Bosch

For Medical Professional only

TANZO®

INJECTION

2.25g, 4.5g

(Piperacillin + Tazobactam U.S.P.)

(Product Specs. : U.S.P.)

ٹینزو انجکشن

(پیپراسیلین + ٹیزوبیکٹم یو۔ایس۔پی)

DESCRIPTION:

Piperacillin and Tazobactam (Tanzo) for Injection is antibacterial combination products consisting of the semisynthetic antibacterial piperacillin sodium and the β-lactamase inhibitor tazobactam sodium for intravenous administration.

Piperacillin sodium is derived from D(-)-α-aminobenzyl-penicillin. The chemical name of piperacillin sodium is sodium (2S,5R,6R) -6-[(R)-2-(4-ethyl-2,3-dioxo-1-piperazinecarboxamido)-2-phenylacetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2- carboxylate. The chemical formula is $C_{23}H_{26}N_5NaO_7S$ and the molecular weight is 539.5.

Tazobactam sodium, a derivative of the penicillin nucleus, is a penicillanic acid sulfone. Its chemical name is sodium (2S,3S,5R)-3-methyl-7-oxo-3-(1H-1,2,3-triazol-1-yl-methyl)-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate-4,4-dioxide. The chemical formula is $C_{10}H_{11}N_4NaO_5S$ and the molecular weight is 322.3.

COMPOSITION:

Each Tanzo 2.25g vial contains:

Piperacillin Sodium U.S.P. eq. to Piperacillin....2gm

Tazobactam Sodium M.S. eq. to Tazobactam...250mg

(Product Specs.: U.S.P.)

Each Tanzo 4.5g vial contains:

Piperacillin Sodium U.S.P. eq. to Piperacillin....4gm

Tazobactam Sodium M.S. eq. to Tazobactam...500mg

(Product Specs.: U.S.P.)

PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Antibacterials 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 .

MICROBIOLOGY:

Gram-positive bacteria:

- Enterococcus faecalis
- Listeria monocytogenes
- Staphylococcus aureus,
- Staphylococcus species,
- Streptococcus pyogenes
- Streptococci
- Enterococcus faecium
- Streptococcus pneumonia
- Streptococcus viridans group
- Corynebacterium jeikeium

Gram-negative bacteria:

- Citrobacter koseri
- Haemophilus influenza
- Moraxella catarrhalis
- Proteus mirabilis
- Acinetobacter baumannii
- Burkholderia cepacia
- Citrobacter freundii
- Enterobacter species
- Escherichia coli
- Klebsiella pneumonia
- Morganella morganii
- Proteus vulgaris
- Providencia ssp.
- Pseudomonas aeruginosa

- Serratia species
- Legionella species
- Stenotrophomonas maltophilia

Anaerobic bacteria:
- Clostridium species
- Eubacterium species
- Peptostreptococcus species
- Bacteroides fragilis group
- Fusobacterium species
- Porphyromonas species
- Prevotella species

Other microorganisms
- Chlamydophilia pneumonia
- Mycoplasma pneumonia

PHARMACOKINETIC PROPERTIES

Absorption

Peak plasma concentrations of piperacillin and tazobactam are attained immediately after completion of an intravenous infusion of TANZO. Piperacillin plasma concentrations, following a 30-minute infusion of TANZO, were similar to those attained when equivalent doses of piperacillin were administered alone. Steady-state plasma concentrations of piperacillin and tazobactam were similar to those attained after the first dose due to the short half-lives of piperacillin and tazobactam.

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

Metabolism

Piperacillin is metabolized to a minor microbiologically active desethyl metabolite. Tazobactam is metabolized to a single metabolite that has been found to be micro-biologically inactive.

Elimination

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. Piperacillin and tazobactam are eliminated by the kidney via 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.

SPECIFIC POPULATIONS

Renal Impairment

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 20 ml/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.

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.

Pediatrics

The clearance of both compounds is slower in the younger patients compared to older children and adults. In a population PK analysis, estimated clearance for 9 month-old to 12 year-old patients was comparable to adults, with a population mean (SE) value of 5.64 (0.34) mL/min/kg. The piperacillin clearance estimate is 80% of this value for pediatric patients 2 - 9 months old. In patients younger than 2 months of age, clearance of piperacillin is slower compared to older children; however, it is not adequately characterized for dosing recommendations. The population mean (SE) for piperacillin volume of distribution is 0.243 (0.011) L/kg and is independent of age. The safety and effectiveness of TANZO have not been established in pediatric patients less than 2 months of age.

Elderly Patient

Mean half-life for piperacilln and tazobactam was 32% and 55% higher, respectively, in the elderly compared to the younger subjects. This difference may be due to age-related changes in creatinine clearance.

THERAPEUTIC INDICATIONS:

Adults
- Intra-abdominal infections
- Nosocomial pneumonia
- Skin and skin structure infections
- Female pelvic infections
- Community-acquired pneumonia

Pediatric 2 months of age and older.
- Intra-abdominal infections
- Nosocomial pneumonia

DOSAGE AND ADMINISTRATION

Adult Patients

Other than Nosocomial Pneumonia.

The usual total daily dosage of TANZO for adult patients with indications other than nosocomial pneumonia is 3.375 g every six hours [totaling 13.5 g (12.0 g piperacillin/1.5 g tazobactam)], to be

administered by intravenous infusion over 30 minutes.

Nosocomial Pneumonia
Initial presumptive treatment of adult patients with nosocomial pneumonia should start with TANZO at a dosage of 4.5 g every six hours plus an aminoglycoside, [totaling 18.0 g (16.0 g piperacillin/2.0 g tazobactam)], administered by intravenous infusion over 30 minutes. Treatment with the aminoglycoside should be continued in patients from whom P. aeruginosa is isolated.

Renal Impairment
In adult patients with renal impairment (creatinine clearance ≤ 40 mL/min) and dialysis patients (hemodialysis and CAPD), the intravenous dose of TANZO should be reduced based on the degree of renal impairment. The recommended daily dosage of TANZO for patients with renal impairment administered by intravenous infusion over 30 minutes is described:

Creatinine clearance, mL/min	All Indications (except nosocomial pneumonia)	Nosocomial Pneumonia
Greater than 40 mL/min	3.375 every 6 hours	4.5 every 6 hours
20 to 40 mL/min*	2.25 every 6 hours	3.375 every 6 hours
Less than 20 mL/min*	2.25 every 8 hours	2.25 every 6 hours
Hemodialysis**	2.25 every 12 hours	2.25 every 8 hours
CAPD	2.25 every 12 hours	2.25 every 8 hours

For patients on hemodialysis, the maximum dose is 2.25 g every twelve hours for all indications other than nosocomial pneumonia and 2.25 g every eight hours for nosocomial pneumonia. Since hemodialysis removes 30% to 40% of the administered dose, an additional dose of 0.75 g TANZO (0.67 g piperacillin/0.08 g tazobactam) should be administered following each dialysis period on hemodialysis days. No additional dosage of TANZO is necessary for CAPD patients.

Pediatric Patients
Appendicitis/Peritonitis or Nosocomial Pneumonia
The recommended dosage for pediatric patients with appendicitis and/or peritonitis or nosocomial pneumonia aged 2 months of age and older, weighing up to 40 kg, and with normal renal function, is described:

Age	Appendicitis and/or Peritonitis	Nosocomial Pneumonia
2 months to 9 months	90 mg/kg (80 mg piperacillin/10 mg tazobactam) every 8 (eight) hours	90 mg/kg (80 mg piperacillin/10 mg tazobactam) every 6 (six) hours
Older than 9 months of age	112.5 mg/kg (100 mg piperacillin/12.5 mg tazobactam) every 8 (eight) hours	112.5 mg/kg (100 mg piperacillin/12.5 mg tazobactam) every 6 (six) hours

Pediatric patients weighing over 40 kg and with normal renal function should receive the adult dose. Dosage of TANZO in pediatric patients with renal impairment has not been determined.

METHOD OF ADMINISTRATION:
TANZO is administered by intravenous infusion (over 30 minutes).

CONTRAINDICATIONS:
The use of TANZO is contraindicated in patients with a history of allergic reactions to any of the penicillins and/or cephalosporins or ß-lactamase inhibitors.

WARNINGS AND PRECAUTIONS:
Hypersensitivity Adverse Reactions:
Serious and occasionally fatal hypersensitivity anaphylactic reactions (including shock) have been reported in patients receiving therapy with TANZO. These reactions are more likely to occur in individuals with a history of penicillin, cephalosporin, or carbapenem hypersensitivity or a history of sensitivity to multiple allergens. If an allergic reaction occurs, TANZO should be discontinued and appropriate therapy instituted.

Severe Cutaneous Adverse Reactions
TANZO 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. If patients develop a skin rash they should be monitored closely and TANZO discontinued if lesions progress.

Hematologic Adverse Reactions
Bleeding manifestations have occurred in some patients receiving beta-lactam drugs, including piperacillin. If bleeding manifestations occur, TANZO should be discontinued and appropriate therapy instituted. The leukopenia/neutropenia associated with TANZO administration appears to be reversible and most frequently associated with prolonged administration.

Central Nervous System Adverse Reactions
As with other penicillins, TANZO may cause neuromuscular excitability or seizures. Closely monitor patients with renal impairment or seizure disorders for signs and symptoms of neuromuscular excitability or seizures.

Nephrotoxicity in Critically ill Patients
The use of TANZO was found to be an independent risk factor for renal failure and was associated with delayed recovery of renal function as compared to other beta-lactam antibacterial drugs in a randomized, multicenter, controlled trial in critically ill patients. Combined use of piperacillin/tazobactam and vancomycin may be associated with an increased incidence of acute kidney injury.

Electrolyte Effects
TANZO contains a total of 2.84 mEq (65 mg) of Na+ (sodium) 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.

Clostridioides difficile-Associated Diarrhea:
Treatment with antibacterial agents alters the normal flora of the

colon leading to overgrowth of C. difficile. CDAD must be considered in all patients who present with diarrhea following antibacterial drug use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

DRUG INTERACTIONS

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 mechanism 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.

Anticoagulant:
During simultaneous administration of heparin, oral anticoagulants and other substances, which 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. Serum levels of methotrexate should be monitored in patients to avoid substance toxicity.

Probenecid:
Concurrent administration of probenecid and piperacillin/tazobactam produced a longer half-life and lower renal clearance for both piperacillin and tazobactam. However, peak plasma concentrations of either drug are unaffected.

Aminoglycosides
The inactivation of tobramycin and gentamicin by piperacillin has been demonstrated in patients with severe renal impairment

Vancomycin:
Increased incidence of acute kidney injury in patients concomitantly administered piperacillin/tazobactam and vancomycin as compared to vancomycin alone. Monitor kidney function in patients concomitantly administered with piperacillin/tazobactam and vancomycin.

Effects on Laboratory Tests
As with other penicillins, the administration of Piperacillin/Tazobactam (TANZO) may result in a false positive reaction for glucose in the urine using a copper-reduction method. It is recommended that glucose tests based on enzymatic glucose oxidase reactions be used.

ADVERSE EFFECTS:
The following adverse effects have been observed with the Piperacillin/Tazobactam therapy:

Very common: Diarrhoea.

Common: candida infection, thrombocytopenia, anaemia, insomnia, headache, abdominal pain, vomiting, constipation, nausea, dyspepsia, rash, pruritus, pyrexia, injection site reaction.

Uncommon: leucopenia, hypokalaemia, seizure hypotension, phlebitis, thrombophlebitis, flushing, erythema multiforme, urticaria, rash maculopapular, Arthralgia, myalgia, Chills.

Rare: Pseudomembranous colitis, agranulocytosis, epistaxis, stomatitis, toxic epidermal necrolysis.

Not Known: pancytopenia, neutropenia, haemolytic anaemia, thrombocytosis, eosinophilia, anaphylactic shock, anaphylactic shock, anaphylactoid reaction, anaphylactic reaction, hypersensitivity, hypersensitivity, delirium eosinophilic pneumonia, hepatitis, jaundice, Stevens-Johnson syndrome , dermatitis exfoliative, drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalized exanthematous pustulosis (AGEP), dermatitis bullous, purpura, renal failure, tubulointerstitial nephritis.

USE IN PREGNANCY AND LACTATION:

Pregnancy:
Piperacillin and tazobactam cross the placenta. It should only be used during pregnancy if clearly indicated, only if the expected benefit outweighs the possible risks to the pregnant woman and foetus.

Lactation:
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.

OVER DOSAGE:
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. In the event of an overdose, piperacillin and tazobactam treatment should be discontinued. No specific antidote is known. Treatment should be supportive and symptomatic. Excessive serum concentrations of either piperacillin or tazobactam may be reduced by haemodialysis

Special precautions for disposal and other handling
The reconstitution and 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.

RECONSTITUTION
Each vial of TANZO 2.25g should be reconstituted with 10ml and 4.5g with 20ml of given diluent. Reconstitution generally occurs within 5 to 10 minutes.

Compatible solvents for reconstitution/dilution:
- Sterile water for injection
- Sodium chloride 9 mg/ml (0.9%) solution for injection
- Glucose solution (5%)

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

The reconstituted solutions can be further diluted to the desired volume (e.g. 50 ml to 150 ml) with one of the following compatible solvents:
- Glucose solution (5%)
- Sodium chloride (0.9%) solution for injection
- Dextran 6% in 0.9% (9 mg/ml) sodium chloride
- Lactated Ringers injection
- Hartmann's solution
- Ringer's acetate
- Ringer's acetate/malate

INCOMPATIBILITIES
This medicinal product must not be mixed with other medicinal products. Whenever piperacillin/tazobactam is used concurrently with another antibiotic (e.g. aminoglycosides), the substances must be administered separately. Due to chemical instability it should not be used in solutions containing only sodium bicarbonate. Tanzo should not be added to blood products or albumin hydrolysates.

SHELF LIFE
Unopened vial: 3 years

PRESENTATION:
TANZO 2.25 g: Pack of single vial with 10 ml diluent
TANZO 4.5 g: Pack of single vial with 2x10 ml diluent

DIRECTIONS:
- Protect from heat, sunlight and moisture.
- Store at controlled room temperature (15ºC-25ºC).
- Vials should be used immediately after reconstitution.
- Discard any unused portion after 24 hours if stored at room temperature (20°C to 25°C) or after 48 hours if stored at refrigerated temperature (2°C to 8°C). Vials should not be frozen after reconstitution.
- The Expiration date refers to the product correctly stored at the required conditon.
- Keep out of reach of children.
- Patients and healthcare professionals can also report suspected adverse drug reaction at ade@bosch-pharma.com.
- To be sold on the prescription of registered medical practitioner only.

ہدایات :-

صرف وریدی استعمال کے لئے۔
ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
دھوپ، گرمی اور نمی سے محفوظ کمرے کے درجہ حرارت ۱۵۔۲۵ ڈگری سینٹی گریڈ پر رکھیں۔
محلول بنانے کے بعد: ریفریجریٹر میں ۲۔۸ ڈگری سینٹی گریڈ پر رکھیں اور ۴۸ گھنٹے کے اندر استعمال کرلیں۔
منجمد ہونے سے بچائیں۔
بچوں کی پہنچ سے دُور رکھیں۔
صرف مستند ڈاکٹر کے نسخے پر فروخت کے لئے۔

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ISO 9001:2015 Certified Company