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

Piperacillin And Tazobactam Injection IP 4.5 g

VARTAZ®-P

Each vial contains:

Piperacillin Sodium IP eq. to Piperacillin	4.0 gm
Tazobactam Sodium IP eq. to Tazobactam	0.5 gm
(Sodium Content 216.06 mg)	

DESCRIPTION:
Piperacillin Sodium is a Antibacterials for systemic use. The chemical name of Piperacillin Sodium (2S,5R,6R)-6-[[(2R)-2-[[(4-ehyl-2,3-dioxopiperazin-1-yl)carbonyl]amino]-2-phenylacetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate.
The empirical formula is $C_{23}H_{26}N_5NaO_7S$ and the molecular weight is 539.5 g/mol.
Tazobactam Sodium is a Beta-lactamase inhibitor. The chemical name of Tazobactam 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-carboxylic acid,4,4-dioxide. The empirical formula is $C_{10}H_{11}N_4NaO_5S$ and the molecular weight is 322.3 g/mol.

THERAPEUTIC INDICATIONS:
Piperacillin/Tazobactam 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 (including pyelonephritis)
- Complicated intra-abdominal infections
- Complicated skin and soft tissue infections (including diabetic foot infections)

Treatment of patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above.
Piperacillin/Tazobactam 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

Piperacillin/Tazobactam may be used in the management of neutropenic children with fever suspected to be due to a bacterial infection.
Consideration should be given to official guidance on the appropriate use of antibacterial agents.

POSOLOGY AND METHOD OF ADMINISTRATION:
Posology:
The dose and frequency of Piperacillin/Tazobactam depends on the severity and localisation of the infection and expected pathogens.
Adult and adolescent patients
The usual dose is 4 gm piperacillin/ 0.5 gm Tazobactam given every 8 hours.
For nosocomial pneumonia and bacterial infections in neutropenic patients, the recommended dose is 4g piperacillin/ 0.5g tazobactam administered every six hours. This regimen may also be applicable to treat patients with other indicated infections when particularly severe.
The following table summarizes the treatment frequency and the recommended dose by indication or condition:

Treatment Frequency	Piperacillin/Tazobactam 4 gm/0.5 gm
Every 6 hours	Severe pneumonia
	Neutropaenic adults with fever suspected to be due to a bacterial infection.
Every 8 hours	Complicated urinary tract infections (including pyelonephritis)
	Complicated intra-abdominal infections
	Skin and soft tissue infections (including diabetic foot infections)

Renal impairment
The intravenous dose should be adjusted to the degree of actual renal impairment as follows (each patient must be monitored closely for signs of substance toxicity; medicinal product dose and interval should be adjusted accordingly):

Creatinine clearance	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 haemodialysis, one additional dose of piperacillin / tazobactam 2 g / 0.25 g should be administered following each dialysis period, because haemodialysis 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.
Paediatric population (2-12 years of age)
Infections
The following table summarizes the treatment frequency and the dose per body weight for paediatric 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 (each patient must be monitored closely for signs of substance toxicity; medicinal product dose and interval should be adjusted accordingly):

Creatinine clearance (ml/min)	Piperacillin/Tazobactam (recommended dose)
>50	No dose adjustment needed.
≤50	70mg piperacillin/ 8.75mg tazobactam/ kg every eight hours.

For children on haemodialysis, one additional dose of 40mg piperacillin/ 5mg tazobactam/ 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 duration of treatment for most indications is in the range of 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
Piperacillin/Tazobactam 4 g / 0.5 g is administered by intravenous infusion (over 30 minutes).
Reconstitution Directions:
Intravenous use
Each vial of Piperacillin/Tazobactam 4g/0.5g Powder for Solution for Infusion should be reconstituted with 20ml of one of the following diluents:
• Sterile water for injections
• 0.9% sodium chloride for injection
To achieve effective reconstitution, invert and shake the vial thoroughly to detach any powder adhering to the walls prior to addition of the diluent. Add the solvent and shake until complete dissolution is achieved.
The reconstituted solution should be further diluted to at least 50ml with one of the reconstitution diluents, or with Dextrose 5% in Water.
Displacement Volume
Each gram of Piperacillin/Tazobactam 4g/0.5g Powder for Solution for Infusion has a displacement volume of 0.7ml.
Piperacillin/Tazobactam 4g/0.5g Powder for Solution for Infusion will displace 3.15ml.
The reconstitution/dilution is to be made under aseptic conditions. The solution is to be inspected visually for particulate matter and discoloration prior to administration. The solution should only be used if the solution is clear and free from particles.
Any unused product or waste material should be disposed of in accordance with local requirements.

CONTRAINDICATIONS:
Hypersensitivity to the active substances, any other penicillin-antibacterial agent or to any of the excipients.
History of acute severe allergic reaction to any other beta-lactam active substances (e.g. cephalosporin, monobactam or carbapenem).

SPECIAL WARNINGS AND PRECAUTIONS FOR USE:
The selection of Piperacillin/Tazobactam to treat an individual patient should consider the appropriateness of using a broad-spectrum semi-synthetic penicillin based on factors such as the severity of the infection and the prevalence of resistance to other suitable antibacterial agents.
Before initiating therapy with Piperacillin/Tazobactam, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, other beta-lactam agents (e.g. cephalosporin, monobactam or carbapenem) and other allergens. Serious and occasionally fatal hypersensitivity (anaphylactic/anaphylactoid [including shock]) reactions have been reported in patients receiving therapy with penicillins, including Piperacillin/Tazobactam.
These reactions are more likely to occur in persons with a history of sensitivity to multiple allergens. Serious hypersensitivity reactions require the discontinuation of the antibiotic, and may require administration of epinephrine and other emergency measures.
Serious skin reactions, such as Stevens-Johnson syndrome and toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalised exanthematous pustulosis have been reported in patients receiving Piperacillin/Tazobactam (See UNDESIRABLE EFFECTS). If patients develop a skin rash they should be monitored closely and Piperacillin/Tazobactam discontinued if lesions progress.
Antibiotic-induced pseudomembranous colitis may be manifested by severe, persistent diarrhoea which may be life-threatening. The onset of pseudomembranous colitis symptoms may occur during or after antibacterial treatment. In these cases Piperacillin/Tazobactam, should be discontinued. Therapy with Piperacillin/Tazobactam may result in the emergence of resistant organisms, which might cause super-infections.
Bleeding manifestations have occurred in some patients receiving beta-lactam antibiotics. These reactions sometimes have 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, the antibiotic should be discontinued and appropriate therapy instituted.
Leukopenia and neutropenia may occur, especially during prolonged therapy. Therefore, periodic assessment of a full blood count should be performed.
As with treatment with other penicillins, neurological complications in the form of convulsions may occur when high doses are administered, especially in patients with impaired renal function.
This medicinal product contains 9.44 mmol (217 mg) of sodium per vial of powder for solution for infusion. To be taken into account by patients on a controlled sodium diet.
Hypokalaemia may occur in patients with low potassium reserves or those receiving concomitant medicinal products that may lower potassium levels; periodic electrolyte determinations may be advisable in such patients.
Haemophagocytic lymphohistiocytosis (HLH)
Cases of HLH have been reported in patients treated with piperacillin/tazobactam, often following treatment longer than 10 days. HLH is a life-threatening syndrome of pathologic immune activation characterised by clinical signs and symptoms of an excessive systemic inflammation (e.g. fever, hepatosplenomegaly, hypertriglyceridaemia, hypofibrinogenaemia, high serum ferritin, cytopenias and haemophagocytosis). Patients who develop early manifestations of pathologic immune activation should be evaluated immediately. If diagnosis of HLH is established, piperacillin/tazobactam treatment should be discontinued.
Renal Impairment
Due to its potential nephrotoxicity (See UNDESIRABLE EFFECTS), piperacillin/tazobactam should be used with care in patients with renal impairment or in hemodialysis patients. Intravenous dosages and administration intervals should be adjusted to the degree of renal function impairment(See POSOLOGY AND METHOD OF ADMINISTRATION).
In a secondary analysis using data from a large multicenter, randomized-controlled trial when glomerular filtration rate (GFR) was examined after administration of frequently used antibiotics in critically ill patients, the use of piperacillin/tazobactamwas associated with a lower rate of reversible GFR improvement compared with the other antibiotics. This secondary analysis concluded that piperacillin/tazobactam was a cause of delayed renal recovery in these patients.

DRUG INTERACTION WITH OTHER MEDICINAL PRODUCTS:
Non-depolarising muscle relaxants: Piperacillin when used concomitantly with vecuronium has been implicated in the prolongation of the neuromuscular blockade of vecuronium. Due to their similar mechanisms of action, it is expected that the neuromuscular blockade produced by any of the non-depolarising muscle relaxants could be prolonged in the presence of piperacillin.

Oral anticoagulants: During simultaneous administration of heparin, oral anticoagulants and other drugs that may affect the blood coagulation system including thrombocyte function, appropriate coagulation tests should be performed more frequently and monitored regularly.
Methotrexate: Piperacillin may reduce the excretion of methotrexate; therefore, serum levels of methotrexate should be monitored in patients to avoid substance toxicity.
Probenecid: As with other penicillins, concurrent administration of probenecid and Piperacillin/Tazobactam produces a longer half-life and lower renal clearance for both piperacillin and tazobactam; however, peak plasma concentrations of either substances are unaffected.
Aminoglycosides: Piperacillin, either alone or with tazobactam, did not significantly alter the pharmacokinetics of tobramycin in subjects with normal renal function and with mild or moderate renal impairment. The pharmacokinetics of piperacillin, tazobactam, and the M1 metabolite were also not significantly altered by tobramycin administration.
The inactivation of tobramycin and gentamicin by piperacillin has been demonstrated in patients with severe renal impairment.
Vancomycin
No pharmacokinetic interactions have been noted between Piperacillin/Tazobactam and vancomycin.
However, a limited number of retrospective studies have detected an increased incidence of acute kidney injury in patients concomitantly administered Piperacillin/Tazobactam and vancomycin as compared to vancomycin alone.
Effects on laboratory tests
Non-enzymatic methods of measuring urinary glucose may lead to false- positive results, as with other penicillins. Therefore, enzymatic urinary glucose measurement is required under Piperacillin/Tazobactam therapy.
A number of chemical urine protein measurement methods may lead to false positive results. Protein measurement with dip sticks is not affected.
The direct Coombs test may be positive.
Bio-Rad Laboratories Platelia Aspergillus EIA tests may lead to false-positive results for patients receiving Piperacillin/Tazobactam. Cross-reactions with non-Aspergillus polysaccharides and polyfuranoses with Bio-Rad Laboratories Platelia Aspergillus EIA test have been reported.
Positive test results for the assays listed above in patients receiving Piperacillin /Tazobactam should be confirmed by other diagnostic methods.

PREGNANCY, LACTATION AND FERTILITY:
Pregnancy: Piperacillin and Tazobactam cross the placenta in humans. Piperacillin and Tazobactam should only be used during pregnancy if clearly indicated, i.e only if the expected benefit outweighs the possible risk to pregnant woman and foetus.
Lactation: Piperacillin is excreted in low concentrations in breast milk. Women who are breast feeding should be treated only if the expected benefit outweighs the possible risks to the woman and child.
Fertility: No effect on fertility and mating after intraperitoneal administration of tazobactam or the combination piperacillin / tazobactam.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
Not Applicable.

UNDESIRABLE EFFECTS:
The most commonly reported adverse reactions are diarrhoea, vomiting, nausea and rash.
Among the most serious adverse reactions pseudo-membranous colitis and toxic epidermal necrolysis.
Infections and Infestations: Candidiasis, Pseudo- membranous colitis
Blood and lymphatic system disorders: Thrombocy topenia, anaemia, leukopenia, agranulocytosis Pancytopenia, neutropenia, Haemolytic anaemia, eosinophilia, thrombocytosis
Immune system Disorders: anaphylactoid reaction, anaphylactic reaction, anaphylactoid shock, anaphylactic shock, hypersensitivity
Metabolism and Nutrition disorders: hypokalaemia
Psychiatric Disorders: insomnia
Nervous system disorders: headache
Vascular Disorders: hypotension, thrombophlebitis, phlebitis, flushing
Respiratory, thoracic and mediastinal Disorders: epistaxis, Eosinophilic pneumonia
Gastrointestinal Disorders: Diarrhoea, abdominal pain, vomiting, nausea, constipation, dyspepsia, stomatitis
Hepatobiliary Disorders: Hepatitis, jaundice
Skin and subcutaneous tissue disorders: rash, pruritus, erythema multiforme, urticaria, rash maculopapular, toxic epidermal necrolysis, Stevens-Johnson syndrome, dermatitis exfoliative, drug reaction with eosinophilia and systemic symptoms (DRESS), acute Generalised exanthematous pustulosis (AGEP), dermatitis bullous purpura
Musculoskeletal and connective tissue disorders: arthralgia, myalgia
Renal and urinary disorders: renal failure, tubulointerstitial, nephritis
General disorders and administration site conditions: pyrexia, injection site reaction, chills
Investigations: Alanine aminotransferase increased, aspartate aminotransferase increased, protein total decreased, blood albumin decreased, Coombs direct test positive, blood creatinine increased, blood alkaline phosphatase increased, blood urea increased, activated partial thromboplastin time prolonged, blood glucose decreased, blood bilirubin increased, prothrombin time prolonged, bleeding time prolonged gamma- glutamyl- transferase increased.
Piperacillin therapy has been associated with an increased incidence of fever and rash in cystic fibrosis patients.

OVERDOSAGE:
Symptoms: There have been post-marketing 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 dose. Patients may experience neuromuscular excitability or convulsions if higher than recommended doses are given intravenously (particularly in the presence of renal failure).
Treatment: In the event of an overdose, Piperacillin/Tazobactam treatment should be discontinued. No specific antidote is known. Treatment should be supportive and symptomatic according to the patient's clinical presentation. Excessive serum concentrations of either piperacillin or tazobactam may be reduced by haemodialysis (See SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

CLINICAL PHARMACOLOGY
PHARMACODYNAMIC:
Pharmacotherapeutic group: Antibacterials for systemic use, combinations of penicillins, including beta-lactamase inhibitors
ATC code: J01CR05
Mechanism of action
Piperacillin, a broad spectrum, semisynthetic penicillin exerts bactericidal activity by inhibition of both septum and cell wall synthesis.
Tazobactam, a beta-lactam structurally related to penicillins, is an inhibitor of many beta-lactamases, which commonly cause resistance to penicillins and cephalosporins but it does not inhibit AmpC enzymes or metallo beta-lactamases. Tazobactam extends the antibiotic spectrum of piperacillin to include many betalactamase-producing bacteria that have acquired resistance to Piperacillin alone.
Pharmacokinetic / Pharmacodynamic relationship
The time above the minimum inhibitory concentration (T>MIC) is considered to be the major pharmacodynamic determinant of efficacy for piperacillin.
Mechanism of resistance
The two main mechanisms of resistance to Piperacillin/Tazobactam are:
Inactivation of the piperacillin component by those beta-lactamases that are not inhibited by tazobactam: beta-lactamases in the Molecular class B, C and D. In addition, tazobactam does not provide protection against extended-spectrum betalactamases (ESBLs) in The Molecular class A and D enzyme groups.
Alteration of penicillin-binding proteins (PBPs), which results in the reduction of the affinity of piperacillin for the molecular target in bacteria.
Additionally, alterations in bacterial membrane permeability, as well as expression of multi-drug efflux pumps, may cause or contribute to bacterial resistance to piperacillin / tazobactam, especially in Gram-negative bacteria.

PHARMACOKINETICS:
Absorption: The peak piperacillin and tazobactam concentrations after 4g/0.5g administered over 30 minutes by intravenous infusion are 298µg/ml and 34µg/ml respectively.
Distribution: 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/Tazobactam is widely distributed in tissue and body fluids including intestinal mucosa, gallbladder, lung, bile and bone. Mean tissue concentrations are generally 50 to 100% of those in plasma.
Biotransformation: Piperacillin is metabolised to a minor microbiologically active desethyl metabolite. Tazobactam is metabolised to a single metabolite, which has been found to be microbiologically inactive.
Elimination: Piperacillin and tazobactam are eliminated by the kidney via glomerular filtration and tubular secretion.
Piperacillin is excreted rapidly as unchanged drug with 68% of the administered dose appearing in the urine. Tazobactam and its metabolite are eliminated primarily by renal excretion with 80% of the administered dose appearing as unchanged drug and the remainder as the single metabolite. Piperacillin, tazobactam, and desethyl piperacillin are also secreted into the bile.
Following single or multiple doses of Piperacillin/Tazobactam to healthy subjects, the plasma half-life of piperacillin and tazobactam ranged from 0.7 to 1.2 hours and was unaffected by dose or duration of infusion. The elimination half-lives of both piperacillin and tazobactam are increased with decreasing renal clearance. There are no significant changes in piperacillin pharmacokinetics due to tazobactam. Piperacillin appears to reduce the clearance of tazobactam.
Special populations: The half-life of piperacillin and of tazobactam increases by approximately 25% and 18%, respectively, in patients with hepatic cirrhosis compared to healthy subjects. The half-life of piperacillin and tazobactam increases with decreasing creatinine clearance. The increase in half-life is two-fold and four-fold for piperacillin and tazobactam, respectively, at creatinine clearance below 20ml/min compared to patients with normal renal function.
Haemodialysis removes 30% to 50% of piperacillin/tazobactam, with an additional 5% of the tazobactam dose removed as the tazobactam metabolite. Peritoneal dialysis removes approximately 6% and 21% of the piperacillin and tazobactam doses, respectively, with up to 18% of the tazobactam dose removed as the tazobactam metabolite.
Paediatric population: The piperacillin clearance estimate is 80% of this value for paediatric patients 2-9 months of age. The population mean (SE) for piperacillin volume of distribution is 0.243 (0.011) l/kg and is independent of age.

STORAGE CONDITION: Store below 25ºC in a cool & dry place.

PRESENTATION:
Primary pack: 20 ml clear glass vial USP Type-III.
Secondary pack: Such a one vial with one 20 ml plastic ampoule of Sterilised water for Injection packed in a monocarton along with pack insert.

Mfd. By:
Bharat Parenterals Limited
Survey No. 144-A, Jarod-Samlaya Road,
Vill.: Haripura, Tal. Savli, Dist. Vadodara - 391520,
Gujarat, India.

Marketed By:
VARENYAM®
Varenyam Healthcare Pvt. Ltd.
FF/SF, Sun Welkin Tower-H,Harni-Halol Road,
Vadodara-390022, Gujarat, India.