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

Piperacillin and Tazobactam Injection IP

PIPBACTUM-LYO™

पिपबैक्टम-लायो

COMPOSITION
Each combipack contains:
(A) 1 vial of Piperacillin and Tazobactam Injection IP
Each vial contains :

Piperacillin Sodium IP (Sterile) eq. to Piperacillin	4000 mg
Tazobactam Sodium IP (Sterile) eq. to Tazobactam	500 mg

(B) 2 Ampoules of Sterile Water for Injections IP
Each ampoule contains:

Sterile Water for Injections IP	10 ml

PHARMACOLOGY
Pharmacodynamics
Piperacillin sodium 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 little clinically relevant in vitro activity against bacteria due to its reduced affinity to penicillin-binding proteins. It is, however, a beta-lactamase inhibitor of the Richmond-Sykes class III (Bush class 2b & 2b') penicillinases and cephalosporinases. It varies in its ability to inhibit class IIA and IV (2a & 4) penicillinases. Tazobactam does not induce chromosomally-mediated beta-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 baumannii
Escherichia coli
Haemophilus influenzae (excluding beta-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*)
Pharmacokinetics
Peak plasma concentrations of piperacillin and tazobactam are attained immediately after completion of an intravenous infusion of piperacillin/ tazobactam. Piperacillin plasma concentrations, following a 30-minute infusion of piperacillin/tazobactam, were similar to those attained when equivalent doses of piperacillin were administered alone, with mean peak plasma concentrations of approximately 298 µg/ml for the 4.5 g piperacillin/tazobactam doses. The corresponding mean peak plasma concentrations of tazobactam were 34 µg/ml.
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.

INDICATIONS
PIPBACTUM-LYO Injection is indicated for the treatment of the following infections in adults and children over 2 years of age:
Adults and adolescents
- Severe pneumonia including hospital-acquired and ventilator-associated pneumonia
- Complicated Urinary Tract infections
- Complicated Intra-abdominal infections
- Complicated Skin and Skin structure infections

Treatment of patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above.
PIPBACTUM-LYO may be used in the management of neutropenic patients with fever suspected to be due to a bacterial infection.
Children 2 to 12 years of age
- Complicated Intra-abdominal infections

PIPBACTUM-LYO may be used in the management of neutropenic children with fever suspected to be due to a bacterial infection

DOSAGE AND ADMINISTRATION
The dose and frequency of PIPBACTUM-LYO depends on the severity and localisation of the infection and expected pathogens.
Adults and Adolescent patients:
Infections
The usual dose is 4 g piperacillin / 0.5 g tazobactam given every 8 hours.
For nosocomial pneumonia and bacterial infections in neutropenic patients, the recommended dose is 4 g piperacillin / 0.5 g tazobactam administered every 6 hours. The following table summarizes the treatment frequency and the recommended dose for adult and adolescent patients by indication or condition:

Treatment frequency	**Piperacillin/Tazobactam 4 g/ 0.5 g**
Every 6 hours	Severe pneumonia Neutropenic adults with fever suspected to be due to a bacterial infection
Every 8 hours	Complicated urinary tract infections Complicated intra-abdominal infections Skin and soft tissue infection

Renal impairment
The intravenous dose should be adjusted to the degree of actual renal impairment as follows:

Creatinine Clearance (ml/min)	Piperacillin/Tazobactam (Recommended dose)
> 40	No dose adjustment necessary
20-40	Maximum dose suggested: 4 g / 0.5 g every 8 hours
< 20	Maximum dose suggested: 4 g / 0.5 g every 12 hours

For patients on hemodialysis, one additional dose of piperacillin / tazobactam 2 g/ 0.25 g should be administered following each dialysis period, because hemodialysis removes 30%-50% of piperacillin in 4 hours.

Hepatic impairment
No dose adjustment is necessary

Elderly patients
No dose adjustment is required for the elderly with normal renal function or creatinine clearance values above 40 ml/min.

Pediatric population (2-12 years of age)
Infections
The following table summarises the treatment frequency and the dose per body weight for pediatric patients 2-12 years of age by indication or condition:

Dose per weight and treatment frequency	Indication/Condition
80 mg Piperacillin / 10 mg Tazobactam per kg body weight / every 6 hours	Neutropenic children with fever suspected to be due to bacterial infections*
100 mg Piperacillin / 12.5 mg Tazobactam per kg body weight / every 8 hours	Complicated intra-abdominal infections*

*Not to exceed the maximum 4 g /0.5 g per dose over 30 minutes

Renal impairment
The intravenous dose should be adjusted to the degree of actual renal impairment as follows:

Creatinine clearance (ml/min)	Piperacillin/Tazobactam (Recommended dose)
>50	No dose adjustment needed
<50	70 mg piperacillin / 8.75 mg tazobactam/kg every 8 hours

For children on hemodialysis, one additional dose of 40 mg piperacillin / 5 mg tzobactam/kg should be administered following each dialysis period.
Use in children aged below 2 years
The safety and efficacy of Piperacillin/Tazobactam in children 0-2 years of age has not been established.

Treatment duration
The usual treatment duration for most indications is 5-14 days. However, the duration of treatment should be guided by the severity of the infection, the pathogen(s) and the patient's clinical and bacteriological progress.

Method of administration
PIPBACTUM-LYO is administered by intarvenous infusion (over 30 minutes)

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

WARNINGS AND PRECAUTIONS
Before initiating therapy with **PIPBACTUM-LYO**, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, or other allergens since serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients on penicillin therapy. If an allergic reaction occurs, **PIPBACTUM-LYO** should be discontinued and appropriate therapy instituted.
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 diarrhoea subsequent to the administration of antibacterial agents.
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.
Bleeding manifestations have occurred in some patients receiving beta-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, **PIPBACTUM-LYO** should be discontinued and appropriate therapy instituted.

Drug Interactions
Aminoglycosides: The mixing of piperacillin/tazobactam with an aminoglycoside in vitro can result in substantial inactivation of the aminoglycoside. The Aminoglycoside should be reconstituted and administered separately.
Probenecid: Probenecid administered concomitantly with piperacillin/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.
Vecuronium: Piperacillin when used concomitantly with vecuronium has been implicated in the prolongation of the neuromuscular blockade of 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.
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.

Pregnancy
Reproduction studies performed in animals have revealed no evidence of impaired fertility due to piperacillin/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 concentrations in human milk; tazobactam concentrations in human milk have not been studied. Caution should be exercised when **PIPBACTUM-LYO** is administered to a woman who is nursing.

Pediatric Use
Safety and efficacy in pediatric patients less than 2 months of age have not been established.

Geriatric Use
Patients over 65 years are not an increased risk of developing adverse effects solely because of age. However, dosage should be adjusted in the presence of renal insufficiency.

ADVERSE DRUG REACTIONS
- Skin rashes including rash and pruritis
- Gastrointestinal including diarrhea, nausea and vomiting.
- Allergic reactions
- Hypokalaemia
- Bronchospasm

OVERDOSAGE
There have been postmarketing reports of overdose with piperacillin/tazobactam. The majority of those events experienced, including nausea, vomiting, and diarrhoea, 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 haemodialysis.

DIRECTION FOR USE
Constitute using 20 ml Sterile Water for Injections IP. The constituted solution should be used immediately after preparation.

STORAGE
Store at controlled room temperature (20°C to 25°C). Protect from light & moisture. Do not freeze.
Keep all medicines out of reach of children.

PRESENTATION
PIPBACTUM-LYO injection 4.5 g is available in a vial packed in mono carton.

GALENGEN

Marketed by :
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TM- Trade Mark Applied

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