Size : 240x130mm

Metabolic and Nutritional - symptomatic hypoglycemia, thirst, (gout, vitamin B_{12} deficiency anemia)

Musculoskeletal - myalgia, arthralgia

Platelets, Bleeding, Clotting - mesenteric embolism, purpura, epistaxis, pulmonary embolism, (ecchymosis, hemoptysis).

Psychiatric - confusion, hallucination, depression

Reproductive, female - leukorrhea, vaginitis (perineal irritation/pain)

Respiratory - pharyngitis, pulmonary edema, bronchospasm, coughing, (atelectasis, dyspnea, hypoxia)

Skin and Appendages - genital pruritus, diaphoresis, (conjunctivitis, xerosis)

Special senses - taste perversion

Urinary - retention,dysuria, oliguria, hematuria, incontinence, (urinary tract infections with trichomonas, yeast in urine)

Vision - Photophobia

Vascular (extracardiac) - flushing (cardiovascular accident)

Hematologic - hemolytic anemia

Renal - rarely, interstitial nephritis

DOSAGE AND ADMINISTRATION
PIPJET is administered by IV infusion over 30 minutes. The usual total daily dose for adults is 12 g/1.5 g for 7 to 10 days, given as 4.5 g every 8 hours.

- ***Nosocomial pneumonia:*** Start with 3.375 g every 4 hours plus an aminoglycoside. The recommended duration of treatment is 7 to 14 days. Continue the aminoglycoside in patients from whom *P. aeruginosa* is isolated. If it is not isolated, the aminoglycoside may be discontinued at the discretion of the treating physician as guided by the severity of the infections and the patient's clinical and bacteriological progress.

- ***Renal function impairment :*** In patients with renal insufficiency (Ccr <90 ml/min) adjust the IV dose to the degree of actual renal function impairment. In patients with nosocomial pneumonia receiving concomitant amino-glycoside therapy, adjust the aminoglycoside dosage

according to the manufacturers recommendations.

PIPJET Dosage Recommendation	
Creatinine clearance (ml/min	**Recommended dosage regimen**
20-80	12g/1.5g/day in divided dosages of 4.5g every 8 hours
< 20	8g/1g/day in divided dosages of 4.5g every 12 hours

- ***Hemodialysis:*** The maximum dose is 2.25 g every 8 hours. In addition because hemodialysis removes 30% to 40% of a dose in 4 hours, give one additional 0.75g dose following each dialysis period. Peritoneal dialysis removes 6% and 21% of the piperacillin and tazobactam doses, respectively.

- ***Duration of therapy:*** Continue administration for a minimum of 48 to 72 hours after fever abates or after evidence of bacterial eradication has been obtained. A minimum of 10 days treatment is recommended for group A, β-hemolytic streptococci infections to guard against the risk of rheumatic fever or glomerulonephritis. However, the recommended duration of **PIPJET** treatment of nosocomial pneumonia is seven to fourteen days. In all conditions the duration of therapy should be guided by severity of infection and patient's clinical and bacteriological progress.

- ***Intravenous administration :*** For conventional vials, reconstitute **PIPJET** per 1 gram of piperacillin with 5 ml of a compatible reconstitution diluent (given below).

Shake well until dissolved

- ***Compatible reconstituent diluents :*** These include 0.9% Sodium Chloride for injection, Sterile Water for Injection, Dextrose 5%, Bacteriostatic Saline/Parabens, Bacteriostatic Water/Benzyl Alcohol. Lactated Ringer's solution is not compatible. Dilute to at least 50 ml to 150 ml. Administer over a period of $\geq$ 30 minutes.

- ***Compatible IV diluent Solutions:*** These include 0.9% Sodium Chloride for injection, Sterile Water for Injection (maximum recommended volume per dose is 50 ml), Dextrose 5%, Dextran 6% in Saline.

OVERDOSAGE
Information on overdosage of **PIPJET** *in humans is not available.* Excessive serum levels of either piperacillin or tazobactam may be reduced by hemodialysis. No specific antidote is known. As with other penicillins neuromuscular excitability or convulsions have occurred following large intravenous doses, primarily in patients with impaired renal function. In the case of motor excitability or convulsions,

general supportive measures, including administration of anticonvulsive agents (e.g diazepam or barbiturates), may be considered.

STORAGE
Store below 25ºC. Protect from light.

STABILITY
Reconstitute conventional vials with 5 ml of compatible diluent per gram of piperacillin. Shake well until dissolved. Use single dose vials immediately after reconstitution.
Discard any unused portion after 24 hours if stored at room temperature or after 48 hours if stored at refrigerated temperature (2º C to 8º C [36º F to 46º F]). Stability in the IV bags has been demonstrated for up to 24 hours at room temperature. The stability in an ambulatory IV infusion pump has been demonstrated for a period of 12 hours at room temperature.

HOW SUPPLIED
PIPJET is supplied in 30 ml injection vial containing sufficient Piperacillin and Tazobactam Injection I.P. to deliver 4.5 g for intravenous administration.

TM - Trademark applied for

Marketed by :
DELIGHT BIOPHARMA PVT LTD
Reg. Off.: 11-10-255/2, Street No.,
Road No. 2, Hyderabad
Corp. Off.: Khasra No. 741, GT Road,
Jamalpur, Roorkee-247667

℞

VENUS

For the use of Registered Medical Practitioners or a Hospital or a Laboratory only

PIPERACILLIN & TAZOBACTAM INJECTION I.P.

PIPJET™

Description
PIPJET (Piperacillin and Tazobactam Injection I.P.) is an injectable antibacterial combination product consisting of the semisynthetic antibiotic piperacillin sodium and the β-lactamase inhibitor tazobactam sodium for intravenous administration.

Composition

Each vial contains:
Piperacillin Sodium
Equivalent to Piperacillin I.P. 4 g
Tazobactam Sodium
Equivalent to Tazobactam I.P. 0.5 g

CATEGORY: Antibiotic, Penicillins.

Piperacillin sodium is derived from D(-)-α-aminobenzyl-penicillin. The chemical formula is $C_{23}H_{26}N_5NAO_7S$ and the molecular weight is 539.5.

Tazobactam sodium, a derrivative of the penicillin nucleus, is a penicillinic acid sulfone. The chemical formula is $C_{10}H_{11}N_4NAO_5S$ and the molecular weight is 322.3.

CLINICAL PHARMACOLOGY
Peak plasma concentration of piperacillin and tazobactam are attained immediately after completion of an IV infusion. Following single or multiple doses to healthy subjects, the plasma half-life of piperacillin and of tazobactam ranged from 0.7-1.2 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 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 concentration 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 increasing with decreasing creatinine clearance. At creatinine clearance below 20 ml/min, the increase in half-life is 2-fold for piperacillin and 4-fold for tazobactam compared to subjects with normal renal function. Dosage adjustment for **PIPJET** are recommended when creatinine clearance is below 40 ml/min in patients receiving the usual recommended daily dose of **PIPJET**.

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 **PIPJET** due to hepatic cirrhosis.

MICROBIOLOGY
Piperacillin sodium exerts bactericidal activity by inhibiting septum formation and cell wall synthesis. *In vitro,* piperacillin is active against a variety of gram-positive and gram-negative aerobic and anaerobic bacteria. Tazobactam sodium has very little intrinsic microbiologic activity due to its very low level binding to penicillin-binding proteins, however, it is a β-lactamase inhibitor of the Richmond-Sykes class III penicillinases and cephalosporinases. Tazobactam does not induce chromosomally mediated β-lactamases.

INDICATIONS
Piperacillin and Tazobactam has been shown to be active against most strains of β-lactamase producing micro-organism both *in vitro* and in clinical infections. It is indicated for the treatment of moderate to severe infections caused by piperacillin resistant, piperacillin and tazobactam-susceptible β-lactamase producing strains of the micro-organism in the

condition listed below:

- *Appendicitis (complicated by rupture or abscess) and peritonitis:* Due to piperacillin-resistant, β-lactamase producing strains of *E.coli* or these members of the bacteriodes group : *B.fragilis, B.ovatus, B. thetaiotaomicron* or *B.vulgatus*.
- *Uncomplicated and complicated skin and skin structure infections:* Those including cellulitis, cutaneous abscesses and ischemic/diabetic foot infections caused by piperacillin-resistant, β-lactamase producing strains of *S.aureus*.
- *Postpartum endometritis or pelvic inflammatory disease:* Due to piperacillin-resistant, β-lactamase producing strains of *E.coli*.
- *Community-acquired pneumonia (moderate to severe):* Due to piperacillin-resistant, β-lactamase producing strains of *S.aureus*.

The treatment of mixed infections caused by piperacillin-susceptible organisms and piperacillin-resistant, β-lactamase producing organisms susceptible to piperacillin and tazobactam should not require adding another antibiotic. An exception is in the treatment of *Pseudomonas aeruginosa* in *nosocomial pneumonia*, which should be in combination with an aminoglycoside.

CONTRAINDICATIONS
PIPJET is contraindicated in patients with a history of allergic reactions to any of the penicillins, cephalosporins or β-lactamase inhibitors.

WARNING
Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients on penicillin therapy. These reactions are more likely to occur in individuals with a history of sensitivity to multiple allergens. Before initiating therapy with **PIPJET**, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cepha-losporins or other allergens. If an allergic reaction occurs, **PIPJET** should be discontinued and appropriate therapy instituted.

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

Treatment with antibacterial agents alters the normal flora of colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibotic-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
General
Bleeding manifestation have occurred in some patients receiving β-lactam antibiotic, including piperacillin. These reactions have sometimes been associated with abnormalities of coagulation tests such as clotting time, platelet aggregation, and prothombin time and are more likely to occur in patients with renal failure. If bleeding manifestation occur. **PIPJET** should be discontinued and appropriate therapy instituted.

As with other penicillins, patients may experience neuromuscular excitability or convulsion if higher than recommended doses are given intravenously (particularly in the presence of renal failure).

PIPJET is a monosodium salt of piperacillin and a monosodium salt of tazobactam and contains a total of 2.35mEq (54mg) 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.

The possibility of the emergence of resistant organisms that might cause super infections should be kept in mind.

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
The mixing of **PIPJET** with an aminoglycoside *in vitro* can result in substantial inactivation of the aminoglycoside. Thus, the aminoglycoside should be reconstituted and administered separately.

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

Vancomycin

No pharmacokinetic interactions have been noted between **PIPJET** and vancomycin.

Vecuronium
Piperacillin when used concimitantly with vecuronium has been implicated in the prolongation of the neuromuscular blockade of vencuronium.

Pregnancy
Reproduction studies performed in animals have revealed no evidence of impaired fertility due to piperacillin and tazobactam administered up to a dose which is similar to the maximum recommended human daily dose based on body surface area (mg/m^2).

Lactation
Piperacillin is excreted in low concentration in human milk; tazobactam concentration in human milk have not been studied. Caution should be exercised when **PIPJET** is administered to a nursing woman.

Pediatric Use
Safety and efficacy in pediatric patients have not been established.

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.

SIDE EFFECTS
General - rigors, back pain, malalse (asthenia, chest pain)

Autonomic Nervous System - hypotension, ileus, syncope

Cardiovascular-tachycardia, including supraventricular and ventricular bradycardia, arrhythmia including atrial fibrillation, ventricular fibrillation, cardiac arrest, cardiac failure, circulatory failure, myocardial infarction(angina).

Central Nervous System-tremor, convulsions, vertigo, aggressive reaction (combative).

Gastrointestinal-malena, flatulence, hemorrhage, gastritis, hiccough, ulcerative stomatitis, (fecal incontinence, gastric ulcer, pancreatitis) hepatitis, cholestatic jaundice.

Pseudomembranous colitis was reported in one patients during the clinical trials. The onset of *pseudomembranous colitis* symptoms may occur during or after antibacterial treatment.

Hearing and Vestibular System - tinnitus, (deafness, earache)
Hypersensitivity - anaphylaxis

Size : 240x130mm