Veritaz 2.25g & 4.5g

(Piperacillin + Tazobactam) Injection USP

Lyophilized Powder for:
- **IV Injection**
- **IV Infusion**

ویریٹاز 2.25 4.5 گرام

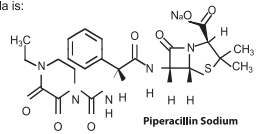
(پیپراسلین + ٹیزوبیکٹم) انجکشن یو ایس پی

لیفوفلائزڈ پاؤڈر برائے:
- آئی وی انجکشن
- آئی وی انفیوژن

DESCRIPTION

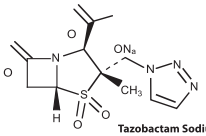
Veritaz (Piperacillin + Tazobactam) for intravenous use is an antimicrobial combination consisting of the semisynthetic antibiotic Piperacillin sodium and the β-lactamase inhibitor Tazobactam sodium for intravenous administration.

Chemically Piperacillin sodium is sodium (2S,5R,6[R)-6-[(R)-2-(4-ethyl-2,3-dioxo-1-piperazinecarboxamido)-2-phenylacetarnido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0] eptanes-2-carboxylate. Its molecular formula is $C_{23}H_{26}N_5NaO_7S$ and the structural formula is:



Piperacillin Sodium

Chemically, Tazobactam is sodium (2S,3S,5R)-3-methyl-7-oxo-3-(1H-1,2,3-triazol-1-ylmethyl)-4-thia-1azabicyclo[3,2,0]heptane-2-carboxylate-4,4-dioxide Its molecular formula is $C_{10}H_{11}N_4NaO_5S$ and the structural formula is:



Tazobactam Sodium

QUALITATIVE & QUANTITATIVE COMPOSITION

Veritaz (Piperacillin + Tazobactam) is available for intravenous administration as:

Veritaz IV Powder for Injection 2.25g

Each vial contains:

Piperacillin Sodium USP Equivalent to Piperacillin ... 2g

Tazobactam Sodium Equivalent to Tazobactam USP... 0.25g

Sodium Content: 108mg (approx.)

Finished Product Specs: USP

Veritaz IV Powder for Injection 4.5g

Each vial contains:

Piperacillin Sodium USP Equivalent to Piperacillin ... 4g

Tazobactam Sodium Equivalent to Tazobactam USP... 0.5g

Sodium Content: 216mg (approx.)

Finished Product Specs: USP

CLINICAL PHARMACOLOGY

Mechanism of Action

Piperacillin sodium exerts bactericidal activity by inhibiting septum formation and cell wall synthesis. Tazobactam is an inhibitor of many β-lactamases, which commonly cause resistance to penicillins and cephalosporins but it does not inhibit AmpC enzymes or metallo β-lactamases.

Tazobactam extends the antibiotic spectrum of Piperacillin to include many β-lactamase producing bacteria that have acquired resistance to Piperacillin alone.

Microbiology

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 baumanii,

Escherichia coli,

Haemophilus influenzae (excluding g-lactamase negative, ampicillin resistant isolates),

Klebsiella pneumonia,

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. vulgates)

Following In vitro data is available however clinical significance is unknown.

Aerobic and Facultative Gram positive microorganisms:

Enterococcus faecalis (ampicillin or penicillin-susceptible isolates only),

Staphylococcus epidermidis (excluding methicillin and oxacillin resistant isolates),

Streptococcus agalactiaet

Streptococcus pneurnoniaet (penicillin susceptible isolates only), Streptococcus pyogenest

Viridans group streptococcit

Aerobic and Facultative Gram negative microorganisms:

Citrobacter koseri,

Moraxella catarrhalis,

Morganella morganii,

Neisseria gonorrhoeae,

Proteus mirabilis,

Proteus vulgaris,

Somalia marcescens,

Providencia stuarti,

Providencia rettgeri,

Salmonella enteric.

Gram positive anaerobes:

Clostridium perfringens

Gram negative anaerobes:

Bacteroides distasonis,

Prevotella melaninogenica.

(These are not Q-lactamase producing bacteria and, therefore, are susceptible to Piperacillin alone.

Pharmacokinetics

Absorption

The peak Piperacillin + Tazobactam concentrations after 4g + 0.5g administered over 30 minutes by intravenous infusion are 298μgiml and 34μg/m1 respectively.

Distribution

Both Piperacillin + 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. Distribution into cerebrospinal fluid is low in subjects with non-inflamed meninges, as with other penicillins.

Metabolism

Piperacillin is metabolised to a minor microbiologicaily 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. Piperaciiin, tazobactarn and desethyl Piperacillin are also secreted into the bile.

Following single or multiple doses of Piperacillin Tazobactam. the plasma half-life of Piperacillin and Tazobactam ranged from 0,7 to 1,2 hours ale 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 However, Piperacillin appears to reduce the clearance of Tazobactam.

Special population

Renal Impairment

The half-life of Piperacillin and Tazobactam increases with decreasing deadline clearance The increase in half-life is two-fold and four-fold for Piperacillin and tazobactam respectively, at creatinine clearance below 20 ml/min compared to patients with normal renal function.

Hepatic Impairment

The half-life of Piperacillin and of Tazobactam increases by approximately 25% and 18%, respectively, in patients with hepatic cirrhosis compared to healthy subjects.

Elderly

The mean half-life for Piperacillin and tazobactarn are 32% and 55% longer, respectively in elderly.

THERAPEUTIC INDICATIONS

Veritaz (Piperacillin + Tazobactam) is indicated for the treatment of 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 bacterernia that occurs in association with, or is suspected to be associated with, any of the infections listed above.
- Management of neutropenic patients with fever suspected to be due to a bacterial infection.

Children (2 to 12 years)

- Complicated intra-abdominal infections
- Management of neutropenic children with fever suspected to be due to a bacterial infection.

DOSAGE & ADMINISTRATION

The dose and frequency of Veritaz (Piperacillin Tazobactam) depends on the severity and localization of the infection and expected pathogens.

Adults and Adolescents

The usual dose is 4g Piperacillin + 0.5g Tazobactam given every eight 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 particular severe.

The following table summarizes the treatment frequency and the recommended dose, for adult and adolescent patients by indication or condition:

Treatment frequency	Piperacillin + Tazobactam 4g + 0.5g
Every 6 hours	Severe pneumonia
	Neutropenic 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)

Children (2 - 12 years)

The following table summarizes the treatment frequency and the dose per body weight for patients 2-12 years of age by indication or condition:

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

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

Duration of Treatment
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.

Special population
Renal Impairment
Adults and Adolescents
The intravenous dose should be adjusted to the degree of actual renal impairment.

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

For patients on hemodialysis, one additional dose of Veritaz (Piperacillin + Tazobactam) 2.25g should be administered following each dialysis period, because hemodialysis removes 30%-50% of Piperacillin in 4 hours.

Children (2 - 12 years)
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	70mg piperacillin + 8.75mg Tazobactam/ kg every 8 hours.

For children on hemodialysis, 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 and Tazobactam in children 0 - 2 years of age has not been established.

Directions for use
Veritaz (Piperacillin + Tazobactam) may be given by slow intravenous injection or by infusion.
Intravenous Injection: Veritaz (Piperacillin + Tazobactam) 2.25g is administered by dissolving in 10mL sterile water for injection over 3 - 5 minutes as intravenous injection. Veritaz (Piperacillin + Tazobactam) 4.5g is administered by dissolving in 20mL sterile water for injection over 3 - 5 minutes as intravenous injection.

Intravenous Infusion: Veritaz (Piperacillin + Tazobactam) 2.25g should be reconstituted with 10mL sterile water for injection. Veritaz (Piperacillin + Tazobactam) 4.5g should be reconstituted with 20mL sterile water for injection.
The reconstituted solution should be further diluted to at least 50mL with sterile water for injection or with dextrose 5% in water and administer over 30 minutes as intravenous infusion.

ADVERSE REACTIONS
Common: Diarrhea, nausea, vomiting and rash including maculopapular rash.

Uncommon: Candidal super infection, leucopenia, neutropenia, thrombocytopenia, hypersensitivity reaction, headache, insomnia, hypotension, phlebitis, thrombophlebitis, constipation, dyspepsia, jaundice, stomatitis, alanine aminotransferase increased, aspartate aminotransferase increased, pruritus, urticaria, blood creatinine increased, pyrexia and injection-site reaction.

Rare: Anemia, purpura, epistaxis, bleeding time prolonged, eosinophilia, hemolytic anemia, anaphylactic/anaphylactoid reaction (including shock), flushing, abdominal pain, pseudo-membranous colitis, blood bilirubin increased, blood alkaline phosphatase increased, gamma glutamyltransferase increased, hepatitis , erythema multiforme, dermatitis bullous, exanthema, arthralgia, myalgia, chills, tubulointerstitial nephritis and renal failure.

Very rare: Agranulocytosis, Coombs' direct test positive, pancytopenia, activated partial thromboplastin time prolonged, prothrombin time prolonged, thrombocythemia, blood albumin decreased, blood glucose decreased, blood protein total decreased, hypokalemia, Stevens-Johnson Syndrome, toxic epidermal necrolysis and blood urea increased.

CONTRAINDICATIONS
Piperacillin + Tazobactam is contraindicated in patients with:
- Known hypersensitivity to penicillin-antibacterial agent or to any excipient of the product.
- History of acute severe allergic reaction to any other ß-lactam active substances (e.g. cephalosporin, monobactam or carbapenem).

PRECAUTIONS
- The selection of Piperacillin + Tazobactam to treat an individual patient should take into account 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.
- Careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, other ß-lactam agents (e.g. cephalosporin, monobactam or carbapenem) before initiating therapy. Serious hypersensitivity reactions require the discontinuation of the antibiotic and may require administration of epinephrine and other emergency measures.
- In patients receiving Piperacillin + Tazobactam serious skin reactions, such as Stevens Johnson syndrome and toxic epidermal necrolysis may occur. If patients develop a skin rash they should be monitored closely and Piperacillin + Tazobactam discontinued if lesions progress.
- The onset of pseudomembranous colitis symptoms may occur during or after antibacterial treatment. Antibiotic-induced pseudomembranous colitis may be manifested by severe, persistent diarrhea which may be life threatening. In these cases Piperacillin + Tazobactam, should be discontinued.
- Caution should be exercised as therapy with Piperacillin + Tazobactam may result in the emergence of resistant organisms, which might cause super-infections.
- Bleeding manifestations may occur in some patients receiving ß-lactam antibiotics. These reactions sometimes may be 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.
- Periodic assessment of a full blood count should be performed as leukopenia and neutropenia may occur, especially during prolonged therapy.
- Caution should be exercised 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 sodium, therefore, caution should be taken for patients on a controlled sodium diet.
- Hypokalemia 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.
- ***Laboratory Tests***
- As with other penicillins, non-enzymatic methods of measuring urinary glucose may lead to false-positive results. 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.
- The direct Coombs test may be positive.

Pregnancy
There are no adequate and well-controlled studies in pregnant women. Piperacillin and Tazobactam cross the placenta and should only be used during pregnancy if clearly indicated.

Nursing mothers
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.

Drug Interactions
Non-depolarising muscle relaxants
Concomitant administration of Piperacillin with vecuronium results 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 relax ants 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
Concomitant administration of 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.

OVERDOSAGE
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 hemodialysis.

HOW SUPPLIED
Veritaz (Piperacillin + Tazobactam) IV Powder for Injection 2.25g is available in pack of 1 vial with 10mL sterile water for injection.

Veritaz (Piperacillin + Tazobactam) IV Powder for Injection 4.5g is available in pack of 1 vial with 20mL sterile water for injection.

STORAGE
Store below 25°C.
Protect from heat, light and moisture.
Reconstituted solution can be stored at 25°C for 24 hours and 2-8°C for 48 hours.

The expiration date refers to the product correctly stored at the required conditions.

Keep out of reach of children.

To be sold on prescription of a registered medical practitioner only.

Please read the contents carefully before use.
This package insert is continually updated from time to time.

Manufactured by:
Stallion Pharmaceuticals (Pvt.) Ltd.
581-Sundar Industrial Estate, Lahore, Pakistan.

Manufactured for :
Indus Pharma (Pvt.) Ltd.
65/27, Korangi Industrial Area,
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