1. NAME OF THE MEDICINAL PRODUCT

Tazocin for Injection 4.5 g/vial

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

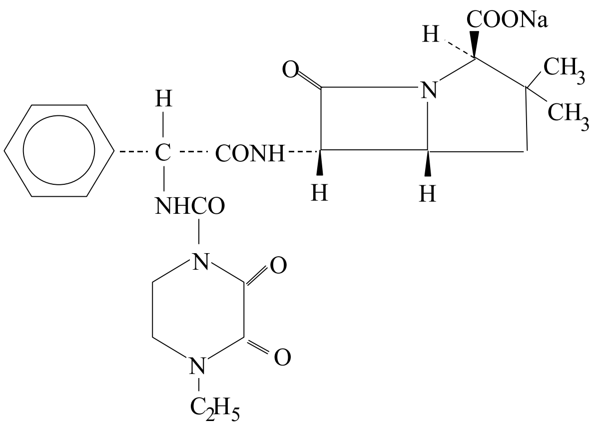
Piperacillin sodium/tazobactam sodium (INN).

Chemical Name

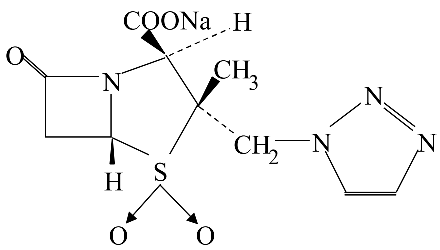
Piperacillin sodium is sodium (2S,5R,6R)-6-[(R)-2-(4-ethyl-2,3-dioxo-1-piperazinecarboxamido)-2-phenylacetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate.

Tazobactam sodium is sodium (2S,3S,5R)-3-methyl-7-oxo-3-(1H-1,2,3-triazol-1-ylmethyl)-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate-4,4-dioxide.

Structure



Piperacillin sodium



Tazobactam sodium

Molecular Formula

Piperacillin sodium: $C_{23}H_{26}N_5NaO_7S$; tazobactam sodium: $C_{10}H_{11}N_4NaO_5S$.

Molecular Weight

Piperacillin sodium: 539.5; tazobactam sodium: 322.3.

Physical Characteristics

Vial containing a white to off-white sterile, lyophilized powder of piperacillin and tazobactam as the sodium salts.

Vials with Lyophilized Powder for Reconstitution

Each vial contains a total of 2.84 mEq (65 mg) of sodium per gram of piperacillin.

4.5 g vial: Each single-dose vial contains piperacillin sodium equivalent to 4 g of piperacillin and tazobactam sodium equivalent to 0.5 g of tazobactam. It also contains 1 mg of edetate disodium (dihydrate) (EDTA) per vial.

3. PHARMACEUTICAL FORM

Sterile, lyophilized powder for solution for injection or infusion.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

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

- Lower respiratory tract infections; urinary tract infections (complicated and uncomplicated); intra-abdominal infections; skin and skin structure infections; bacterial septicemia.
- Polymicrobial infections: TAZOCIN is indicated for polymicrobial infections including those where aerobic and anaerobic organisms are suspected (intra-abdominal, skin and skin structure, lower respiratory tract).

TAZOCIN, in combination with an aminoglycoside, is indicated for bacterial infections in neutropenic adults or children.

Children Under the Age of 12 Years

In hospitalized children aged 2 to 12 years, TAZOCIN is indicated for the treatment of intra-abdominal infections including appendicitis complicated by rupture or abscess, peritonitis, and biliary infections. It has not been evaluated in this indication for pediatric patients below the age of 2 years.

Whilst TAZOCIN is indicated only for the conditions listed above, infections caused by piperacillin susceptible organisms are also amendable to TAZOCIN treatment due to its piperacillin content. Therefore, the treatment of mixed infections caused by piperacillin susceptible organisms and β-lactamase producing organisms susceptible to TAZOCIN should not require the addition of another antibiotic.

TAZOCIN is particularly useful in the treatment of mixed infections and in presumptive therapy prior to the availability of the results of sensitivity tests because of its broad spectrum of activity.

TAZOCIN acts synergistically with aminoglycosides against certain strains of *Pseudomonas aeruginosa*. Combined therapy has been successful, especially in patients with impaired host defences. Both drugs should be used in full therapeutic doses. As soon as results of culture and susceptibility tests become available, antimicrobial therapy should be adjusted if necessary.

Note: For associated bacteremia due to extended-beta-lactamase (ESBL) producing organisms, see section 5.1.

4.2. Posology and method of administration

Dosage

Neutropenic patients with signs of infection (e.g., fever) should receive immediate empirical antibiotic therapy before laboratory results are available.

Adults and children over 12 years

The usual dosage for adults and children over 12 years with normal renal function is 4.5 g TAZOCIN given every eight hours. The total daily dose depends on the severity and localization of the infection and can vary from 2.25 g to 4.5 g TAZOCIN administered every six or eight hours.

In neutropenia, the recommended dose is 4.5 g TAZOCIN given every six hours in combination with an aminoglycoside.

Children under the age of 12 years

TAZOCIN is only recommended for the treatment of children with neutropenia. For children weighing over 50 kg, follow adult dosing guidance, including the aminoglycoside. For children with normal renal function and weighing less than 50 kg, the dose should be adjusted to 90 mg/kg (80 mg piperacillin/10 mg tazobactam) administered every six hours in combination with an aminoglycoside.

Until further experience is available, TAZOCIN should not be used in children who do not have neutropenia.

Hospitalized children with intra-abdominal infection

For children aged 2 to 12 years, weighing up to 40 kg, and with normal renal function, the recommended dose is 112.5 mg/kg (100 mg piperacillin/12.5 mg tazobactam) every 8 hours. For children aged 2 to 12 years, weighing over 40 kg, and with normal renal function, follow the adult dosing guidance, i.e., 4.5 g (4 g piperacillin/0.5 g tazobactam) every 8 hours. The duration of therapy should be guided by the severity of the infection and the patient's clinical and bacteriological progress.

Elderly

TAZOCIN may be used at the same dose levels as adults except in cases of renal impairment (see below):

Renal insufficiency in adults and children weighing >50 kg

In adults and children weighing >50 kg with renal insufficiency, the intravenous dose should be adjusted to the degree of actual renal impairment. The suggested daily doses are as follows:

INTRAVENOUS DOSAGE SCHEDULE FOR ADULTS AND CHILDREN >50 KG WITH IMPAIRED RENAL FUNCTION

Creatinine Clearance (mL/min)	**Recommended Piperacillin/Tazobactam Dosage**
20-80	12 g/1.5 g/day Divided Doses 4 g/500 mg q 8H
<20	8 g/1 g/day Divided Doses 4 g/500 mg q 12H

For patients on hemodialysis, the maximum daily dose is 8 g/1 g TAZOCIN. In addition, because hemodialysis removes 30%-50% of piperacillin in 4 hours, one additional dose of 2 g/250 mg TAZOCIN should be administered following each dialysis period. For patients with renal failure and hepatic insufficiency, measurement of serum levels of TAZOCIN will provide additional guidance for adjusting dosage.

Renal insufficiency in adults and children weighing <50 kg

In adults and children weighing <50 kg with renal insufficiency, the intravenous dose should be adjusted to the degree of actual renal impairment. The suggested daily doses are as follows:

INTRAVENOUS DOSAGE SCHEDULE FOR ADULTS AND CHILDREN <50 KG WITH IMPAIRED RENAL FUNCTION

Creatinine Clearance (mL/min)	Recommended Piperacillin/Tazobactam Dosage
40-80	90 mg (80 mg piperacillin/10 mg tazobactam)/kg q 6H
20-40	90 mg (80 mg piperacillin/10 mg tazobactam)/kg q 8H
<20	90 mg (80 mg piperacillin/10 mg tazobactam)/kg q 12H

For children weighing <50 kg on hemodialysis, the recommended dose is 45 mg/kg q 8H.

The pharmacokinetics of TAZOCIN have not been studied in pediatric patients with renal impairment. Each patient must be monitored closely for signs of drug toxicity. Drug dose and interval dose should be adjusted accordingly. In patients with renal insufficiency or hemodialysis patients, intravenous dosages and administration intervals should be adjusted to the degree of renal function impairment.

Duration of therapy

Therapy is recommended for a minimum of 5 days and maximum of 14 days, considering that dose administration should continue at least 48 hours after the resolution of clinical signs and symptoms or fever.

Administration

TAZOCIN must be given by slow intravenous injection (over at least 3-5 minutes) or by slow intravenous infusion (e.g., over 20-30 minutes).

TAZOCIN should not be mixed with other drugs in a syringe or infusion bottle since compatibility has not been established. In particular, whenever TAZOCIN is used concurrently with another antibiotic, especially an aminoglycoside (with the exceptions shown below), TAZOCIN must not be mixed in intravenous solutions or administered concurrently due to physical incompatibility.

Co-administration of piperacillin/tazobactam with aminoglycosides

Due to the *in vitro* inactivation of the aminoglycoside by the β-lactam antibiotics, piperacillin/tazobactam and the aminoglycoside are recommended for separate administration. Piperacillin/tazobactam and the aminoglycoside should be reconstituted and diluted separately when concomitant therapy with aminoglycosides is indicated.

The following compatibility information does not apply to the piperacillin/tazobactam formulation not containing EDTA.

In circumstances where co-administration is preferred, the reformulated piperacillin/tazobactam containing EDTA supplied in vials is compatible for simultaneous co-administration via Y-site infusion only with the following aminoglycosides under the following conditions:

Aminoglycoside	Piperacillin/ Tazobactam Dose (g)	Piperacillin/ Tazobactam Diluent Volume (mL)	Aminoglycoside Concentration Range‡ (mg/mL)	Acceptable Diluents
Amikacin	2.25, 3.375, 4.5	50, 100, 150	1.75 – 7.5	0.9% sodium chloride or 5% dextrose
Gentamicin	2.25, 3.375, 4.5	50, 100, 150	0.7 – 3.32	0.9% sodium chloride or 5% dextrose

‡ The dose of aminoglycoside should be based on patient weight, status of infection (serious or life-threatening), and renal function (creatinine clearance).

Compatibility of piperacillin/tazobactam with other aminoglycosides has not been established. Only the concentration and diluents for amikacin and gentamicin with the dosages of piperacillin/tazobactam listed in the table above have been established as compatible for co-administration via Y-site infusion. Simultaneous co-administration via Y-site infusion in any manner other than listed above may result in inactivation of the aminoglycoside by piperacillin/tazobactam.

4.3. Contraindications

Hypersensitivity to any of the β-lactams (including penicillins and cephalosporins) or to β-lactamase inhibitors.

4.4. Special warnings and precautions for use

Before initiating therapy with TAZOCIN, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, 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 discontinuation of the antibiotic, and may require administration of epinephrine and other emergency measures.

Piperacillin/tazobactam may cause severe cutaneous adverse reactions, such as Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (see section 4.8). If patients develop a skin rash they should be monitored closely and TAZOCIN discontinued if lesions progress.

Rare cases of hemophagocytic lymphohistiocytosis (HLH) have been observed following therapy (>10 days) with piperacillin/tazobactam, often as a complication of DRESS. HLH is a pathologic immune activation which leads to excessive systemic inflammation and can be life-threatening and early diagnosis and rapid initiation of immunosuppressive therapy is essential. Characteristic signs and symptoms include fever, hepatosplenomegaly, cytopenias, hyperferritinemia, hypertriglyceridemia, hypofibrinogenemia, and hemophagocytosis. If TAZOCIN is suspected as possible trigger, treatment should be discontinued.

Rhabdomyolysis has been reported with the use of piperacillin/tazobactam. If signs or symptoms of rhabdomyolysis are observed, TAZOCIN should be discontinued and appropriate therapy initiated.

Antibiotic-induced pseudomembranous colitis may manifest as severe, persistent diarrhea which may be life-threatening. The onset of pseudomembranous colitis symptoms may occur during or after antibacterial treatment.

In case of severe, persistent diarrhea, the possibility of antibiotic-induced, life-threatening pseudomembranous colitis must be taken into consideration. Therefore, TAZOCIN must be discontinued immediately in such cases, and suitable therapy be initiated (e.g., oral metronidazole or oral vancomycin). Preparations, which inhibit peristalsis, are contraindicated.

While piperacillin/tazobactam possesses the characteristic low toxicity of the penicillin group of antibiotics, periodic assessment of organ system functions including renal, hepatic, and hematopoietic during prolonged therapy is advisable.

Bleeding manifestations have occurred in some patients receiving β-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 (see section 4.5). If bleeding manifestations occur, the antibiotic should be discontinued and appropriate therapy instituted.

This product contains 2.84 mEq (65 mg) of sodium per gram of piperacillin which may slightly increase a patient's overall sodium intake. Hypokalemia may occur in patients with low potassium reserves or in those who are receiving concomitant medications that may lower potassium levels; periodic electrolyte determinations may be advisable in such patients.

As with other antibiotics, the possibility of the emergence of resistant organisms, including fungi, which might cause superinfections, should be kept in mind, particularly during prolonged treatment. Microbiological follow-up may be required to detect any important superinfections. If this occurs, appropriate measures should be taken. As with other penicillins, patients may experience neuromuscular excitability or convulsions if higher than recommended doses are given intravenously.

Leukopenia and neutropenia may occur, especially during prolonged therapy. Therefore, periodic assessment of hematopoietic function should be performed.

As with treatment with other penicillins, neurological complications in the form of convulsions (seizures) may occur when high doses are administered, especially in patients with impaired renal function (see section 4.8).

Antimicrobials used in high doses for short periods to treat gonorrhea may mask or delay the symptoms of incubating syphilis. Therefore, prior to treatment, patients with gonorrhea should also be evaluated for syphilis. Specimens for darkfield examination should be obtained from patients with any suspect primary lesion, and serologic tests should be made for a minimum of 4 months.

Use in Patients with Hepatic Impairment

No dosage adjustment of TAZOCIN is necessary in patients with hepatic impairment.

Renal Impairment

Due to its potential nephrotoxicity (see section 4.8), 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 (see section 4.2).

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.

Combined use of piperacillin/tazobactam and vancomycin may be associated with an increased incidence of acute kidney injury (see section 4.5).

4.5. Interaction with other medicinal products and other forms of interaction

Non-depolarizing Muscle Relaxants

Piperacillin, when used concomitantly with vecuronium, has been implicated in prolonging 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-depolarizing muscle relaxants could be prolonged in the presence of piperacillin.

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 (see section 4.4).

Methotrexate

Piperacillin may reduce the excretion of methotrexate; therefore, serum levels of methotrexate should be monitored in patients to avoid drug toxicity.

Probenecid

As with other penicillins, concurrent administration of probenecid and TAZOCIN produces a longer half-life and lower renal clearance for both piperacillin and tazobactam; however, peak plasma concentrations of either drug 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, please refer to section 4.2.

Vancomycin

Studies have detected an increased incidence of acute kidney injury in patients concomitantly administered piperacillin/tazobactam and vancomycin as compared to vancomycin alone (see section 4.4).

No pharmacokinetic interactions have been noted between piperacillin/tazobactam and vancomycin.

As with other penicillins, the administration of piperacillin/tazobactam may result in a false-positive reaction for glucose in urine using a copper-reduction method. It is thus recommended that glucose tests based on enzymatic glucose oxidase reactions be used.

There have been reports of positive test results using the Bio-Rad Laboratories Platelia *Aspergillus* enzyme immunoassay (EIA) test in patients receiving piperacillin/tazobactam injection who were subsequently found to be free of *Aspergillus* infection. Cross-reactions with non-Aspergillus polysaccharides and polyfuranoses with Bio-Rad Laboratories Platelia *Aspergillus* EIA test have been reported.

Therefore, positive test results in patients receiving TAZOCIN should be interpreted cautiously and confirmed by other diagnostic methods.

4.6. Fertility, pregnancy and lactation

Studies in animals have not shown teratogenicity with piperacillin/tazobactam combination when administered intravenously but have shown reproductive toxicity in rats at maternally toxic doses when administered intravenously or intraperitoneally. There are no adequate and well-controlled studies with the piperacillin/tazobactam combination or with piperacillin or tazobactam alone in pregnant women. Piperacillin and tazobactam cross the placenta. Pregnant women should be treated only if the expected benefit outweighs the possible risks to the pregnant woman and the fetus.

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.

4.7. Effects on ability to drive and use machines

No studies on the effect of ability to drive or use machines have been performed.

4.8. Undesirable effects

Table 1. Adverse Drug Reactions (ADRs) by System Organ Class and Council for International Organizations of Medical Science (CIOMS) Frequency Category Listed in Order of Decreasing Medical Seriousness or Clinical Importance Within Each Frequency Category and SOC

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		candida infection*		pseudomembranous colitis	
Blood and lymphatic system disorders		thrombocytopenia, anemia*	leukopenia	agranulocytosis	pancytopenia*, neutropenia, hemolytic anemia*, thrombocytosis*, eosinophilia*
Immune system disorders					anaphylactoid shock*, anaphylactic shock*, anaphylactoid reaction*, anaphylactic reaction*, hypersensitivity*, Kounis syndrome*,**
Metabolism and nutrition disorders			hypokalemia		

Psychiatric disorders		insomnia			delirium*
Nervous system disorders		headache	seizure*		
Vascular disorders			hypotension, phlebitis, thrombophlebitis, flushing		
Respiratory, thoracic and mediastinal disorders				epistaxis	eosinophilic pneumonia*
Gastrointestinal disorders	diarrhea	abdominal pain, vomiting, constipation, nausea, dyspepsia		stomatitis	
Hepatobiliary disorders					hepatitis*, jaundice
Skin and subcutaneous tissue disorders		rash, pruritus	erythema multiforme*, urticaria, rash maculo-papular*	toxic epidermal necrolysis*	Stevens-Johnson syndrome*, drug reaction with eosinophilia and systemic symptoms (DRESS)*, acute generalized exanthematous pustulosis (AGEP)*, dermatitis exfoliative*, dermatitis bullous, linear IgA disease*, purpura
Musculoskeletal connective tissue and bone disorders			arthralgia, myalgia		rhabdomyolysis*
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

* Adverse Drug Reaction (ADR) identified post-marketing.
** Acute coronary syndrome associated with an allergic reaction.

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 the adverse events experienced including nausea, vomiting, and diarrhea 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

Treatment should be supportive and symptomatic according to the patient’s clinical presentation.

No specific antidote is known. Excessive serum concentrations of either piperacillin or tazobactam may be reduced by hemodialysis (see section 5.2).

In case of severe, anaphylactic reactions, the usual counter measures are to be initiated.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic Group

Antibacterials for systemic use, combinations of penicillins including β-lactamase inhibitors; ATC code: J01C R05.

Mechanism of Action

TAZOCIN (sterile piperacillin sodium/tazobactam sodium) is an injectable antibacterial combination consisting of the semisynthetic antibiotic piperacillin sodium and the β-lactamase inhibitor tazobactam sodium for intravenous administration. Thus, piperacillin/tazobactam combines the properties of a broad-spectrum antibiotic and a β-lactamase inhibitor.

Piperacillin sodium exerts bactericidal activity by inhibiting septum formation and cell wall synthesis. Piperacillin and other β-lactam antibiotics block the terminal transpeptidation step of cell wall peptidoglycan biosynthesis in susceptible bacteria by interacting with penicillin-binding proteins (PBPs), the bacterial enzymes that carry out this reaction. *In vitro*, piperacillin is active against a variety of gram-positive and gram-negative aerobic and anaerobic bacteria.

Piperacillin has reduced activity against bacteria harboring certain β-lactamase enzymes, which chemically inactivate piperacillin and other β-lactam antibiotics. Tazobactam sodium, which has very little intrinsic antimicrobial activity, due to its low affinity for PBPs, can restore or enhance the activity of piperacillin against many of these resistant organisms. Tazobactam is a potent inhibitor of many class A β-lactamases (penicillinases, cephalosporinases and extended spectrum enzymes). It has variable activity against class A carbapenemases and class D β-lactamases. It is not active against most class C cephalosporinases and inactive against Class B metallo-β-lactamases.

Two features of piperacillin/tazobactam lead to increased activity against some organisms harboring β-lactamases that, when tested as enzyme preparations, are less inhibited by tazobactam and other inhibitors: tazobactam does not induce chromosomally mediated β-lactamases at tazobactam levels achieved with the recommended dosing regimen and piperacillin is relatively refractory to the action of some β-lactamases.

Like other β-lactam antibiotics, piperacillin, with or without tazobactam, demonstrates time-dependent bactericidal activity against susceptible organisms.

Mechanism of Resistance

There are three major mechanisms of resistance to β-lactam antibiotics: changes in the target PBPs resulting in reduced affinity for the antibiotics, destruction of the antibiotics by bacterial β-lactamases, and low intracellular antibiotic levels due to reduced uptake or active efflux of the antibiotics.

In gram-positive bacteria, changes in PBPs are a major mechanism of resistance to β-lactam antibiotics, including piperacillin/tazobactam. This mechanism is responsible for methicillin resistance in staphylococci and penicillin resistance in *Streptococcus pneumoniae* as well as viridans group streptococci and enterococci. Resistance caused by changes in PBPs also occurs to a lesser extent in fastidious gram-negative species, such as *Haemophilus influenzae* and *Neisseria gonorrhoeae*. Piperacillin/tazobactam is not active against strains in which resistance to β-lactam antibiotics is determined by altered PBPs. As indicated above, there are some β-lactamases that are not inhibited by tazobactam.

Methodology for Determining the *In Vitro* Susceptibility of Bacteria to Piperacillin/Tazobactam

Susceptibility testing should be conducted using standardized laboratory methods, such as those described by the Clinical and Laboratory Standards Institute (CLSI). These include dilution methods (minimal inhibitory concentration [MIC] determination) and disk susceptibility methods. Both CLSI and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) provide susceptibility interpretive criteria for some bacterial species based on these methods. It should be noted that for the disk diffusion method, CLSI and EUCAST use disks with different drug contents of piperacillin and tazobactam.

CLSI Reference Information

The CLSI interpretive criteria for susceptibility testing of piperacillin/tazobactam are listed in the following table:

CLSI Susceptibility Interpretive Criteria for Piperacillin/Tazobactam

Pathogen	Minimal Inhibitory Concentration (mg/L of Piperacillin)[a]				Disk[b] Diffusion Inhibition Zone (mm Diameter)			
	S	**SDD**	**I**	**R**	**S**	**SDD**	**I**	**R**
Enterobacterales[c]	≤8	16		≥32	≥25	21-24		≤20
Pseudomonas aeruginosa[d]	≤16		32 - 64	≥128	≥21		15 - 20	≤14
Acinetobacter spp.	≤16		32 - 64	≥128	≥21		18 - 20	≤17
Certain other non-*Enterobacterales*[e]	≤16		32 - 64	≥128				
Haemophilus influenzae and *Haemophilus parainfluenzae*	≤1		-	≥2	≥21		-	-
Anaerobes[f]	≤16		32 - 64	≥128	-		-	-

Source: Clinical and Laboratory Standards Institute. *Performance Standards for Antimicrobial Susceptibility Testing.* CLSI document M100:ED32 2022. This document is updated annually and may be accessed at http://clsi-m100.com/.
S = Susceptible. SDD = Susceptible dose-dependent. I = Intermediate. R = Resistant.
[a] MICs are determined using a fixed concentration of 4 mg/L tazobactam and by varying the concentration of piperacillin.
[b] CLSI inhibition zones are based on disks containing 100 µg of piperacillin and 10 µg of tazobactam.
[c] Breakpoints for susceptible are based on a dosage regimen of 3.375-4.5 g administered every 6 h as a 30-min infusion. Breakpoints for SDD are based on a dosage regimen of 4.5 g administered every 6 h as a 3 h infusion or 4.5 g administered every 8 h as a 4 h infusion.
[d] Breakpoints are based on a dosage regimen of at least 3 g piperacillin administered every 6 h.
[e] Refer to CLSI Document M100 Table 2B-5 for the list of organisms included.
[f] With the exception of *Bacteroides fragilis*, MICs are determined by agar dilution only.
Susceptibility of *Staphylococcus aureus* to piperacillin/tazobactam is determined by the susceptibility to oxacillin (CLSI document M100 Table 2C. *Staphylococcus* spp.).

Standardized susceptibility test procedures require the use of quality control microorganisms to control the technical aspects of the test procedures. Quality control microorganisms are specific strains with intrinsic biological properties relating to resistance mechanisms and their genetic expression within the microorganism; the specific strains used for susceptibility test quality control are not clinically significant.

Organisms and quality control ranges for piperacillin/tazobactam to be utilized with CLSI methodology and susceptibility test interpretive criteria are listed in the following table:

Quality Control Ranges for Piperacillin/Tazobactam to be Used in Conjunction with CLSI Susceptibility Test Interpretive Criteria		
	Minimal Inhibitory Concentration (mg/L of piperacillin)	**Disk Diffusion Inhibition Zone (mm Diameter)**
Quality Control Strain		
Escherichia coli ATCC 25922	1 - 4	24 - 30
Pseudomonas aeruginosa ATCC 27853	1 - 8	25 - 33
Staphylococcus aureus ATCC 29213	0.25 - 2	-
Staphylococcus aureus ATCC 25923	-	27 - 36
Enterococcus faecalis ATCC 29212	1 - 4	
Escherichia coli ATCC 35218	0.5 - 2	24 - 30
Klebsiella pneumoniae ATCC 700603	8 - 32	
Haemophilus influenzae ATCC 49247	0.06 - 0.5	33 - 38
Bacteroides fragilis ATCC 25285	0.12 - 0.5[a]	-
Bacteroides thetaiotaomicron ATCC 29741	4 - 16[a]	-
Clostridioides (formerly *Clostridium*) *difficile* ATCC 700057	4 - 16[a]	
Eggerthella lenta (formerly *Eubacterium lentum*) ATCC 43055	4 - 16[a]	

Source: Clinical and Laboratory Standards Institute. *Performance Standards for Antimicrobial Susceptibility Testing.* CLSI document M100 ED32. 2022.
[a] These ranges are for agar dilution only.

EUCAST Reference Information

EUCAST has also established clinical breakpoints for piperacillin/tazobactam against some organisms. Like CLSI, the EUCAST MIC susceptibility criteria are based on a fixed concentration of 4 mg/L of tazobactam. However, for inhibition zone determination, the disks contain 30 µg of piperacillin and 6 µg of tazobactam. The EUCAST Breakpoint Tables v. 12.0 2022 indicates that the standard dosage on which breakpoints are based is 4 g piperacillin + 0.5 g tazobactam iv 4 times daily or 3 times by extended 4-hour infusion, although 3 times daily iv is adequate for some infections such as complicated UTI, intra-abdominal infections and diabetic foot infections when not caused by isolates resistant to third-generation cephalosporins. A higher dosage (4 times daily by extended 3-hour infusion) may be indicated in some cases.

The EUCAST breakpoints for piperacillin/tazobactam are listed in the following table:

EUCAST Susceptibility Interpretive Criteria for Piperacillin/Tazobactam				
	Minimal Inhibitory Concentration (mg/L of Piperacillin)[a]		**Disk[b] Diffusion Inhibition Zone (mm Diameter)**	
Pathogen[c]	S	R	S	R
*Enterobacteriales (*formerly *Enterobacteriaceae)*	≤8	>8	≥20	<20
Pseudomonas species	≤0.001[1]	>16	≥50	<18
Staphylococcus species	-[2]	-	-	
Enterococcus species	-[3]	-	-	
Streptococcus Groups A, B, C and G	-[4]	-	-	
Streptococcus pneumoniae	-[5]	-	-	
Viridans group streptococci	-[6]	-	-	
Haemophilus influenzae	≤0.25	>0.25	≥27[7]	<27
Moraxella catarrhalis	-[8]	-	-	-
Bacteroides species (except *B. thetaiotaomicron*)	≤8	>8	≥20	<20
Prevotella species	≤0.5	>0.5	≥26	<26
Fusobacterium necrophorum	≤0.5	>0.5	≥32	<32
Clostridium perfringens	≤0.5	>0.5	≥24	<24
Cutibacterium acnes	≤0.25	>0.25	≥27	<27
Vibrio species	≤1	>1	≥26	<26
Achromobacter xylosoxidans	≤4	>4	≥26	<26
Non-species related (PK-PD)	≤8	>16	-	-

Sources:
EUCAST Clinical Breakpoint Table v. 12.0, 1 January 2022.
S = Susceptible. R = Resistant.
[a] MICs are determined using a fixed concentration of 4 mg/L tazobactam and by varying the concentration of piperacillin.
[b] EUCAST inhibition zones are based on disks containing 30 µg of piperacillin and 6 µg of tazobactam.
[c] For pathogens not specifically stated use Non-species related (PK-PD).

[1] For several agents, EUCAST has introduced breakpoints which categorize wild-type organisms (organisms without phenotypically detectable acquired resistance mechanisms to the agent) as "Susceptible, increased exposure (I)" instead of "Susceptible, standard dosing regimen (S)". Susceptible breakpoints for these organism agent combinations are listed as arbitrary, "off scale" breakpoints of S ≤0.001 mg/L.
[2] Most *S. aureus* are penicillinase producers and some are methicillin resistant. Either mechanism renders them resistant to benzylpenicillin, phenoxymethylpenicillin, ampicillin, amoxicillin, piperacillin and ticarcillin. Isolates that test

EUCAST Susceptibility Interpretive Criteria for Piperacillin/Tazobactam				
	Minimal Inhibitory Concentration (mg/L of Piperacillin)[a]		**Disk[b] Diffusion Inhibition Zone (mm Diameter)**	
Pathogen[c]	S	R	S	R

susceptible to benzylpenicillin and cefoxitin can be reported susceptible to all penicillins. Isolates that test resistant to benzylpenicillin but susceptible to cefoxitin are susceptible to β-lactam β-lactamase inhibitor combinations, the isoxazolyl penicillins (oxacillin, cloxacillin, dicloxacillin and flucloxacillin) and nafcillin. For agents given orally, care to achieve sufficient exposure at the site of the infection should be exercised. Isolates that test resistant to cefoxitin are resistant to all penicillins. Most staphylococci are penicillinase producers and some are methicillin resistant. Either mechanism renders them resistant to benzylpenicillin, phenoxymethylpenicillin, ampicillin, amoxicillin, piperacillin and ticarcillin. No currently available method can reliably detect penicillinase production in all species of staphylococci but methicillin resistance can be detected with cefoxitin as described. Ampicillin susceptible *S. saprophyticus* are *mecA*-negative and susceptible to ampicillin, amoxicillin and piperacillin (without or with a beta-lactamase inhibitor).

[3] Susceptibility to ampicillin, amoxicillin and piperacillin (with and without beta-lactamase inhibitor) can be inferred from ampicillin. Ampicillin resistance is uncommon in *E. faecalis* (confirm with MIC) but common in *E. faecium*.

[4] The susceptibility of streptococcus groups A, B, C and G to penicillins is inferred from the benzylpenicillin susceptibility (indications other than meningitis) with the exception of phenoxymethylpenicillin and isoxazolyl penicillins for streptococcus group B.

[5] The oxacillin 1 μg disk screen test or a benzylpenicillin MIC test shall be used to exclude beta-lactam resistance mechanisms. When the screen is negative (oxacillin inhibition zone ≥20 mm, or benzylpenicillin MIC ≤0.06 mg/L) all beta-lactam agents for which clinical breakpoints are available, including those with "Note" can be reported susceptible without further testing, except for cefaclor, which if reported, should be reported as "susceptible, increased exposure" (I). When the screen is positive (inhibition zone <20 mm, or benzylpenicillin MIC >0.06 mg/L). The addition of a beta-lactamase inhibitor does not add clinical benefit.

[6] Benzylpenicillin (MIC or disk diffusion) can be used to screen for beta-lactam resistance in viridans group streptococci. Isolates categorised as screen negative can be reported susceptible to beta-lactam agents for which clinical breakpoints are listed (including those with "Note"). Isolates categorised as screen positive should be tested for susceptibility to individual agents or reported resistant. For benzylpenicillin screen negative isolates (inhibition zone ≥18 mm or MIC ≤0.25 mg/L), susceptibility can be inferred from benzylpenicillin or ampicillin. For benzylpenicillin screen positive isolates (inhibition zone <18 mm or MIC >0.25 mg/L), susceptibility is inferred from ampicillin.

[7] The benzylpenicillin 1 unit disk screen test shall be used to exclude beta-lactam resistance mechanisms. When the screen is negative (inhibition zone ≥12 mm) all penicillins for which clinical breakpoints are available, including those with "Note", can be reported susceptible without further testing, except for amoxicillin oral and amoxicillin-clavulanic acid oral, which if reported, should be reported "susceptible, increased exposure" (I). When the screen is positive (inhibition zone <12 mm). Read the outer edge of zones where an otherwise clear inhibition zone contains an area of growth around the disk.

[8] Susceptibility can be inferred from amoxicillin-clavulanic acid.

Quality control ranges for EUCAST susceptibility breakpoints are listed in the following table.

Quality Control Ranges for Piperacillin/Tazobactam to be Used in Conjunction with EUCAST Susceptibility Test Interpretive Criteria		
	Minimal Inhibitory Concentration (mg/L of piperacillin)	**Disk Diffusion Inhibition Zone (mm Diameter)**
Quality Control Strain		
Escherichia coli ATCC 25922	1 - 4	21 - 27
Pseudomonas aeruginosa ATCC 27853	1 - 8	23 - 29
Haemophilus influenzae ATCC 49766	-[1]	32 - 40
Escherichia coli ATCC 35218	0.5 - 2	21 - 27
Klebsiella pneumoniae ATCC 700603*	8 - 32	14 - 20

Source: The European Committee on Antimicrobial Susceptibility Testing. Routine and extended internal quality control for MIC determination and disk diffusion as recommended by EUCAST. Version 12.0, 2022. http://www.eucast.org.
[1] Either *E. coli* ATCC 35218 or *K. pneumoniae* ATCC 700603 can be used to check the inhibitor component (see Routine quality control for β-lactam-inhibitor combinations). Use *E. coli* ATCC 25922 to control the piperacillin component (according to methodology for *E. coli*).
* Two colony types are normally observed for this strain and should be included when subculturing and testing the strain.

Antibacterial Spectrum based on *in vitro* data (Groupings of relevant species according to piperacillin / tazobactam susceptibility)

Commonly susceptible species

Aerobic gram-positive microorganisms:

Enterococcus faecalis (ampicillin-or penicillin-susceptible isolates only)
Listeria monocytogenes
Staphylococcus aureus (methicillin-susceptible isolates only)
Staphylococcus spp., coagulase-negative (methicillin-susceptible isolates only)
Streptococcus agalactiae (Group B streptococci)†
Streptococcus pyogenes (Group A streptococci)†

Aerobic gram-negative microorganisms:

Citrobacter koseri
Haemophilus influenzae
Moraxella catarrhalis
Proteus mirabilis

Anaerobic gram-positive microorganisms:

Clostridium spp.
Eubacterium spp.
Anaerobic gram-positive cocci††

Anaerobic gram-negative microorganisms:

Bacteroides fragilis group
Fusobacterium spp.
Porphyromonas spp.
Prevotella spp.

Species for which acquired resistance may be a problem

Aerobic gram-positive microorganisms:

Enterococcus faecium
Streptococcus pneumoniae[††]
Viridans group streptococci[††]

Aerobic gram-negative microorganisms:

Acinetobacter baumannii
Citrobacter freundii
Enterobacter spp.
Escherichia coli
Klebsiella pneumoniae
Morganella morganii
Proteus vulgaris
Providencia spp.
Pseudomonas aeruginosa
Serratia spp.

Inherently resistant organisms

Aerobic gram-positive microorganisms:

Corynebacterium jeikeium

Aerobic gram-negative microorganisms:

Burkholderia cepacia
Legionella spp.
Stenotrophomonas maltophilia

Other microorganisms:

Chlamydophila pneumoniae
Mycoplasma pneumoniae

[†]Streptococci are not β-lactamase producing bacteria; resistance in these organisms is due to alterations in penicillin-binding proteins (PBPs) and, therefore, piperacillin/tazobactam-susceptible isolates are susceptible to piperacillin alone. Penicillin resistance has not been reported in *S. pyogenes*.

[††]Including *Anaerococcus, Finegoldia, Peptococcus, Peptoniphilus,* and *Peptostreptococcus* spp. (CLSI M100 Ed. 29, 2019).

MERINO Trial (blood stream infections due to ESBL producing organisms)

In a prospective, randomized non-inferiority clinical trial, definitive (i.e., based on susceptibility confirmed *in vitro*) treatment with piperacillin/tazobactam did not meet non-inferiority in regard to 30-day mortality in the treatment of blood stream infections due to ESBL producing *E. coli* or *Klebsiella pneumoniae* in critically ill adult patients. A total of 23 of 187 patients (12.3%) randomized to piperacillin/tazobactam met the primary outcome of mortality at 30 days compared with 7 of 191 (3.7%) randomized to meropenem (risk difference, 8.6% [1-sided 97.5% CI − ∞ to 14.5%]; P = 0.90 for non-inferiority). Clinical and microbiological resolution by day 4 occurred in 121 of 177 patients (68.4%) in the piperacillin/tazobactam group compared with 138 of 185 (74.6%), randomized to meropenem (risk difference, −6.2% [95% CI, −15.5 to 3.1%]; P = 0.19). The cause of the mortality imbalance is not clear. This study was not sponsored by Pfizer.

5.2. Pharmacokinetic properties

Adults

Peak plasma concentrations of piperacillin and tazobactam are attained immediately after completion of an intravenous infusion of TAZOCIN. Piperacillin plasma concentrations, following a 30-minute infusion of TAZOCIN, were similar to those attained when equivalent doses of piperacillin were administered alone, with mean peak plasma concentrations of approximately 134, 242 and 298 µg/mL for the 2.25 g, 3.375 g and 4.5 g TAZOCIN (piperacillin/tazobactam) doses, respectively. The corresponding mean peak plasma concentrations of tazobactam were 15, 24 and 34 µg/mL, respectively.

Following a 30-minute I.V. infusion of 3.375 g TAZOCIN every 6 hours, steady-state plasma concentrations of piperacillin and tazobactam were similar to those attained after the first dose. In like manner, steady-state plasma concentrations were not different from those attained after the first dose when 2.25 g or 4.5 g doses of TAZOCIN were administered via 30-minute infusions every 6 hours. Steady-state plasma concentrations after 30-minute infusions every 6 hours are provided in the table below.

STEADY-STATE MEAN PLASMA CONCENTRATIONS IN ADULTS AFTER 30-MINUTE INTRAVENOUS INFUSION OF PIPERACILLIN/TAZOBACTAM EVERY 6 HOURS								
PIPERACILLIN								
		Plasma Concentrations (µg/mL)**						**AUC** (µg•h/mL)**
Piperacillin/ Tazobactam Dose[a]	**No. of Evaluable Subjects**	**30 min**	**1 h**	**2 h**	**3 h**	**4 h**	**6 h**	**AUC_{0-6}**
2.25 g	8	134 (14)	57 (14)	17.1 (23)	5.2 (32)	2.5 (35)	0.9 (14)[b]	131 (14)
3.375 g	6	242 (12)	106 (8)	34.6 (20)	11.5 (19)	5.1 (22)	1.0 (10)	242 (10)
4.5 g	8	298 (14)	141 (19)	46.6 (28)	16.4 (29)	6.9 (29)	1.4 (30)	322 (16)

STEADY-STATE MEAN PLASMA CONCENTRATIONS IN ADULTS AFTER 30-MINUTE INTRAVENOUS INFUSION OF PIPERACILLIN/TAZOBACTAM EVERY 6 HOURS								
TAZOBACTAM								
		Plasma Concentrations (µg/mL)**						**AUC** (µg•h/mL)**
Piperacillin/ Tazobactam Dose[a]	**No. of Evaluable Subjects**	**30 min**	**1 h**	**2 h**	**3 h**	**4 h**	**6 h**	**AUC_{0-6}**
2.25 g	8	14.8 (14)	7.2 (22)	2.6 (30)	1.1 (35)	0.7 (6)[c]	<0.5	16.0 (21)
3.375 g	6	24.2 (14)	10.7 (7)	4.0 (18)	1.4 (21)	0.7 (16)[b]	<0.5	25.0 (8)
4.5 g	8	33.8 (15)	17.3 (16)	6.8 (24)	2.8 (25)	1.3 (30)	<0.5	39.8 (15)

** Numbers in parentheses are coefficients of variation (CV%).
[a]: Piperacillin and tazobactam were given in combination.
[b]: N = 4
[c]: N = 3

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 are widely distributed into tissues and body fluids including intestinal mucosa, gallbladder, lung, female reproductive tissues (uterus, ovary, and fallopian tube), interstitial fluid, bile and bone. 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.

Metabolism

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

Elimination

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 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 administration of single or multiple TAZOCIN doses to healthy subjects, the plasma half-life of piperacillin and of 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 the pharmacokinetics of piperacillin due to tazobactam. Piperacillin appears to reduce the rate of elimination of tazobactam.

Special Populations

The half-lives of piperacillin and of tazobactam increase by approximately 25% and 18%, respectively, in patients with hepatic cirrhosis compared to healthy subjects. However, this difference does not warrant dosage adjustment of TAZOCIN due to hepatic cirrhosis.

The half-lives of piperacillin and tazobactam increase 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.

Hemodialysis 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.

5.3. Preclinical safety data

Carcinogenicity

Carcinogenicity studies have not been conducted with piperacillin, tazobactam, or the combination.

Mutagenicity

Piperacillin/tazobactam was negative in microbial mutagenicity assays. Piperacillin/tazobactam was negative in the unscheduled DNA synthesis (UDS) test. Piperacillin/tazobactam was negative in a mammalian point mutation (Chinese hamster ovary cell hypoxanthine phosphoribosyltransferase [HPRT]) assay. Piperacillin/tazobactam was negative in a mammalian cell (BALB/c-3T3) transformation assay. *In vivo*, piperacillin/tazobactam did not induce chromosomal aberrations in rats dosed intravenously.

Piperacillin was negative in microbial mutagenicity assays. There was no DNA damage in bacteria (Rec assay) exposed to piperacillin. Piperacillin was negative in the UDS test. In a mammalian point mutation (mouse lymphoma cells) assay, piperacillin was positive. Piperacillin was negative in a cell (BALB/c-3T3) transformation assay. *In vivo*, piperacillin did not induce chromosomal aberrations in mice dosed intravenously.

Tazobactam was negative in microbial mutagenicity assays. Tazobactam was negative in the UDS test. Tazobactam was negative in a mammalian point mutation (Chinese hamster ovary cell HPRT) assay. In another mammalian point mutation (mouse lymphoma cells) assay, tazobactam was positive. Tazobactam was negative in a cell (BALB/c-3T3) transformation assay. In an *in vitro* cytogenetics (Chinese hamster lung cells) assay, tazobactam was negative. *In vivo*, tazobactam did not induce chromosomal aberrations in rats dosed intravenously.

Reproductive Toxicity

In embryo-fetal development studies there was no evidence of teratogenicity following intravenous administration of tazobactam or the piperacillin/tazobactam combination; however, in rats there were slight reductions in fetal body weight at maternally toxic doses.

Intraperitoneal administration of piperacillin/tazobactam was associated with slight reductions in litter size and an increased incidence of minor skeletal anomalies (delays in bone ossification) at doses that produced maternal toxicity. Peri-/post-natal development was impaired (reduced pup weights, increase in still birth, increase in pup mortality) concurrent with maternal toxicity.

Impairment of Fertility

Reproduction studies in rats revealed no evidence of impaired fertility due to tazobactam, or piperacillin/tazobactam when administered intraperitoneally.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Citric Acid (monohydrate), Edetate Disodium (dihydrate), Nitrogen, Sodium Bicarbonate and Water for Injection.

6.2. Incompatibilities

Solutions known to be compatible with TAZOCIN containing EDTA for reconstitution are:

- 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

The reconstituted solution of TAZOCIN containing EDTA may be further diluted to the desired volume (e.g., 50 mL to 150 mL) with one of the compatible solvents for intravenous use listed below:

- 0.9% Sodium chloride for injection
- Sterile water for injection[†]
- Dextrose 5%
- Dextran 6% in saline
- Lactated Ringer's injection
- Hartmann's solution
- Ringer's acetate
- Ringer's acetate/malate

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

Whenever TAZOCIN is used concurrently with another antibiotic (e.g., aminoglycosides), the drugs must be administered separately. The mixing of TAZOCIN with an aminoglycoside *in vitro* can result in substantial inactivation of the aminoglycoside.

The mixing of β-lactam antibiotics with aminoglycosides *in vitro* can result in substantial inactivation of the aminoglycoside. However, amikacin and gentamicin were determined to be compatible with TAZOCIN *in vitro* in certain diluents at specific concentrations (see section 4.2).

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

Because of chemical instability, TAZOCIN should not be used with solutions containing only sodium bicarbonate.

TAZOCIN should not be added to blood products or albumin hydrolysates.

6.3. Shelf-life

Refer to outer carton.

6.4. Special precautions for storage

Before reconstitution, store TAZOCIN vials below 30°C. TAZOCIN vials should be used immediately after reconstitution. For vials not used immediately after reconstitution, please follow these guidelines:

- After reconstitution: Discard any unused portion after 24 hours if stored below 25°C or after 48 hours if refrigerated (2°C-8°C).
- Vials should not be frozen after reconstitution.

6.5. Nature and contents of container

Vials containing 4.5 g TAZOCIN:

1 box of 1 vial
1 box of 10 vials
1 box of 12 vials

(Not all pack sizes may be marketed)

6.6. Special precautions for disposal and other handling

Directions for Reconstitution and Dilution for 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 5 to 10 minutes.

Vial Size (PIPERACILLIN/TAZOBACTAM)	**Volume of Compatible Solvent to be Added to Vial**
4.5 g	20 mL

7. PRODUCT OWNER

Pfizer Inc.
New York
United States

TAZ-SIN-0424/0
Date of last revision: April 2024