

Generic Name: Sterile Piperacillin/Tazobactam Sodium
Trade Name: TAZOCIN®
CDS Effective Date: September 13, 2021
Supersedes: March 26, 2019
Approved by BPOM: July 28, 2023

PT PFIZER INDONESIA LOCAL PRODUCT DOCUMENT

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PRESENTATION

TAZOCIN, piperacillin/tazobactam parenteral combination, is a white to off-white sterile, cryodesiccated powder consisting of piperacillin and tazobactam as their sodium salts packaged in glass vials. The product does not contain excipients or preservatives.

Each TAZOCIN 4.5 g single-dose vial contains an amount of drug sufficient for withdrawal of piperacillin sodium equivalent to 4 g of piperacillin and tazobactam sodium equivalent to 0.5 g of tazobactam. The product also contains 1 mg edetate disodium (dihydrate) (EDTA) per vial.

INDICATIONS AND USAGE

TAZOCIN is indicated for the treatment of patients with moderate to severe infections caused by piperacillin resistant, piperacillin/tazobactam susceptible, β -lactamase producing strains of the designated microorganisms in the specified conditions listed below:

Appendicitis (complicated by rupture or abscess) and peritonitis caused by piperacillin resistant, β -lactamase producing strains of *Escherichia coli* or the following members of the *Bacteroides fragilis* group: *B. fragilis*, *B. ovatus*, *B. thetaiotaomicron* or *B. vulgatus*. The individual members of this group were studied in less than 10 cases.

Uncomplicated and complicated skin and skin structure infections, including cellulitis, cutaneous abscesses, and ischemic/diabetic foot infections caused by piperacillin resistant, β -lactamase producing strains of *Staphylococcus aureus*.

Postpartum endometritis or pelvic inflammatory disease caused by piperacillin resistant, β -lactamase producing strains of *Escherichia coli*.

Community-acquired pneumonia (moderate severity only) caused by piperacillin resistant, β -lactamase producing strains of *Haemophilus influenzae*.

As a combination product, TAZOCIN is indicated only for the specified conditions listed above. Infections caused by piperacillin susceptible organisms, for which piperacillin has been shown to be effective are also amenable to TAZOCIN treatment due to its piperacillin content. The tazobactam component of this combination product does not decrease the activity of the piperacillin component against piperacillin susceptible organisms. Therefore, the treatment of mixed infections caused by piperacillin susceptible organisms and piperacillin resistant, β -lactamase producing organisms susceptible to TAZOCIN should not require the addition of another antibiotic.

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TAZOCIN is useful as presumptive therapy in the indicated conditions prior to the identification of causative organisms because of its broad spectrum of bactericidal activity against gram-positive and gram-negative aerobic and anaerobic organisms. Appropriate cultures should usually be performed before initiating antimicrobial treatment in order to isolate and identify the organisms causing infection and to determine their susceptibility to TAZOCIN. Antimicrobial therapy should be adjusted, if appropriate, once the results of culture(s) and antimicrobial susceptibility testing are known.

Adults and children:

Febrile neutropenic infections. Combination treatment with an aminoglycoside is recommended.

DOSAGE AND ADMINISTRATION

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

Duration of Therapy

The usual duration of TAZOCIN treatment is from seven to ten days.

The duration of therapy should be guided by the severity of the infection and the patient's clinical and bacteriological progress.

Adults and Children Aged 12 Years and Older

In general, the recommended total daily dosage is 12 g of piperacillin/1.5 g of tazobactam given in divided doses every 6 or 8 hours. Doses as high as 18 g of piperacillin/2.25 g of tazobactam per day in divided doses can be used in severe infections.

In neutropenia, the recommended dose is 4.5 g TAZOCIN (4 g piperacillin/500 mg tazobactam) given every 6 hours in combination with aminoglycoside.

Pediatric Neutropenia

Febrile neutropenic patients in combination with an aminoglycoside:

For children aged 2-12 years with normal renal function and weighing less than 50 kg, the dose should be adjusted to 80 mg of piperacillin/10 mg of tazobactam per kilogram of body weight every 6 hours, in combination with the appropriate dose of an aminoglycoside.

For children weighing over 50 kg, follow the adult dosing, in combination with the appropriate dose of an aminoglycoside.

Use in Patients with Renal Impairment

In patients with renal impairment or in hemodialysis patients, intravenous dosages and administration intervals should be adjusted to the degree of renal function impairment as follows.

The recommended daily doses are as follows:

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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 hemodialysis, the maximum dose is 2.25 g TAZOCIN eight hours. For patients on hemodialysis, one additional dose of piperacillin/tazobactam 2 g/0.25 g should be administered following each dialysis period, because hemodialysis removes 30%-50% of piperacillin in 4 hours.

Use in Patients with Hepatic Impairment

No dosage adjustment is necessary in patients with hepatic impairment.

Co-administration of Piperacillin/Tazobactam with Aminoglycosides

Due to the *in vitro* inactivation of the aminoglycoside by β -lactam antibiotics, TAZOCIN and the aminoglycoside are recommended for separate administration. TAZOCIN and the aminoglycoside should be reconstituted and diluted separately when concomitant therapy with aminoglycosides is indicated (see Section **COMPATIBILITIES, INCOMPATIBILITIES**).

In circumstances where co-administration is preferred, the reformulated TAZOCIN 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	TAZOCIN (g) dose	TAZOCIN 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	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 TAZOCIN with other aminoglycosides has not been established. Only the concentration and diluents for amikacin and gentamicin with the dosages of TAZOCIN 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 TAZOCIN.

CONTRAINDICATIONS

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

SPECIAL WARNINGS

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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 TAZOCIN.

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 **ADVERSE REACTIONS**). If patients develop a skin rash they should be monitored closely and Piperacillin/tazobactam discontinued if lesions progress.

Rare cases of haemophagocytic 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, hyperferritinaemia, hypertriglyceridaemia, hypofibrinogenaemia, and haemophagocytosis. If piperacillin tazobactam is suspected as possible trigger, treatment should be discontinued.

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.

PRECAUTIONS

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 **INTERACTIONS**). 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 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.

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 **ADVERSE REACTIONS**).

Use in Patients with Hepatic Impairment

No dosage adjustment of piperacillin/tazobactam is necessary in patients with hepatic impairment.

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Renal Impairment

Due to its potential nephrotoxicity (see Section **ADVERSE REACTIONS**), 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 **DOSAGE AND ADMINISTRATION**).

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 **INTERACTIONS**).

PREGNANCY

Studies in mice and rats have not demonstrated any reproductive or embryo-fetal effects with piperacillin-tazobactam combination when administered intravenously. 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.

LACTATION

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.

GERIATRIC USE

Patients over 65 years are not at an increased risk of developing adverse effects solely because of age. However, dosage should be adjusted in the presence of renal insufficiency.

INTERACTIONS

Non-Depolarizing Muscle Relaxants

Piperacillin when used concomitantly with vecuronium has been implicated in prolonging of the neuromuscular blockade of vecuronium. Due to their similar mechanism of action, it is expected that the neuromuscular blockade produced by any of the non-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

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should be performed more frequently and monitored regularly (see Section **PRECAUTIONS**).

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 mild or moderate renal impairment. The pharmacokinetics of piperacillin, tazobactam, and the M1 metabolite were also not significantly altered by tobramycin administration.

TAZOCIN is not compatible with tobramycin for simultaneous co-administration via Y-site infusion.

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 **PRECAUTIONS**). Some of these studies have reported that the interaction is vancomycin dose-dependent. Expert guidelines recommend intensive vancomycin dosing and maintenance of trough levels between 15 mg/L and 20 mg/L which is an increase from previously published recommendations of target trough concentrations of 5-10 mg/L. Attaining these trough concentrations often requires practitioners to prescribe vancomycin doses which exceed manufacturers' recommendations. Therefore, it is possible that in addition to the increased risk of vancomycin-induced nephrotoxicity reported with adherence to these guidelines the risk of nephrotoxicity may also increase due to an interaction with piperacillin/tazobactam.

No pharmacokinetic interactions have been noted between PIPERACILLIN/TAZOBACTAM and vancomycin.

INTERFERENCE WITH LABORATORY AND OTHER DIAGNOSTIC TESTS

As with other penicillins, the administration of TAZOCIN 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 TAZOCIN 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.

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

ADVERSE REACTIONS

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, anaemia*	leukopenia	agranulocytosis	pancytopenia*, neutropenia, haemolytic anaemia*, thrombocytosis*, eosinophilia*
Immune system disorders					anaphylactoid shock*, anaphylactic shock*, anaphylactoid reaction*, anaphylactic reaction*, hypersensitivity*
Metabolism and nutrition disorders			hypokalaemia		
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	diarrhoea	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 generalised

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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)
					exanthematous pustulosis (AGEP)*, dermatitis exfoliative*, dermatitis bullous, purpura
Musculoskeletal and connective tissue disorders			arthralgia, myalgia		
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.

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

OVERDOSAGE

Symptoms

There have been post-marketing reports of overdose with TAZOCIN. 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

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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 hemodialysis.

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.

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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.

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	I	R	S	I	R
<i>Enterobacteriaceae</i>	≤16	32-64	≥128	≥21	18-20	≤17
<i>Acinetobacter</i> spp.	≤16	32-64	≥128	≥21	18-20	≤17
<i>Pseudomonas aeruginosa</i>	≤16	32-64	≥128	≥21	15-20	≤14
Certain other non-fastidious gram-negative bacilli ^c	≤16	32-64	≥128	-	-	-
<i>Haemophilus influenzae</i> and <i>Haemophilus parainfluenzae</i>	≤1	-	≥2	≥21	-	-
Anaerobes ^d	≤16	32-64	≥128	-	-	-

Source: Clinical and Laboratory Standards Institute. *Performance Standards for Antimicrobial Susceptibility Testing*; CLSI document M100:ED29. CLSI, Wayne, PA, 2019. This document is updated annually and may be accessed at <http://clsi-m100.com/>.

S = Susceptible. I = Intermediate. R = Resistant.

^a MICs are determined using a fixed concentration of 4 mg/L tazobactam and by varying the concentration of piperacillin.

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^b CLSI interpretive criteria are based on disks containing 100 µg of piperacillin and 10 µg of tazobactam.

^c Refer to CLSI Document M100 Table 2B-5 for the list of organisms included.

^d With the exception of *Bacteroides fragilis*, MICs are determined by agar dilution only.

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		
Quality Control Strain	Minimal Inhibitory Concentration (mg/L of piperacillin)	Disk Diffusion Inhibition Zone (mm Diameter)
<i>Escherichia coli</i> ATCC 25922	1-4	24-30
<i>Escherichia coli</i> ATCC 35218	0.5-2	24-30
<i>Pseudomonas aeruginosa</i> ATCC 27853	1-8	25-33
<i>Haemophilus influenzae</i> ATCC 49247	0.06-0.5	33-38
<i>Staphylococcus aureus</i> ATCC 29213	0.25-2	-
<i>Staphylococcus aureus</i> ATCC 25923	-	27-36
<i>Bacteroides fragilis</i> ATCC 25285	0.12-0.5 ^a	-
<i>Enterococcus faecalis</i> ATCC 29212	1-4	-
<i>Bacteroides thetaiotaomicron</i> ATCC 29741	4-16 ^a	-
<i>Clostridioides</i> (formerly <i>Clostridium</i>) <i>difficile</i> ATCC 700057	4-16 ^a	-
<i>Eggerthella lenta</i> (formerly <i>Eubacterium lentum</i>) ATCC 43055	4-16 ^a	-

Source: Clinical and Laboratory Standards Institute. *Performance Standards for Antimicrobial Susceptibility Testing*. CLSI document M100ED29. CLSI, Wayne, PA, 2019.

^a Agar dilution only.

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 rationale document for piperacillin/tazobactam (Piperacillin-tazobactam. Rationale for the EUCAST clinical breakpoints, version 1.0. 22nd November 2010) states that breakpoints for *Pseudomonas aeruginosa* apply to dosages of 4 g, 4 times daily, whereas the breakpoints for other organisms are based on 4 g, 3 times daily.

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

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EUCAST Susceptibility Interpretive Criteria For Piperacillin/Tazobactam				
Pathogen	Minimal Inhibitory Concentration (mg/L of Piperacillin) ^a		Disk ^b Diffusion Inhibition Zone (mm Diameter)	
	S	R	S	R
<i>Enterobacteriales</i> (formerly <i>Enterobacteriaceae</i>)	≤8	>16	≥20	<17
<i>Pseudomonas aeruginosa</i>	≤16	>16	≥18	<18
<i>Haemophilus influenzae</i>	≤0.25	≤0.25	≥27	<27
Gram-positive anaerobes	≤8	>16	-	-
Gram-negative anaerobes	≤8	>16	-	-
Non-species related (PK-PD)	≤4	>16	-	-

Sources: EUCAST Clinical Breakpoint Table v. 9.0, 1 January, 2019.

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 interpretive criteria are based on disks containing 30 µg of piperacillin and 6 µg of tazobactam.

Per EUCAST, for species without piperacillin/tazobactam breakpoints, susceptibility in staphylococci is inferred from cefoxitin/oxacillin susceptibility. For groups A, B, C and G streptococci and *Streptococcus pneumoniae*, susceptibility is inferred from benzylpenicillin susceptibility. For other streptococci, enterococci, and β-lactamase-negative *Haemophilus influenzae*, susceptibility is inferred from amoxicillin-clavulanate susceptibility. There are no EUCAST breakpoints for *Acinetobacter*. The EUCAST rationale document for piperacillin/tazobactam states that in endocarditis caused by streptococci other than groups A, B, C and G and *S. pneumoniae*, national or international guidelines should be referred to.

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		
Quality Control Strain	Minimal Inhibitory Concentration (mg/L of piperacillin)	Disk Diffusion Inhibition Zone (mm Diameter)
<i>Escherichia coli</i> ATCC 25922	1-4	21-27
<i>Escherichia coli</i> ATCC 35218	0.5-2	21-27
<i>Pseudomonas aeruginosa</i> ATCC 27853	1-8	23-29
<i>Klebsiella pneumoniae</i> 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 9.0, 2019. <http://www.eucast.org>.

Antibacterial Spectrum

Piperacillin/tazobactam has been shown to be active against most strains of the following microorganisms, both *in vitro* and in the indicated clinical infections.

Aerobic and facultative gram-positive microorganisms:

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Staphylococcus aureus (methicillin-susceptible strains only)

Aerobic and facultative gram-negative microorganisms:

Acinetobacter baumannii

Escherichia coli

Haemophilus influenzae (excluding β -lactamase negative, ampicillin-resistant isolates)

Klebsiella pneumoniae

Pseudomonas aeruginosa (given in combination with an aminoglycoside to which the isolate is susceptible)

Gram-negative anaerobes:

Bacteroides fragilis group (*B. fragilis*, *B. ovatus*, *B. thetaiotaomicron*, and *B. vulgatus*).

The following *in vitro* data are available, but their clinical significance is unknown.

At least 90% of the following microorganisms exhibit an *in vitro* MIC less than or equal to the susceptible breakpoint for piperacillin/tazobactam. However, the safety and effectiveness of piperacillin/tazobactam in treating clinical infections due to these bacteria have not been established in adequate and well-controlled clinical trials.

Aerobic and facultative gram-positive microorganisms:

Enterococcus faecalis (ampicillin- or penicillin-susceptible isolates only)

Staphylococcus epidermidis (methicillin-susceptible isolates only)

Streptococcus agalactiae[†]

Streptococcus pneumoniae[†] (penicillin-susceptible isolates only)

Streptococcus pyogenes[†]

Viridans group streptococci[†]

Aerobic and facultative gram-negative microorganisms:

Citrobacter koseri

Moraxella catarrhalis

Morganella morganii

Neisseria gonorrhoeae

Proteus mirabilis

Proteus vulgaris

Serratia marcescens

Providencia stuartii

Providencia rettgeri

Salmonella enterica

Gram-positive anaerobes:

Clostridium perfringens

Gram-negative anaerobes:

Bacteroides distasonis

Prevotella melaninogenica

[†]These are not β -lactamase producing bacteria and, therefore, are susceptible to piperacillin

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alone.

Pharmacokinetic Properties

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.

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

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 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 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.

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.

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Preclinical Safety Data

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.

COMPATIBILITIES, 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.

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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 **DOSAGE AND ADMINISTRATION**).

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.

HANDLING

Directions for Reconstitution and Dilution for Use

Intravenous use only: 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
4.50 g	20 mL

HOW SUPPLIED

TAZOCIN (sterile piperacillin sodium and tazobactam sodium) is supplied in the following sizes: Each TAZOCIN 4.5 g vial provides piperacillin sodium equivalent to 4 g of piperacillin and tazobactam sodium equivalent to 0.5 g of tazobactam. Each vial contains 11.17 mEq (256 mg) of sodium.

Before reconstitution, store TAZOCIN vials below 25°C. TAZOCIN vials should be used immediately after reconstitution. For vials not used immediately after reconstitution, please follow these guidelines:

- Discard any unused portion after 24 hours if stored below 25°C, but outside of the refrigerator.
- Discard any unused portion after 7 days, if refrigerated (between 2°C to 8°C)
- Vials should not be frozen after reconstitution.

PRODUCT LICENCE NUMBERS

TAZOCIN; Box, 12 vials @ 4.5 g, Reg. No. DKI1134400144A1

HARUS DENGAN RESEP DOKTER

Manufactured and packaged by:

Wyeth Lederle S.r.l

Via Franco Gorgone Zona Industriale

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I-95100 Catania CT, Italy

Imported by:
PT. Pfizer Indonesia
Jakarta, Indonesia