

PROGEN PHARMACEUTICAL DISTRIBUTORS

**PIPERACILLIN + TAZOBACTAM**  
PROBITAZ IV

1 vial + 20ml Ampoule

**PIPERACILLIN  
TAZOBACTAM  
PROBITAZ IV**

**4 g/500 mg Powder for Injection (I.V.)  
Antibacterial**

**Rx**

Manufactured by:  
**Ary Parenterals**  
Vill, Gullarwala, Sai Road,  
Baddi, District Solan,  
Himachal Pradesh, India  
For:  
**Austere Pharmaceuticals**  
D/238, Pushpam Complex,  
Isanpur, Vaive Road,  
Isanpur, Ahmedabad, India  
Imported by:  
**BIOCARE LIFESCIENCES, INC.**  
Unit LC-23, Sita Centre Bldg., Malugay St. cor.  
Sen. Gil Puyat Ave., Brgy. Bel-Air, Makati City

Distributed by:  
**PROGEN PHARMACEUTICAL DISTRIBUTORS**  
Unit 1167 11/7 88 Corporate Center,  
Sedeño St., Salcedo Village,  
Makati City

**PIPERACILLIN + TAZOBACTAM**

**PROBITAZ IV**  
4g/500mg Powder for Intravenous Injection  
ANTIBACTERIAL

**Formulation:**  
Each vial contains:  
Sterile Piperacillin sodium USP eq. to Piperacillin (anhydrous) ..... 4g  
Sterile Tazobactam sodium USP eq. to Tazobactam (anhydrous) ..... 500mg  
Each ampoule contains:  
Sterile Water for Injection BP ..... 20ml.

**Caution:** Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

**Storage:** Store at temperatures not exceeding 30°C. Protect from light. Do not freeze. Keep the medicine out of reach of children.

**Indications:** Piperacillin/Tazobactam is indicated for the following:  
**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 bacteremia 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.

**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).

**Direction for reconstitution:** Dissolve the contents in 20ml Sterile Water for Injection BP. After reconstitution discard unused portion.

**If any foreign particle is visible in the vial after dissolving the contents, please do not use the solution.**

For suspected adverse drug reaction, report to the FDA: [www.fda.gov.ph](http://www.fda.gov.ph)

Registration No. DRXY-XXXX

Piperacillin + Tazobactam	Sterile Water for Injection BP
4g/500mg Powder for Injection (I.V.) vial	20ml ampoule
Mfg. Lic. No. : MB/09/821 & MNB/09/820	Mfg. Lic. No. : MB/09/821 & MNB/09/820
Batch No. :	Batch No. :
Mfg. Date :	Mfg. Date :
Exp. Date :	Exp. Date :

**PIPERACILLIN + TAZOBACTAM**

**PROBITAZ IV**  
4g/500mg Powder for Intravenous Injection  
ANTIBACTERIAL

**PIPERACILLIN  
TAZOBACTAM  
PROBITAZ IV**  
 4 g/500 mg Powder for Injection (L.V.)  
 Antibacterial

**Rx**

**PROGEN PHARMACEUTICAL DISTRIBUTORS**  
 10010 15th St. # 1000, Houston, TX 77036  
 713.861.1000

**Directions for reconstitution:** Dilute the contents in 20mL Sterile Water for Injection. After reconstitution, the concentration is 4 g/20 mL.

**For suspected adverse drug reaction, report to the FDA, www.fda.gov/adr**  
 Registration No.:  
 Mfg. Lic. No.: MNB/09/820 & MB/09/821  
 Batch No.:  
 Mfg. Date:  
 Exp. Date:

**Manufactured by:**  
 Affy Parenterals,  
 10010 15th St., Houston, TX 77036  
 Biocare Lifesciences, Inc.  
 10010 15th St., Houston, TX 77036

**Approved Pharmacies:**  
 Affy Parenterals, Houston, TX  
 Biocare Lifesciences, Houston, TX  
 Progen Pharmaceutical Distributors, Houston, TX

**Warnings:**  
 1. Allergic reactions have been reported in patients receiving piperacillin-tazobactam. Anaphylaxis and anaphylactoid reactions have been reported.

**Contraindications:**  
 1. Hypersensitivity to piperacillin, tazobactam, or any component of this formulation.

**Caution:**  
 1. Patients receiving piperacillin-tazobactam should be monitored for signs of renal impairment.

**Adverse Reactions:**  
 1. The most common adverse reactions are diarrhea, nausea, and vomiting.

**Drug Interactions:**  
 1. Piperacillin-tazobactam may interact with other drugs.

**Use in Pregnancy and Lactation:**  
 1. Piperacillin-tazobactam is classified as Pregnancy Category B.

**Use in Children:**  
 1. Piperacillin-tazobactam is approved for use in children.

**Use in Elderly:**  
 1. Piperacillin-tazobactam should be used with caution in elderly patients.

**Use in Renal Impairment:**  
 1. Piperacillin-tazobactam should be used with caution in patients with renal impairment.

**Use in Hepatic Impairment:**  
 1. Piperacillin-tazobactam should be used with caution in patients with hepatic impairment.

**Use in Patients with History of Alcoholism:**  
 1. Piperacillin-tazobactam should be used with caution in patients with a history of alcoholism.

**Use in Patients with History of Seizures:**  
 1. Piperacillin-tazobactam should be used with caution in patients with a history of seizures.

**Use in Patients with History of Hypertension:**  
 1. Piperacillin-tazobactam should be used with caution in patients with a history of hypertension.

**Use in Patients with History of Heart Disease:**  
 1. Piperacillin-tazobactam should be used with caution in patients with a history of heart disease.

**Use in Patients with History of Lung Disease:**  
 1. Piperacillin-tazobactam should be used with caution in patients with a history of lung disease.

**Use in Patients with History of Kidney Disease:**  
 1. Piperacillin-tazobactam should be used with caution in patients with a history of kidney disease.

**Use in Patients with History of Liver Disease:**  
 1. Piperacillin-tazobactam should be used with caution in patients with a history of liver disease.

**Use in Patients with History of Blood Disorders:**  
 1. Piperacillin-tazobactam should be used with caution in patients with a history of blood disorders.

**Use in Patients with History of Diabetes:**  
 1. Piperacillin-tazobactam should be used with caution in patients with a history of diabetes.

**Use in Patients with History of Thyroid Disease:**  
 1. Piperacillin-tazobactam should be used with caution in patients with a history of thyroid disease.

**Use in Patients with History of Hypertension:**  
 1. Piperacillin-tazobactam should be used with caution in patients with a history of hypertension.

**Use in Patients with History of Heart Disease:**  
 1. Piperacillin-tazobactam should be used with caution in patients with a history of heart disease.

**Use in Patients with History of Lung Disease:**  
 1. Piperacillin-tazobactam should be used with caution in patients with a history of lung disease.

**Use in Patients with History of Kidney Disease:**  
 1. Piperacillin-tazobactam should be used with caution in patients with a history of kidney disease.

**Use in Patients with History of Liver Disease:**  
 1. Piperacillin-tazobactam should be used with caution in patients with a history of liver disease.

**Use in Patients with History of Blood Disorders:**  
 1. Piperacillin-tazobactam should be used with caution in patients with a history of blood disorders.

**Use in Patients with History of Diabetes:**  
 1. Piperacillin-tazobactam should be used with caution in patients with a history of diabetes.

**Use in Patients with History of Thyroid Disease:**  
 1. Piperacillin-tazobactam should be used with caution in patients with a history of thyroid disease.



20 mL

**Sterile Water  
for Injection**

**DILUENT**

*If any foreign particle is visible in the vial after dissolving the contents, please do not use the solution.*

**Rx**

**STORAGE CONDITION:**  
 Store at temperatures not exceeding 30°C.

Manufactured by: **Affy Parenterals**  
 Imported by: **Biocare Lifesciences, Inc.**  
 Distributed by:  
**Progen Pharmaceutical Distributors**

Batch No. :  
 Mfg. Date :  
 Exp. Date :

# PIPERACILLIN + TAZOBACTAM

## PROPITAZ IV

4g/500mg Powder for Solution for Intravenous Infusion  
ANTIBACTERIAL

### Formulation:

Each vial contains:

Sterile Piperacillin sodium USP eq. to Piperacillin (anhydrous).....4 g

Sterile Tazobactam sodium USP eq. to Tazobactam (anhydrous).....500 mg

Each ampoule contains:

Sterile Water for Injection BP.....20 mL

**Description:** A white to off-white sterile powder.

### Indications

Piperacillin/Tazobactam is indicated for 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.

### Dosage and 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

##### Infections

The usual dose is 4 g piperacillin / 0.5 g tazobactam given every 8 hours.

For nosocomial pneumonia and bacterial infections in neutropenic patients, the recommended dose is 4 g piperacillin / 0.5 g tazobactam administered every 6 hours. This regimen may also be applicable to treat patients with other indicated infections when particularly severe.

The following table summarises 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)

#### 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)
≥ 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.

#### Dose in elderly patients

No dose adjustment is required for the elderly with normal renal function or creatinine clearance values above 40 mL/min.

#### Paediatric population (2-12 years of age)

##### Infections

The following table summarises 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 8 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	70 mg piperacillin / 8.75 mg tazobactam / kg every 8 hours.

For children on haemodialysis, one additional dose of 40 mg piperacillin / 5 mg 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.

No data from controlled clinical studies are available.

#### 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.

#### Route of administration

Piperacillin/Tazobactam 4 g/500 mg] is administered by 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

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.

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.

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 haematopoietic function 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.

Each bottle of Piperacillin/Tazobactam 4 g/500 mg contains 9.44 mmol (217 mg) of sodium. 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.

#### Interaction with other medicinal products and other forms of interaction

##### 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 substances 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.

**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.

**Fertility, pregnancy and lactation**

**Pregnancy**

There are no or a limited amount of data from the use of Piperacillin/Tazobactam in pregnant women.

Studies in animals have shown developmental toxicity, but no evidence of teratogenicity, at doses that are maternally toxic (see section 5.3).

Piperacillin and tazobactam cross the placenta. 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; tazobactam concentrations in human milk have not been studied. Women who are breast feeding should be treated only if the expected benefit outweighs the possible risks to the woman and child.

**Fertility**

A fertility study in rats showed no effect on fertility and mating after intraperitoneal administration of tazobactam or the combination piperacillin / tazobactam (see section 5.3).

**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**

The most commonly reported adverse reactions (occurring in 1 to 10 patients in 100) are diarrhoea, vomiting, nausea and rash.

In the following table, adverse reactions are listed by system organ class and MedDRA-preferred term. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. (Table 1)

Piperacillin therapy has been associated with an increased incidence of fever and rash in cystic fibrosis patients.

**Overdose**

**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.

Table 1.

**Pharmacological properties**

**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.

**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 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.

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.

**Breakpoints**

EUCAST Clinical MIC Breakpoints piperacillin / tazobactam (2009-12-02, v 1).

For susceptibility testing purposes, the concentration of tazobactam is fixed at 4 mg/L

Pathogen	Species-related breakpoints (S/R>)
Enterobacteriaceae	8/16
Pseudomonas	16/16
Gram-negative and Gram-positive anaerobes	8/16
Non-species related breakpoints	4/16

The susceptibility of streptococci is inferred from the penicillin susceptibility.

The susceptibility of staphylococci is inferred from the oxacillin susceptibility.

Table 1.

System Organ Class	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1,000 to < 1/100	Rare ≥ 1/10,000 to < 1/1,000	Very rare (< 1/10,000)
Infections and infestations		candidal superinfection		
Blood and lymphatic system disorders		leukopenia, neutropenia, thrombocytopenia	anaemia, haemolytic anaemia, purpura, epistaxis, bleeding time prolonged, eosinophilia	agranulocytosis, pancytopenia, activated partial thromboplastin time prolonged, prothrombin time prolonged, Coombs direct test positive, thrombocythaemia
Immune system disorders		hypersensitivity	anaphylactic/ anaphylactoid reaction (including shock)	
Metabolism and nutrition disorders				hypokalaemia, blood glucose decreased, blood albumin decreased, blood protein total decreased
Nervous system disorders		headache, insomnia		
Vascular disorders		hypotension, thrombophlebitis, phlebitis	flushing	
Gastrointestinal disorders	diarrhoea, vomiting, nausea	jaundice, stomatitis, constipation, dyspepsia	pseudo-membranous colitis, abdominal pain	
Hepatobiliary disorders		alanine aminotransferase increased, aspartate aminotransferase increased	hepatitis, blood bilirubin increased, blood alkaline phosphatase increased, gamma-glutamyltrans-ferase increased	
Skin and subcutaneous tissue disorders	rash, including maculopapular rash	urticaria, pruritus	erythema multiforme, dermatitis bullous, exanthema	toxic epidermal necrolysis, Stevens-Johnson syndrome
Musculoskeletal and connective tissue disorders			arthralgia, myalgia	
Renal and urinary disorders		blood creatinine increased	renal failure, tubulointerstitial nephritis	blood urea increased
General disorders and administration site conditions		pyrexia, injection-site reaction	chills	

**Susceptibility**

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

**Pharmacokinetic properties**

**Absorption**

The peak piperacillin and tazobactam concentrations after 4 g / 0.5 g administered over 30 minutes by intravenous infusion are 298 µg/ml and 34 µg/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. Distribution into cerebrospinal fluid is low in subjects with non-inflamed meninges, as with other penicillins.

**Biotransformation**

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

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 slightly 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 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.

#### **Paediatric population**

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 of age. The population mean (SE) for piperacillin volume of distribution is 0.243 (0.011) l/kg and is independent of age.

#### **Elderly patients**

The mean half-life for piperacillin and tazobactam were 32% and 55% longer, respectively, in the elderly compared with younger subjects. This difference may be due to age-related changes in creatinine clearance.

#### **Race**

No difference in piperacillin or tazobactam pharmacokinetics was observed between Asian (n=9) and Caucasian (n=9) healthy volunteers who received single 4 g / 0.5 g doses.

#### **Pharmaceutical particulars**

##### **List of excipients**

None.

##### **Incompatibilities**

This medicinal product must not be mixed with other medicinal products except those mentioned under Special Precautions for Disposal and Other Handling.

This product must not be mixed or co-administered with any aminoglycoside. The mixing of beta-lactam antibiotics with an aminoglycoside in vitro can result in substantial inactivation of the aminoglycoside.

Piperacillin / tazobactam should not be mixed with other substances in a syringe or infusion bottle since compatibility has not been established.

Piperacillin / tazobactam should be administered through an infusion set separately from any other drugs unless compatibility is proven.

Due to chemical instability, piperacillin / tazobactam should not be used in solutions containing only sodium bicarbonate.

Lactated Ringer's (Hartmann's) solution is not compatible with piperacillin / tazobactam.

Piperacillin / tazobactam should not be added to blood products or albumin hydrolysates.

##### **Shelf life**

Unopened: 2 years

After reconstitution (and dilution):

Chemical and physical in-use stability has been demonstrated for 24 hours at 20-25°C and for 48 hours at 2-8°C.

From a microbiological point of view, once opened, the product should be used immediately.

If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2-8°C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

##### **Special precautions for storage**

This medicinal product does not require any special storage conditions.

For storage conditions of the reconstituted/diluted medicinal product, see Shelf life.

##### **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.

##### **Intravenous use**

Reconstitute each vial with the volume of solvent shown in the table below, using one of the compatible solvents for reconstitution. Swirl until dissolved. When swirled constantly, reconstitution generally occurs within 3 minutes (for details on handling, please see below).

Content of vial	Volume of solvent* to be added to vial
4g/0.5g (4g piperacillin and 0.5g tazobactam)	20 mL

\* Compatible solvents for reconstitution:

- water for injection;

- sodium chloride 9 mg/ml (0.9 %) solution in water for injection;

- glucose 50 mg/ml (5 %) solution in water for injection;

- glucose 50 mg/ml (5 %) solution in sodium chloride 9 mg/ml (0.9%) solution.

The reconstituted solutions should be withdrawn from the vial by syringe. When reconstituted as directed, the vial contents withdrawn by syringe will provide the labelled amount of piperacillin and tazobactam.

The reconstituted solutions may be further diluted to the desired volume (e.g. 50 ml to 150 ml) with one of the following compatible solvents:

- sodium chloride 9 mg/ml (0.9 %) solution in water for injection;

- glucose 50 mg/ml (5 %) solution in water for injection;

- dextran (grade 40) 60 mg/ml (6%) solution in sodium chloride 9 mg/ml (0.9%) solution.

Any unused product or waste material should be disposed in accordance with local requirements.

For single use only. Discard any unused solution.

##### **Storage**

Store at temperatures not exceeding 30 °C. Protect from light. Use immediately after reconstitution. Do not freeze. Keep the medicine out of reach of children.

**Caution:** Foods, Drugs, Devices and Cosmetics Act prohibit dispensing without prescription.

**Packing:** One vial of Piperacillin+ Tazobactam (Propitaz IV) 4g/500mg Powder for Solution for Intravenous Infusion and one ampoule of 20ml Sterile Water For Injection BP.

**Registration No.** DRP-XXXX

Manufactured by :  
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