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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, **PIPTALON** should be discontinued and appropriate therapy instituted. As with other penicillins, patients may experience neuromuscular excitability or convulsions if higher than recommended doses are given intravenously (particularly in the presence of renal failure).

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.

Piperacillin/Tazobactam could produce the same phenomenon if given along with vecuronium. Due to their similar mechanism of action, it is expected that the neuromuscular blockade produced by any of the non-depolarizing muscle relaxants could be prolonged in the presence of Piperacillin.

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.

Renal Impairment: Please refer under DOSAGE AND ADMINISTRATION.

Hepatic impairment: No dosage adjustment of Piperacillin/ Tazobactam is necessary in patients with hepatic impairment.

Pregnancy: There are no adequate and well-controlled studies with the Piperacillin/Tazobactam combination or with Piperacillin or Tazobactam alone in pregnant women. Because animal reproduction studies are not always predictive of the human response, this drug should be used during pregnancy only if clearly needed.

Lactation: Piperacillin is excreted in low concentrations in human milk; Tazobactam concentrations in human milk have not been studied. Caution should be exercised when is administered to a nursing woman.

Paediatric Use: Safety and efficacy in paediatric patients less than 2 months of age have not been established. For data on renal impairment please refer under DOSAGE AND ADMINISTRATION. No data are available in case of pediatric patients with impaired hepatic function.

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. contains 64 mg (2.79 mEq) of sodium per gram of Piperacillin in the combination product. At the usual recommended doses, patients would receive between 768 and 1024 mg/day (33.5 and 44.6 mEq) of sodium. The geriatric population may respond with a blunted natriuresis to salt loading. This may be clinically important with regard to such diseases as congestive heart failure.

UNDESIRABLE EFFECTS

90% of the adverse events reported in clinical trials were mild-moderate in severity and transient in nature.

The common adverse events were:··

- Skin rashes (1.3%) including rash and pruritis
- Gastrointestinal (0.9%) including diarrhoea, nausea and vomiting
- Allergic reactions (0.5%)

OVERDOSAGE

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 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. Following a single 3.375 g dose of Piperacillin/Tazobactam, the percentage of the Piperacillin and Tazobactam dose removed by haemodialysis was approximately 31% and 39%, respectively.

INCOMPATIBILITY

should not be mixed with other drugs in a syringe or infusion bottle since compatibility has not been established. is not chemically stable in solutions that contain only sodium bicarbonate and solutions that significantly alter the pH.

Lactated ringer's solution is not compatible with should not be added to blood products or albumin hydrolysates. When concomitant therapy with aminoglycosides is indicated, and the aminoglycoside should be reconstituted and administered separately, due to the in vitro inactivation of the aminoglycoside by the penicillin.

Storage : Store in a cool, dry & dark place. (20ºC to 25ºC).

Reconstituted solutions:

Discard any unused portion after 24 hours if stored at room temperature or after 48 hours if refrigerated (2-8 degree C). Vials should not be frozen after reconstitution.

Mfd. by : Protech Telelinks
(A WHO-GMP Certified Co.)
Mauza Ogli, Suketi Road, Kala Amb,
District Sirmour (H.P.)173030

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℞

Piperacillin & Tazobactam Injection IP 4.5gm

PIPERAFORT®

पिपराफोर्ट

Composition :
Each vial contains :
Piperacillin Sodium (Sterile) IP
eq. to Anhydrous Piperacillin 4 gm
Tazobactam Sodium (Sterile) IP
eq. to Anhydrous Tazobactam 0.5 gm

DOSAGE FORM/S

Powder for reconstitution and I.V. use only.

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 II 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) The following in vitro data are available, **but their clinical significance is unknown.** At least 90% of the following microorganisms exhibit an in vitro minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for Piperacillin/Tazobactam. However, the safety and effectiveness of Piperacillin/Tazobactam in treating clinical infections due to these bacteria have not been established in adequate and well controlled clinical trials.

Aerobic and facultative Gram-positive microorganisms:

Enterococcus faecalis (ampicillin or penicillin-susceptible isolates only)

Staphylococcus epidermidis (excluding methicillin and oxacillin resistant isolates)

Streptococcus agalactiae

Streptococcus pneumoniae (penicillin-susceptible isolates only)

Streptococcus pyogenes

Viridans group streptococci

Aerobic and facultative Gram-negative microorganisms:

Citrobacter koseri

Moraxella catarrhalis

Morganella morganii

Neisseria gonorrhoeae

Proteus mirabilis

Proteus vulgaris

Serratia marcescens

Providencia stuartii

Providencia rettgeri

Salmonella enterica

Gram-positive anaerobes:

Clostridium perfringens

Gram-negative anaerobes:

Bacteroides distasonis

Prevotella melaninogenica

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 4.5 g Piperacillin/Tazobactam doses. The corresponding mean peak plasma concentrations of Tazobactam is 34 µg/ml. 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.

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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. The half-lives of Piperacillin and Tazobactam increase with decreasing creatinine clearance. The increase is two-fold and four-fold for Piperacillin and Tazobactam, respectively, at creatinine clearance of below 20ml/min compared to patients with normal 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. Plasma concentrations of Piperacillin and Tazobactam are prolonged in hepatically impaired patients. The half-life of Piperacillin and of Tazobactam increases by approximately 25% and 18%, respectively, in patients with hepatic cirrhosis compared to healthy subjects. However, dosage adjustments in patients with hepatic impairment are not necessary.

Paediatrics:

Piperacillin and Tazobactam pharmacokinetics were studied in paediatric patients 2 months of age and older. 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 paediatric 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 distribution volume is 0.243 (0.011) L/kg and is independent of age.

INDICATIONS

is indicated for treatment of the following systemic and/or local bacterial infections in which susceptible organisms have been detected or are suspected:

Adults and the Elderly

Lower respiratory tract infections

Urinary tract infections (complicated and uncomplicated)

Intra-abdominal infections including peritonitis and appendicitis complicated rupture or abscess

Skin and skin structure infections (complicated and uncomplicated)

Post-partum endometritis and pelvic infections

Polymicrobial infections

Bacterial septicaemia

Bacterial infections in neutropenic adults in combination with an aminoglycoside

Paediatrics

- Intra-abdominal infections including appendicitis complicated by rupture with peritonitis and/or abscess formation, biliary infections.
- Bacterial infections in neutropenic children in combination with an aminoglycoside.

Infections caused by Piperacillin-susceptible organisms, for which Piperacillin has been shown to be effective, are also amenable to Piperacillin/ Tazobactam treatment due to its Piperacillin content. The Tazobactam component of this combination product does not decrease the activity of the Piperacillin component against Piperacillin susceptible organisms. Therefore, the treatment of mixed infections caused by Piperacillin-susceptible organisms and Piperacillin-resistant, beta-lactamase producing organisms susceptible to Piperacillin /Tazobactam should not require the addition of another antibiotic. Piperacillin/Tazobactam is useful as presumptive therapy in the indicated conditions prior to the identification of causative organisms because of its broad spectrum of bactericidal activity against gram-positive and gram-negative aerobic and anaerobic organisms.

DOSAGE AND ADMINISTRATION

should be administered by intravenous infusion over 20- 30 minute

Adolescents, Adults and Elderly with normal renal function

Total daily dose of is 13.5g (12.0 g Piperacillin/1.5 g Tazobactam) in three to four equally divided doses. Initial presumptive treatment of patients with nosocomial pneumonia and febrile neutropenia should start with at a dosage of 4.5 g every six hours plus an aminoglycoside, totalling 18.0 g (16.0 g Piperacillin/2.0 g Tazobactam). Treatment with the aminoglycoside should be continued in patients from whom Pseudomonas aeruginosa is isolated. If Pseudomonas aeruginosa is not isolated, the aminoglycoside may be discontinued at the discretion of the treating physician.

Paediatrics

can be administered in paediatric patients above 2 months of age.

Intra-abdominal infections

- 2 months to 9 months of age: 80 mg Piperacillin/10 mg Tazobactam per kg q 8hr
- 9 months or older weighing upto 40 kg: 100mg Piperacillin/12.5 mg Tazobactam per kg q 8hr
- Weighing over 40 kg:- as per adult dose

Neutropenia

- <50 kg: 80 mg Piperacillin/10 mg Tazobactam per kg q 6 hr plus an aminoglycoside
- >50 kg: 4.5 g q 8 hr plus an aminoglycoside

Duration of Therapy

The usual duration of treatment is from seven to ten days. However, the recom mended duration of treatment of nosocomial pneumonia is 7 to 14 days. In all conditions, the duration of therapy should be guided by the severity of the infection and the patient's clinical and bacteriological progress.

Renal Insufficiency

In patients with renal insufficiency (creatinine clearance < 40 ml/min), the intravenous dose of should be adjusted to the degree of actual renal function impairment. In patients with nosocomial pneumonia receiving concomitant aminoglycoside therapy, the aminoglycoside dosage should be adjusted according to the recommendations of the manufacturer. The recommended daily doses of for patients with renal insufficiencies are as follows:

Adults

Recommended Dosing of PIPTALON in Patients with Normal Renal Function and Renal Insufficiency (As total grams Piperacillin/Tazobactam)

Renal Function (Creatinine Clearance, ml/min)	*All Indications (except nosocomial pneumonia)*	*Nosocomial Pneumonia*
>40 ml/min	3.375 q 6 h	4.5 q 6 h
20-40 ml/min *	2.25 q 6 h	3.375 q 6 h
<20 ml/min *	2.25 q 8 h	2.25 q 6 h
Haemodialysis **	2.25 q 12 h	2.25 q 8 h
CAPD	2.25 q 12 h	2.25 q 8 h
* Creatinine clearance for patients not receiving haemodialysis		
** 0.75 g should be administered following each haemodialysis session on haemodialysis days		

For patients on haemodialysis, 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 haemodialysis removes 30% to 40% of the administered dose, an additional dose of 0.75 g should be administered following each dialysis period on haemodialysis days. No additional dosage of is necessary for CAPD patients.

Paediatrics

Creatinine Clearance (ml/min)	Recommended Piperacillin / Tazobactam Dosage
≥40	No adjustment
20-39	90mg (80mg Piperacillin / 10mg Tazobactam) /kg q8H, not exceeding 13.5g/day
< 20	90mg (80mg Piperacillin / 10mg Tazobactam) /kg q12H, not exceeding 9g/day

For children weighing < 50kg on haemodialysis the recommended dose is 45mg (40mg Piperacillin /5mg Tazobactam) per kg every 8 hours.

The above dosage modifications are only an approximation. Each patient must be monitored closely for signs of drug toxicity. Drug dose and interval should be adjusted accordingly.

DIRECTIONS FOR RECONSTITUTION AND DILUTION FOR USE

Intravenous Administration

For conventional vials, reconstitute per gram of Piperacillin with 5 ml of a compatible reconstitution diluent 4.5 g with 20 ml. When swirled constantly, reconstitution generally occurs within 5 to 10 minutes. Use immediately after reconstitution. Discard any unused portion after 24 hours if stored at room temperature (20°C to 25°C [68°F to 77°F]), or after 48 hours if stored at refrigerated temperature (2°C to 8°C [36°F to 46°F]).

Compatible Reconstitution Diluents

0.9% Sodium Chloride for Injection

Sterile Water for Injection ‡

Dextrose 5%

Bacteriostatic Saline/Parabens

Bacteriostatic Water/Parabens

Bacteriostatic Saline/Benzyl Alcohol

Bacteriostatic Water/Benzyl Alcohol

Intravenous injection should be given over at least 3-5 minutes.

Reconstituted solution should be further diluted (recommended volume per dose of 50 ml to 150 ml) with a compatible intravenous diluent solution listed below. Administer by infusion over a period of at least 20-30 minutes. During the infusion it is desirable to discontinue the primary infusion solution.

Compatible Intravenous Diluent Solutions

0.9% Sodium Chloride for Injection

Sterile Water for Injection (Maximum recommended volume per dose of Sterile Water for Injection is 50 ml)

Dextrose 5%

Dextran 6% in Saline

CONTRAINDICATIONS

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 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 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.