobactam should not be added to blood products or albumin hydrolysates.

When concomitant therapy with aminoglycosides is indicated, Piperacillin and Tazobactam and the aminoglycoside should be reconstituted and administered separately.

Shelf life : Please refer carton/label.

Storage: Store between 20°C- 25°C. Protected from light and moisture.
Keep out of reach of children.

Special Precautions for Disposal and Other Handling
Any unused medicinal product should be disposed off in accordance with the local requirements.

Nature and Contents of Container
Biopiper TZ®4.5g and **Biopiper TZ® 2.25g** are supplied in a USP Type I glass vial with a rubber stopper and flip-off seal, packed in a single monocarton along with package insert.

Marketed by:
Biocon Biologics India Limited
Biocon House, Semicon Park,
Electronics City, Phase - II,
Bengaluru - 560 100, India.

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To report adverse events and/or product complaints visit our website **www.biocon.com** or call toll free No: **1800 102 9465** or e mail us at **drugsafety@biocon.com**

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