PENCITAL™ *Injection*

(Piperacillin + Tazobactam)

For intravenous use only

QUALITATIVE AND QUANTITATIVE COMPOSITION

PENCITAL™ 2.25g Injection
Each vial contains:
Piperacillin (as Piperacillin Sodium) MS.....2g
Tazobactam (as Tazobactam Sodium) MS.....0.25g
Sodium Content: 103mg (approx.)

PENCITAL™ 4.5g Injection
Each vial contains:
Piperacillin (as Piperacillin Sodium) MS.....4g
Tazobactam (as Tazobactam Sodium) MS.....0.50g
Sodium content: 206mg (approx.)

PHARMACEUTICAL FORM

Powder for Solution for Infusion

CLINICAL PARTICULARS

THERAPEUTIC INDICATIONS:
Adults and adolescents:

- Severe pneumonia including hospital-acquired and ventilator-associated pneumonia.
- Complicated urinary tract infections (including pyelonephritis).
- Postpartum endometritis or pelvic inflammatory disease caused by β-lactamase producing isolates of *Escherichia coli*.
- Complicated intra-abdominal infections.
- Complicated skin and soft tissue infections (including diabetic foot infections).

Treatment of patients with bacteremia that occurs in association with, or is suspected to be associated with, any of the infections listed above.
PENCITAL™ may be used in the management of neutropenic patients with fever suspected to be due to a bacterial infection.
Note: Use for bacteremia due to extended-spectrum-beta-lactamase (ESBL) producing *E. coli* and *K. pneumoniae* (ceftriaxone non-susceptible), is not recommended in adult patients.
Paediatrics:

- Complicated intra-abdominal infections in children 2 to 12 years of age; including appendicitis and/or peritonitis in children 2 months of age and older.
- Hospital acquired/nosocomial pneumonia in children 2 months of age and older.
- 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 anti-bacterial agents.

POSOLOGY AND METHOD OF ADMINISTRATION:
Posology: The dose and frequency of PENCITAL™ depends on the severity and localization of the infection and expected pathogens.
Adult and adolescent patients: ***Infections:*** Usual dose is 4g piperacillin / 0.5g 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 6 hours. This regimen may also be applicable to treat patients with other indicated infections when particularly severe.
Recommended dose for adults and adolescents by indication or condition:

- Severe pneumonia, neutropenic adults with fever suspected to be due to a bacterial infection: 4g/0.5g every 6 hours.
- Complicated urinary tract infections (including pyelonephritis), complicated intra-abdominal infections, skin and soft tissue infections (including diabetic foot infections): 4g/0.5g every 8 hours.

Patients with renal impairment: Intravenous dose should be adjusted to the degree of actual renal impairment as follows (patient must be monitored closely for signs of substance toxicity; dose and interval should be adjusted accordingly):

- **CrCl (ml/min) > 40:** No dose adjustment necessary.
- **CrCl (ml/min) 20-40:** ***Maximum dose suggested:*** 4g/0.5g every 8 hours.
- **CrCl (ml/min) < 20:*Maximum dose suggested:*** 4g/0.5g every 12 hours.

For patients on haemodialysis, one additional dose of piperacillin/tazobactam 2g/0.25g should be administered following each dialysis period, because haemodialysis removes 30%-50% of piperacillin in 4 hours. ***Patients with 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 40ml/min.
Paediatric population: ***Infections:***

- Neutropenic children (2 to 12 years of age) with suspected fever due to a bacterial infection: 90mg/kg i.e., 80mg piperacillin/10mg tazobactam per kg body weight every 6 hours.
- Complicated intra-abdominal infections in children 2-12 years of age; including appendicitis and/or peritonitis in children older than 9 months of age: 112.5mg/kg i.e., 100mg piperacillin/12.5mg tazobactam per kg body weight every 8 hours.
- Appendicitis and/or peritonitis in children 2 months to 9 months of age: 90mg/kg i.e., 80mg piperacillin/10mg tazobactam per kg body weight every 8 hours.
- Nosocomial pneumonia in children older than 9 months of age: 112.5mg/kg i.e., 100mg piperacillin/12.5mg tazobactam per kg body weight every 6 hours.
- Nosocomial pneumonia in children 2 months to 9 months of age: 90mg/kg i.e., 80mg piperacillin/10mg tazobactam per kg body weight every 6 hours.
- Do not exceed the maximum 4g/0.5g per dose over 30mins.

Patients with 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):

- **CrCl (ml/min) > 50:** No dose adjustment needed.
- **CrCl (ml/min) ≤50:** 70mg piperacillin / 8.75mg tazobactam / kg every 8 hours.

For children on haemodialysis, one additional dose of 40mg piperacillin/5mg tazobactam/kg should be administered following each dialysis period.
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: Intravenous infusion (over 30 minutes).

CONTRAINDICATIONS:

- Hypersensitivity to the active substances or to any other penicillin-antibacterial agent.
- 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:

- 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 are known to occur in patients receiving therapy with penicillins, including piperacillin/tazobactam.
- May cause severe cutaneous adverse reactions, such as Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms, and acute generalized exanthematous pustulosis. Monitor closely and discontinue if lesions progress.
- Antibiotic-induced pseudomembranous colitis may be manifested by severe, persistent diarrhoea which may be life-threatening. 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.
- Cases of haemophagocytic lymphohistiocytosis (HLH) are known to be reported in paediatric and adult patients treated with piperacillin/tazobactam. Signs and symptoms of HLH may include fever, rash, lymphadenopathy, hepatosplenomegaly and cytopenia. If HLH is suspected, discontinue piperacillin/tazobactam immediately and institute appropriate management.
- 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. If bleeding manifestations occur, the antibiotic should be discontinued.
- Leukopenia and neutropenia may occur, during prolonged therapy; periodic assessment of haematopoietic function should be performed.
- Neurological complications e.g. convulsions (seizures) may occur when high doses are administered, especially in patients with impaired renal function.

Sodium Content:
PENCITAL™ 4.5g: contains 206mg sodium per vial, equivalent to 10.3% of the WHO recommended maximum daily intake of 2g sodium for an adult.
PENCITAL™ 2.25g: contains 103mg sodium per vial, equivalent to 5.1% of the WHO recommended maximum daily intake of 2g sodium for an adult. This should be taken into consideration for patients who are 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.
Renal Impairment: Due to its potential nephrotoxicity, piperacillin/tazobactam should be used with care in patients with renal impairment or in haemodialysis patients. Intravenous dosages and administration intervals should be adjusted to the degree of renal function impairment.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION:
Non-depolarizing muscle relaxants: Piperacillin when used concomitantly with vecuronium has been implicated in the prolongation of the neuromuscular blockade of vecuronium. **Anticoagulants:** Monitor coagulation parameters in patients receiving piperacillin/tazobactam and heparin or oral anticoagulants. **Methotrexate:** Piperacillin may reduce the excretion of methotrexate; therefore, serum levels of methotrexate should be monitored. **Probenecid:** Peak plasma concentrations of either substance are unaffected. **Aminoglycosides:** Piperacillin, either alone or with tazobactam, is not known to significantly alter the pharmacokinetics of tobramycin in subjects with normal renal function and with mild or moderate renal impairment. **Vancomycin:** Co-administration may increase the incidence of acute kidney injury. Monitor kidney function. **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. The direct Coombs test may be positive. Positive test results for the assays listed above in patients receiving piperacillin/tazobactam should be confirmed by other diagnostic methods.

PREGNANCY AND LACTATION:
Pregnancy: Piperacillin / tazobactam should only be used during pregnancy if clearly indicated, i.e. only if the expected benefit outweighs the possible risks to the pregnant woman and foetus.
Breast-feeding: Piperacillin is excreted in low concentrations in human milk. Women who are breast-feeding should be treated only if the expected benefit outweighs the possible risks to the woman and child.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES: No studies on the effect on the ability to drive and use machines have been performed.

UNDESIRABLE EFFECTS:

- Most commonly reported adverse reaction is diarrhoea.
- Among the most serious adverse reactions pseudo-membranous colitis and toxic epidermal necrolysis are known to occur.
- The frequencies for pancytopenia, anaphylactic shock and Stevens-Johnson syndrome cannot be estimated from the currently available data.
- Piperacillin therapy has been associated with an increased incidence of fever and rash in cystic fibrosis patients.
- Beta-lactam antibiotics, including piperacillin/tazobactam, may lead to manifestations of encephalopathy and convulsions.

Common: Candida infection, thrombocytopenia, anemia, insomnia, headache, abdominal pain, vomiting, constipation, nausea, dyspepsia, rash, pruritus, pyrexia, injection site reaction, 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. **Uncommon:** Leukopenia, hypokalaemia, seizure, hypotension, phlebitis, thrombophlebitis, flushing, erythema multiforme, urticaria, rash maculopapular, arthralgia, myalgia, chills, blood bilirubin increased, blood glucose decreased, prothrombin time prolonged. **Rare:** Pseudomembranous colitis, agranulocytosis, epistaxis, stomatitis, toxic epidermal necrolysis. **Frequency Not Known:** Pancytopenia, neutropenia, haemolytic

anaemia, thrombocytosis, eosinophilia, anaphylactoid shock, anaphylactic shock, anaphylactoid reaction, anaphylactic reaction, hypersensitivity, delirium, eosinophilic pneumonia, hepatitis, jaundice, Stevens-Johnson syndrome, dermatitis exfoliative, drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalised exanthematous pustulosis (AGEP), dermatitis bullous, purpura, renal failure, tubulointerstitial nephritis, bleeding time prolonged, gamma-glutamyltransferase increased.

OVERDOSE:
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.

PHARMACOLOGICAL PROPERTIES

PHARMACODYNAMIC PROPERTIES:
Pharmacotherapeutic group: Antibacterial for systemic use, combinations of penicillins incl. beta-lactamase inhibitors; **ATC code:** J01C R05
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 beta-lactamase-producing bacteria that have acquired resistance to piperacillin alone.
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 beta-lactamases (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.

Breakpoints: EUCAST Clinical MIC Breakpoints for piperacillin/tazobactam:

Pathogen	Species-related breakpoints (S≤/R>), mg/L of piperacillin
Enterobacterales (formerly *Enterobacteriaceae*)	8/16
Pseudomonas aeruginosa	<0.001/16[1]
Staphylococcus species	-2
Enterococcus species	-3
Streptococcus Groups A, B, C, and G	-4
Streptococcus pneumoniae	-5
Viridans group streptococci	-6
Haemophilus influenzae	0.25/0.25
Moraxella catarrhalis	-7
Gram-positive anaerobes (except *Clostridioides difficile*)	8/16
Gram-negative anaerobes	8/16
Non-species related (PK/PD) breakpoints	4/16

[1]For several agents, EUCAST has introduced breakpoints which categorise wild-type organisms (organisms without phenotypically detectable acquired resistance mechanisms to the agent) as "Susceptible, increased exposure (I)" instead of "Susceptible, standard dosing regimen (S)". Susceptible breakpoints for these organism-agent combinations are listed as arbitrary, "off scale" breakpoints of S ≤ 0.001mg/L.
[2]Most staphylococci are penicillinase producers, and some are methicillin resistant. Either mechanism renders them resistant to benzylpenicillin, phenoxymethylpenicillin, ampicillin, amoxicillin, piperacillin and ticarcillin. Staphylococci that test susceptible to benzylpenicillin and cefoxitin can be reported susceptible to all penicillins. Staphylococci that test resistant to benzylpenicillin but susceptible to cefoxitin are susceptible to β-lactamase inhibitor combinations, the isoxazolylpenicillins (oxacillin, cloxacillin, dicloxacillin and flucloxacillin) and nafcillin. For agents given orally, care to achieve sufficient exposure at the site of the infection should be exercised. Staphylococci that test resistant to cefoxitin are resistant to all penicillins. Ampicillin susceptible *S. saprophyticus* are *mecA*-negative and susceptible to ampicillin, amoxicillin and piperacillin (without or with a beta-lactamase inhibitor).
[3]Susceptibility to ampicillin, amoxicillin and piperacillin (with and without beta-lactamase inhibitor) can be inferred from ampicillin. Ampicillin resistance is uncommon in *E. faecalis* (confirm with MIC) but common in *E. faecium*.
[4]The susceptibility of Streptococcus Groups A, B, C and G to penicillins is inferred from the benzylpenicillin susceptibility with the exception of phenoxymethylpenicillin and isoxazolylpenicillins for *Streptococcus* Group B. *Streptococcus* groups A, B, C and G do not produce beta-lactamase. The addition of a beta-lactamase inhibitor does not add clinical benefit.
[5]The oxacillin 1µg disk screen test or a benzylpenicillin MIC test shall be used to exclude beta-lactam resistance mechanisms. When the screen is negative (oxacillin inhibition zone ≥20mm, or benzylpenicillin MIC ≤.0.06mg/L) all beta-lactam agents for which clinical breakpoints are available, including those with "Note" can be reported susceptible without further testing, except for cefaclor, which if reported, should be reported as "susceptible, increased exposure" (I). Streptococcus pneumoniae do not produce beta-lactamase. The addition of a beta-lactamase inhibitor does not add clinical benefit. Susceptibility inferred from ampicillin (MIC or zone diameter).
[6]For isolates susceptible to benzylpenicillin, susceptibility can be inferred from benzylpenicillin or ampicillin. For isolates resistant to benzylpenicillin, susceptibility is inferred from ampicillin.
[7]Susceptibility can be inferred from amoxicillin-clavulanic acid.

Susceptibility: ***Groupings of relevant species according to piperacillin/tazobactam susceptibility:***
COMMONLY SUSCEPTIBLE SPECIES: Aerobic Gram-positive micro-organisms: *Enterococcus faecalis* (ampicillin or penicillin-susceptible isolates only), *Listeria monocytogenes*, *Staphylococcus aureus* (methicillin-susceptible isolates only), *Staphylococcus species, coagulase negative (methicillin-susceptible isolates only)*, *Streptococcus agalactiae* (Group B streptococci)†, *Streptococcus pyogenes* (Group A streptococci)†. ***Aerobic Gram-negative micro-organisms:*** *Citrobacter koseri, Haemophilus influenzae, Moraxella catarrhalis, Proteus mirabilis.* ***Anaerobic Gram-positive micro-organisms:*** *Clostridium species*, *Eubacterium species*, *Anaerobic gram-positive cocci*††. ***Anaerobic Gram-negative micro-organisms:*** *Bacteroides fragilis* group, *Fusobacterium* species, *Porphyromonas* species, *Prevotella* species.
SPECIES FOR WHICH ACQUIRED RESISTANCE MAY BE A PROBLEM: Aerobic Gram-positive micro-organisms: *Enterococcus faecium*, *Streptococcus pneumoniae*†, *Streptococcus viridans group*†. ***Aerobic Gram-negative micro-organisms:*** *Acinetobacter baumannii, Citrobacter freundii, Enterobacter species, Escherichia coli, Klebsiella pneumoniae. Morganella morganii, Proteus vulgaris, Providencia* spp., *Pseudomonas aeruginosa, Serratia species.*
INHERENTLY RESISTANT ORGANISMS: Aerobic Gram-positive micro-organisms: *Corynebacterium jeikeium.* ***Aerobic Gram-negative micro-organisms:*** *Burkholderia cepacia, Legionella* species, *Ochrobactrum anthropi, Stenotrophomonas maltophilia.* ***Other micro-organisms:*** *Chlamydophila pneumoniae, Mycoplasma pneumoniae.*
†*Streptococci* are not β-lactamase producing bacteria; resistance in these organisms is due to alterations in penicillin-binding proteins (PBPs) and, therefore, susceptible isolates are susceptible to piperacillin alone.
Penicillin resistance has not been reported in *S. pyogenes.* ††Including *Anaerococcus, Finegoldia, Parvimonas, Peptoniphilus, and Peptostreptococcus* spp.

PHARMACOKINETIC PROPERTIES:
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 tissues 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 that has been found to be microbiologically inactive. **Elimination:** Piperacillin and tazobactam are eliminated via the kidney by glomerular filtration and tubular secretion. Piperacillin is excreted rapidly as unchanged substance, 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 substance and the remainder as the single metabolite. Piperacillin, tazobactam, and desethyl piperacillin are also secreted into the bile.

Direction for Reconstitution: 2.25g and 4.5g vials should be reconstituted with 10mL and 20mL solvent respectively. Swirl until dissolved.

SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING:

- Vial is a single dose and discard any portion of the contents remaining after use.
- Standard aseptic techniques should be used for solution preparation and administration.
- The solution should be shaken before use.
- Reconstituted solution should be used immediately after reconstitution.
- The solution should be inspected visually for particles and discolouration prior to administration.
- The solution should only be used if the solution is clear and free from particles.

Compatible Reconstitution Diluents:

- 0.9% sodium chloride for injection.
- Dextrose 5%.
- Bacteriostatic water/parabens.
- Bacteriostatic water/benzyl alcohol.
- Sterile water for injection.
- Bacteriostatic saline/parabens.
- Bacteriostatic saline/benzyl alcohol.

Reconstituted solutions should be further diluted (recommended volume per dose of 50mL to 150mL) in a compatible intravenous solution. 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 Solutions:

- 0.9% sodium chloride for injection.
- Dextran 6% in saline.
- Lactated Ringer's Solution.
- Sterile water for injection*.
- Dextrose 5%.

Maximum recommended volume per dose of sterile water for injection is 50mL.

SHELF LIFE

See expiry on the pack.

AVAILABILITY

PENCITAL™ 2.25g injection is available in a pack of 1 x 2.25g vial + 1 x 10ml Sterile water for injection.
PENCITAL™ 4.5g injection is available in a pack of 1 x 4.5g vial + 2 x 10ml Sterile water for injection.

INSTRUCTIONS

Dosage: As directed by the physician.
To be sold on the prescription of a registered medical practitioner only.
Keep out of reach of children.
Avoid exposure to heat, light and humidity.
Do not store over 25ºC.
Do not freeze the reconstituted solution.

پینسیٹال™ انجکشن
(پیپراسلین + ٹیزوبیکٹم)

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
ہدایات: صرف رجسٹرڈ ڈاکٹر کے نسخے کے مطابق فروخت کریں۔
بچوں کی پہنچ سے دور رکھیں۔
دوا کو گرمی، روشنی اور نمی سے محفوظ رکھیں۔
درجہ حرارت ۲۵ ڈگری سینٹی گریڈ سے زیادہ نہ ہو۔
تیار شدہ انجکشن کو منجمد ہونے سے محفوظ رکھیں۔

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

Manufactured for:
Healthtek (Pvt.) Limited
Plot No. 14, Sector 19, Korangi Industrial Area, Karachi - Pakistan

An associate company of:
SAMI Pharmaceuticals (Pvt.) Ltd.
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R.N-02/NA/11/2022