SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Trade Name: Injpip TZ 4.5

Generic Name: Piperacillin and Tazobactam for Injection 4.5 gm

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains:
Piperacillin Sodium USP
Equivalent to Piperacillin……...4.0 gm
Tazobactam Sodium
Equivalent to Tazobactam…… 0.5 gm
Sodium Content: 9.44 mmol (217 mg)

3. PHARMACEUTICAL FORM

Dry Powder for Injection

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Piperacillin/Tazobactam is indicated for the treatment of 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

4.2 Posology and method of 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 eight hours.

For nosocomial pneumonia and bacterial infections in neutropenic patients, the recommended dose is 4 g piperacillin / 0.5 g tazobactam administered every six 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 4 g / 0.5 g
Every six hours	Severe pneumonia
	Neutropenic adults with fever suspected to be due to a bacterial infection.
Every eight 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 (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 eight hours
< 20	Maximum dose suggested: 4 g / 0.5 g 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 four hours.

Hepatic Impairment

No dose adjustment is necessary (see section 5.2).

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 six hours	Neutropenic children with fever suspected to be due to bacterial infections*
100 mg Piperacillin / 12.5 mg Tazobactam per kg body weight / every eight 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 eight 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 2 g / 0.25 g is administered by intravenous infusion (over 30 minutes).

Piperacillin/Tazobactam 4 g / 0.5 g is administered by intravenous infusion (over 30 minutes).

For reconstitution instructions, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substances, any other penicillin-antibacterial agent or to any of the excipients listed in section 6.1.

History of acute severe allergic reaction to any other beta-lactam active substances (e.g cephalosporin, monobactam or carbapenem).

4.4 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.

Serious skin reactions, such as Stevens-Johnson syndrome and toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms, and acute generalised exanthematous pustulosis have been reported in patients receiving Piperacillin/Tazobactam. If patients develop a skin rash they should be monitored closely and Piperacillin/Tazobactam discontinued if lesions progress.

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 a full blood count 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.

This medicinal product contains 9.44 mmol (217 mg) of sodium per vial of powder for solution for infusion.To be taken into account by patients 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 hemodialysis patients. Intravenous dosages and administration intervals should be adjusted to the degree of renal function impairment.

In a secondary analysis using data from a large multicenter, randomized-controlled trial when glomerular filtration rate (GFR) was examined after administration of frequently used antibiotics in critically ill patients, the use of piperacillin/tazobactam was associated with a lower rate of reversible GFR improvement compared with the other antibiotics. This secondary analysis concluded that piperacillin/tazobactam was a cause of delayed renal recovery in these patients.

4.5 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 drugs 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.

For information related to the administration of Piperacillin/Tazobactam with aminoglycosides.

Vancomycin

No pharmacokinetic interactions have been noted between Piperacillin/ Tazobactam and vancomycin.

However, a limited number of retrospective studies have detected an increased incidence of acute kidney injury in patients concomitantly administered Piperacillin/Tazobactam and vancomycin as compared to vancomycin alone.

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.

4.6 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.

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 breast 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.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed

4.8 Undesirable effects

The most commonly reported adverse reaction is diarrhoea (occurring in 1 patient out of 10) are diarrhoea, nausea, vomiting and rash.

Among the most serious adverse reactions pseudo-membranous colitis and toxic epidermal necrolysis occur in 1 to 10 patients in 10,000. The frequencies for pancytopenia, anaphylactic shock and Stevens-Johnson syndrome cannot be estimated from the currently available data.

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.

System Organ Class	**Very common** ≥ 1/10	**Common** ≥ 1/100 to < 1/10	**Uncommon** ≥ 1/1,000 to < 1/100	**Rare** ≥ 1/10,000 to < 1/1,000	**Frequency not known (cannot be estimated from available data)**
Infections and infestations		candidiasis*		pseudo-membranous colitis	
Blood and lymphatic system		thrombocytopenia, anaemia*	leukopenia,	agranulocytosis,	Pancytopenia*, neutropenia, haemolytic

disorders					anaemia*, eosinophilia*, thrombocytosis*
Immune system disorders					anaphylactoid reaction*, anaphylactic reaction*, anaphylactoid shock*, anaphylactic shock*, hypersensitivity*
Metabolism and nutrition disorders			hypokalaemia,		
Psychiatric disorders		insomnia			
Nervous system disorders		headache, insomnia			
Vascular disorders			hypotension, thrombophlebitis, phlebitis, flushing		
Respiratory, thoracic and mediastinal disorders				epistaxis	eosinophilic pneumonia
Gastrointestinal disorders	diarrhoea	abdominal pain, vomiting, nausea, constipation, dyspepsia		stomatitis	
Hepatobiliary disorders					Hepatitis*, jaundice,
Skin and subcutaneous tissue disorders		rash, pruritus	erythema multiforme*, urticaria, rash maculopapular*	toxic epidermal necrolysis*	Stevens-Johnson syndrome*, dermatitis exfoliative, drug reaction with eosinophilia and systemic symptoms (DRESS)*, acute generalised exanthematous pustulosis (AGEP)*, dermatitis bullous purpura
Musculoskeletal and connective			arthralgia, myalgia		

tissue disorders					
Renal and urinary disorders					renal failure, tubulointerstitial nephritis*
General disorders and administration site conditions		pyrexia, injection site reaction	chills		
Investigations		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	blood glucose decreased, blood bilirubin increased, prothrombin time prolonged		bleeding time prolonged, gamma-glutamyltransferase increased

*ADR identified post marketing

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

4.9 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 (see section 4.4).

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use, Combinations of penicillins, including 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..

Tazobactum extends the antibiotic spectrum of piperacillin to include many beta-lactamase-producing bacteria that have acquired resistance to piperacillin alone.

Phamacokinetic / 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 2009 (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.

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.

Groupings of relevant species according to piperacillin / tazobactam susceptibility

Commonly susceptible species

Gram positive aerobes

Enterococcus faecalis

Listeria monocytogenes

Staphylococcus aureus, methicillin susceptible[£]

Staphylococcus species, *coagulase negative,* methicillin-susceptible

Streptococcus pyogenes

Group B streptococci

Gram negative aerobes

Citrobacter koseri

Haemophilus influenza

Moraxella catarrhalis

Proteus mirabilis

Gram positive anaerobes

Clostridium spp.

Eubacterium spp.

Peptostreptococcus spp.

Gram negative anaerobes

Bacteroides fragilis group

Fusobacterium spp.

Porphyromonas spp.

Prevotella spp.

Species for which acquired resistance may be a problem

Gram positive aerobes

Enterococcus faecium [$,.+]

Streptococcus pneumonia

Streptococcus viridans group

Gram negative aerobes

Actinobacter baumannii [$]

Burkholderia cepacia

Citrobacter freundii

Enterobacter spp.

Escherichia coli

Klebsiella pneumonia

Morganella morganii

Proteus vulgaris

Providencia ssp.

Pseudomonas aeruginosa

Serratia spp.

Inherently resistant organisms

Gram positive aerobes

Corynebacterium jeikeium

Gram negative aerobes

Legionella spp

Stenotrophomonas maltophilia [+,$]

Other microorganisms

Chlamydophilia pneumonia

Mycoplasma pneumonia

[$] Species showing natural intermediate susceptibility

[+] Species for which high resistance rates (more than 50%) have been observed in one or more areas/countries/regions within the EU.

[£] All methicillin-resistant staphylococci are resistant to piperacillin / tazobactam.

5.2 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 tissue and body fluids including intestinal mucosa, gallbladder, lung, bile and bone. Mean tissue concentrations are generally 50 to 100% of those in plasma. Distribution into cerebrospinal fluid is low in subjects with non-inflamed meninges, as with other penicillins.

Biotransformation

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

Elimination

Piperacillin and tazobactam are eliminated by the kidney via glomerular filtration and tubular secretion.

Piperacillin is excreted rapidly as unchanged drug with 68% of the administered dose appearing in the urine. Tazobactam and its metabolite are eliminated primarily by renal excretion with 80% of the administered dose appearing as unchanged drug and the remainder as the single metabolite. 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 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.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity and genotoxicity. Carcinogenicity studies have not been conducted with Piperacillin/Tazobactam.

A fertility and general reproduction study in rats using intraperitoneal administration of tazobactam or the combination Piperacillin/Tazobactam reported a decrease in litter size and an increase in fetuses with ossification delays and variations of ribs, concurrent with maternal toxicity. Fertility of the F1 generation and embryonic development of F2 generation were not impaired.

Teratogenicity studies using intravenous administration of tazobactam or the combination Piperacillin/Tazobactam in mice and rats resulted in slight reductions in rat fetal weights at maternally toxic doses but did not show teratogenic effects.

Peri/postnatal development was impaired (reduced pup weights, increase in pup mortality, increase in stillbirths) concurrently with maternal toxicity after intraperitoneal administration of tazobactam or the combination Piperacillin/ Tazobactam in the rat

6. Pharmaceutical particulars

6.1 List of excipients
None

6.2 Incompatibilities
None known

6.3 Shelf life
24 Months

6.4 Special precautions for storage

Store below 30°C. Protect From Light.

6.5 Nature and contents of container

30 ml, USP type III, clear glass vial closed with bromo butyl rubber stopper and sealed with flip off seal

6.6 Special precautions for disposal and other handling

Reconstitution and Dilution Of Powder Formulations

Pharmacy Bulk Vials

Reconstituted stock solution must be transferred and further diluted for intravenous infusion.

The pharmacy bulk vial is for use in a hospital pharmacy admixture service only under a laminar flow hood. After reconstitution, entry into the vial must be made with a sterile transfer set or other sterile dispensing device, and contents should be dispensed as aliquots into intravenous solution using aseptic technique. Use entire contents of pharmacy bulk vial promptly. Discard 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]).

Reconstitute the pharmacy bulk vial with exactly 152 mL of a compatible reconstitution diluent, listed below, to a concentration of 200 mg/mL of Piperacillin and 25 mg/mL of Tazobactam. Shake well until dissolved. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to and during administration whenever solution and container permit.

Single Dose Vials

Reconstitute Piperacillin & Tazobactam vials with a compatible reconstitution diluent from the list provided below.

2.25 g, 3.375 g, and 4.5 g Piperacillin & Tazobactam should be reconstituted with 10 mL, 15 mL, and 20 mL, respectively. Swirl until dissolved.

Compatible Reconstitution Diluents for Pharmacy and Single Dose Vials

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

Reconstituted Piperacillin & Tazobactam solutions for both bulk and single dose vials should be further diluted (recommended volume per dose of 50 mL to 150 mL) in a compatible intravenous solution listed below. 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 for Pharmacy and Single Dose Vials

0.9% sodium chloride for injection
sterile water for injection‡
Dextran 6% in saline
Dextrose 5%
Lactated Ringer's Solution (compatible only with reformulated Piperacillin & Tazobactam containing EDTA and is compatible for co-administration via a Y-site)

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

Piperacillin & Tazobactam should not be mixed with other drugs in a syringe or infusion bottle since compatibility has not been established.

Piperacillin & Tazobactam is not chemically stable in solutions that contain only sodium bicarbonate and solutions that significantly alter the pH.

Piperacillin & Tazobactam should not be added to blood products or albumin hydrolysates. Parenteral drug products should be inspected visually for particulate matter or discoloration prior to administration, whenever solution and container permit.

Stability of Piperacillin & Tazobactam Powder Formulations Following Reconstitution

Piperacillin & Tazobactam reconstituted from bulk and single vials is stable in glass and plastic containers (plastic syringes, I.V. bags and tubing) when used with compatible diluents. The pharmacy bulk vial should NOT be frozen after reconstitution. Discard unused portions after storage for 24 hours at room temperature or after storage for 48 hours at refrigerated temperature (2°C to 8°C [36°F to 46°F]).

Single dose or pharmacy vials should be used 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]). Vials should not be frozen after reconstitution.

Stability studies in the I.V. bags have demonstrated chemical stability (potency, pH of reconstituted solution and clarity of solution) for up to 24 hours at room temperature and up to one week at refrigerated temperature. Piperacillin & Tazobactam contains no preservatives. Appropriate consideration of aseptic technique should be used.

Piperacillin & Tazobactam reconstituted from bulk and single vials can be used in ambulatory intravenous infusion pumps. Stability of Piperacillin & Tazobactam in an ambulatory intravenous infusion pump has been demonstrated for a period of 12 hours at room temperature. Each dose was reconstituted and diluted to a volume of 37.5 mL or 25 mL. One-day supplies of dosing solution were aseptically transferred into the medication reservoir (I.V. bags or cartridge). The reservoir was fitted to a preprogrammed ambulatory intravenous infusion pump per the manufacturer's instructions. Stability of Piperacillin & Tazobactam is not affected when administered using an ambulatory intravenous infusion pump.

7. Marketing authorisation holder

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8. Marketing authorisation number(s)

04361/06664/NMR/2018

9. Date of first authorisation/renewal of the authorisation

Date of First authorization: 20-03-2019

10. Date of revision of the text

17-07-2023