TAZOCIN® EF
(Piperacillin sodium/tazobactam sodium)

1. NAME OF THE MEDICINAL PRODUCT

Tazocin® EF

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

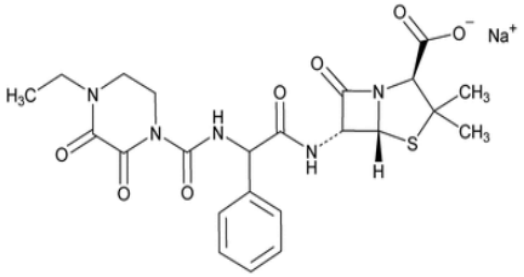
Piperacillin sodium/tazobactam sodium (INN).

Chemical Name

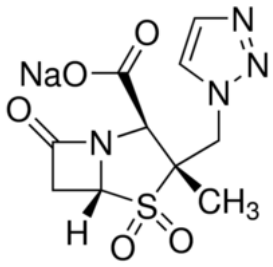
Piperacillin sodium is sodium (2S,5R,6R)-6-[(R)-2-(4-ethyl-2,3-dioxo-1-piperazinecarboxamido)-2-phenylacetamido]-3,3-dimethyl-7-oxo-4-thia-l-azabicyclo[3.2.0]heptane-2-carboxylate.

Tazobactam sodium is sodium (2S,3S,5R)-3-methyl-7-oxo-3-(lH-l,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

Piperacillin sodium is a white crystalline powder. It is freely soluble in water, alcohol, and methyl alcohol but is practically insoluble in ethyl acetate.

Tazobactam sodium is a white to pale yellow non-hydroscopic crystalline powder.

Vials with Lyophilized Powder for Reconstitution

Each vial contains a total of 2.84 mEq (65 mg) of sodium per gram of piperacillin.[158]

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

Piperacillin/tazobactam is indicated for the treatment of the following systemic and/or local bacterial infections caused by gram-positive and gram-negative aerobic and anaerobic organisms susceptible to piperacillin/tazobactam or piperacillin:

Adults

- Lower respiratory tract infections.
- Urinary tract infections.
- Intra-abdominal infections.
- Skin and skin structure infections.
- Bacterial septicemia.
- Gynecological infections, including post-partum endometritis and pelvic inflammatory disease (PID).
- Febrile neutropenic infections. Combination treatment with an aminoglycoside is recommended.[153]
- Bone and joint infections.
- Polymicrobial infections (gram-positive/gram-negative aerobes and anaerobes).

Children (2 years of age or older)

- Febrile neutropenic infections. Combination treatment with an aminoglycoside is recommended.[153]
- Intra-abdominal infections.

In serious infections, empiric therapy with piperacillin/tazobactam may be initiated before susceptibility test results are available.

Note: For associated bacteraemia due to extended-beta-lactamase (ESBL) producing organisms, see section 5.1.[181]

For countries with approved **intramuscular use only**:

- Acute exacerbation of chronic obstructive pulmonary disease.[2,3]
- Uncomplicated urinary tract infections.[3]

4.2. POSOLOGY AND METHOD OF ADMINISTRATION

Piperacillin/tazobactam must be given by slow intravenous infusion (e.g., over 20-30 minutes).

For countries with approved **intramuscular use only:** 2 g of piperacillin/250 mg of tazobactam per injection site must not be exceeded.

Duration of Therapy

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.

For countries with approved **intramuscular use only:** the dose and frequency of piperacillin/tazobactam depends on the severity and localization of the infection and suspected pathogens. The usual dose for adults and adolescents is 2 g/0.25 g every 6 to 12 hours administered by intramuscular injection.

Pediatric Neutropenia

Febrile neutropenic patients in combination with an aminoglycoside:

For children 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.

Pediatric Intra-abdominal Infection

For children aged 2 to 12 years, weighing up to 40 kg, and with normal renal function, the recommended dose is 100 mg piperacillin/12.5 mg tazobactam per kilogram of body weight every 8 hours.

For children aged 2 to 12 years, weighing over 40 kg, and with normal renal function, follow the adult dosing guidance. Therapy is recommended for a minimum of 5 days and a maximum of 14 days, considering that dose administration should continue at least 48 hours after the resolution of clinical signs and symptoms.

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.[4,5,6,161,163]

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, 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.[7]

Co-administration of Piperacillin/Tazobactam with Aminoglycosides

Due to the *in vitro* inactivation of the aminoglycoside by 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 (see section **6.2. Incompatibilities**).

In circumstances where co-administration is preferred, 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:[8]

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[9]
‡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.

Geriatric Population

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.[10]

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 piperacillin/tazobactam, 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.[11,12,13] These reactions are more likely to occur in persons with a history of sensitivity to multiple allergens.[14] 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, and acute generalised exanthematous pustulosis (see section **4.8. Undesirable effects**). If patients develop a skin rash they should be monitored closely and piperacillin/tazobactam discontinued if lesions progress.[151,156]

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.[15,16]

Bleeding manifestations have occurred in some patients receiving β-lactam antibiotics.[17,18,19,20,21] 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[22,23,24] (see section **4.5. Interaction with other medicinal products and other forms of interaction**). 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.[158] 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.[25]

As with treatment with other penicillins, neurological complications in the form of convulsions (seizures)[170] may occur when high doses are administered, especially in patients with impaired renal function (see section **4.8. Undesirable effects**).[26]

As with other antibiotic preparations, use of this drug may result in overgrowth of non-susceptible organisms, including fungi. Patients should be carefully monitored during therapy. If superinfection occurs, appropriate measures should be taken.

Use in Patients with Hepatic Impairment

(see section **4.2. Posology and method of administration**).

Renal Impairment

Due to its potential nephrotoxicity (see section **4.8. Undesirable effects**), 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. Posology and method of 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.[162,164]

Combined use of piperacillin/tazobactam and vancomycin may be associated with an increased incidence of acute kidney injury[167] (see section **4.5. Interaction with other medicinal products and other forms of interaction**).

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.[27,28] 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[168]

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[19] (see section **4.4. Special warnings and precautions for use**).

Methotrexate

Piperacillin may reduce the excretion of methotrexate;[29,30] therefore, serum levels of methotrexate should be monitored in patients to avoid drug 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 drug are unaffected.[31]

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.[32] The pharmacokinetics of piperacillin, tazobactam, and the M1 metabolite were also not significantly altered by tobramycin administration.[32]

Vancomycin

Studies have detected an increased incidence of acute kidney injury in patients concomitantly administered piperacillin/tazobactam and vancomycin as compared to vancomycin alone[157] (see section **4.4. Special warnings and precautions for use**). Some of these studies have reported that the interaction is vancomycin dose-dependent. Expert guidelines[165,166] 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.[167]

No pharmacokinetic interactions have been noted between piperacillin/tazobactam and vancomycin.[33]

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.[34]

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 piperacillin/tazobactam should be interpreted cautiously and confirmed by other diagnostic methods.[35,36,37,38]

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.[39,40,41,42,43,44,45] 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.[46,47,48,49] 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.[50,51] 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[154,155]

System Organ Class	Adverse Drug Reactions
Infections and infestations	pseudomembranous colitis[85], candida infection[*52]
Blood and lymphatic system disorders	pancytopenia[*62], agranulocytosis[60], neutropenia[54], haemolytic anaemia[*59], thrombocytopenia[55], anaemia*[56], leukopenia[53], thrombocytosis*[65], eosinophilia[*58]
Immune system disorders	anaphylactoid shock[*11], anaphylactic shock[*11], anaphylactoid reaction[*11], anaphylactic reaction[*11], hypersensitivity[*66]
Metabolism and nutrition disorders	hypokalaemia[70]
Psychiatric disorders	delirium[*168], insomnia[72]
Nervous system disorders	seizure[*170], headache[71]
Vascular disorders	hypotension[73], phlebitis[74], thrombophlebitis[75], flushing[76]
Respiratory, thoracic and mediastinal disorders	eosinophilic pneumonia[*160], epistaxis[57]
Gastrointestinal disorders	stomatitis[83], abdominal pain[84], vomiting[79], diarrhoea[77], constipation[80], nausea[78], dyspepsia[81]
Hepatobiliary disorders	hepatitis[*91], jaundice[82]
Skin and subcutaneous tissue disorders	toxic epidermal necrolysis[*98], Stevens-Johnson syndrome[*97], drug reaction with eosinophilia and systemic symptoms (DRESS)[*156], acute generalised exanthematous pustulosis (AGEP)[*156], dermatitis exfoliative[*160], erythema multiforme[*96], dermatitis bullous[95], rash[92], pruritus[93], urticaria[94], rash maculo-papular[*155], purpura[57]
Musculoskeletal and connective tissue disorders	arthralgia[99], myalgia[100]
Renal and urinary disorders	renal failure[103], tubulointerstitial nephritis[*102]
General disorders and administration site conditions	pyrexia[105], injection site reaction[106], chills[107]
Investigations	Coombs direct test positive[61], activated partial thromboplastin time prolonged[63], prothrombin time prolonged[64], bleeding time prolonged[57], blood albumin decreased[67], protein total decreased[69], blood glucose decreased[68], aspartate aminotransferase increased[87], alanine aminotransferase increased[86], blood alkaline phosphatase increased[89], blood bilirubin increased[88], gamma-glutamyl transferase increased[90], blood creatinine increased[101], blood urea increased[104]

[*] Adverse Drug Reaction (ADR) identified post-marketing

Piperacillin therapy has been associated with an increased incidence of fever and rash in cystic fibrosis patients.[19,108,109,110,111]

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).[111,112,113]

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[114,115] (see section **5.2. Pharmacokinetic properties**).

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® EF (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.[152]

Piperacillin sodium exerts bactericidal activity by inhibiting septum formation and cell wall synthesis.[172] 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.[173] *In vitro*, piperacillin is active against a variety of gram-positive and gram-negative aerobic and anaerobic bacteria.[152,173,174,175]

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).[173,176] 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.[152,176,180]

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[174] and piperacillin is relatively refractory to the action of some β-lactamases.[152,173,180]

Like other β-lactam antibiotics, piperacillin, with or without tazobactam, demonstrates time-dependent bactericidal activity against susceptible organisms.[152,177,180]

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. [152,173,174,180]

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.[178] Resistance caused by changes in PBPs also occurs to a lesser extent in fastidious gram-negative species such as *Haemophilus influenzae* and *Neisseria gonorrhoeae*.[179] 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.[152,176,180]

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.[181]

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.[152,180]

FDA Reference Information (US FDA requirement for the USPI)

For specific information regarding susceptibility test interpretive criteria and associated test methods and quality control standards recognized by FDA for this drug, please see:
https://www.fda.gov/STIC.

CLSI Reference Information (for markets referencing the CLSI)

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
Enterobacteriaceae	≤16	32 - 64	≥128	≥21	18 - 20	≤17
Acinetobacter spp.	≤16	32 - 64	≥128	≥21	18 - 20	≤17
Pseudomonas aeruginosa	≤16	32 - 64	≥128	≥21	15 - 20	≤14
Certain other non-fastidious gram-negative bacilli[c]	-	-	-	≥21	18 - 20	≤17
Haemophilus influenzae and *Haemophilus parainfluenzae*	≤1	-	≥2	≥21	-	-
Anaerobes[d]	≤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.
[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.[152]

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
Escherichia coli ATCC 35218	0.5-2	24-30
Pseudomonas aeruginosa ATCC 27853	1-8	25-33
Haemophilus influenzae ATCC 49247	0.06-0.5	33-38
Staphylococcus aureus ATCC 29213	0.25-2	-

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		
Staphylococcus aureus ATCC 25923	-	27 - 36
Bacteroides fragilis ATCC 25285	0.12-0.5[a]	-
Enterococcus faecalis ATCC 29212	1-4	
Bacteroides thetaiotaomicron ATCC 29741	4-16[a]	-
Clostridiodes (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 M100ED29. CLSI, Wayne, PA, 2019. [a] Agar dilution only.		

EUCAST Reference Information (for markets referencing the EUCAST)

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.[152,180]

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	S	R	S	R
Enterobacteriales (formerly *Enterobacteriaceae)*	≤8	>16	≥20	<17
Pseudomonas aeruginosa	≤16	>16	≥18	<18
Haemophilus influenzae	≤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 SUSCEPTIBILITY INTERPRETIVE CRITERIA FOR PIPERACILLIN/TAZOBACTAM				
	Minimal Inhibitory Concentration (mg/L of Piperacillin)[a]		Disk[b] Diffusion Inhibition Zone (mm Diameter)	
Pathogen	S	R	S	R
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[152] 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
Escherichia coli ATCC 35218	0.5-2	21-27
Pseudomonas aeruginosa ATCC 27853	1-8	23-29
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 9.0, 2019. http://www.eucast.org.		

Antibacterial Spectrum (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.

Anaerobic gram-positive microorganisms:

Clostridium perfringens

Anaerobic gram-negative microorganisms:

Bacteroides distasonis
Prevotella melaninogenica

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).

5.2. PHARMACOKINETIC PROPERTIES

Absorption

Intramuscular use only.

Piperacillin and tazobactam are well absorbed when administered intramuscularly, with an absolute bioavailability of 71% for piperacillin and 84% for tazobactam.[120]

Distribution

Both piperacillin and tazobactam are approximately 30% bound to plasma proteins.[120,121,122] The protein binding of either piperacillin or tazobactam is unaffected by the presence of the other compound.[122] 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.[121,123,124,125,126,127,128,129,130] Mean tissue concentrations are generally 50% to 100% of those in plasma.[123]

Metabolism

Piperacillin is metabolized to a minor microbiologically active desethyl metabolite.[120,131] Tazobactam is metabolized to a single metabolite that has been found to be microbiologically inactive.[120]

Elimination

Piperacillin and tazobactam are eliminated via the kidney by glomerular filtration and tubular secretion.[120]

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.[116,132,133]

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.[134,135] The elimination half-lives of both piperacillin and tazobactam are increased with decreasing renal clearance.[5,6,136,137,138]

There are no significant changes in the pharmacokinetics of piperacillin due to tazobactam.[139,140] Piperacillin appears to reduce the rate of elimination of tazobactam.[120]

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.[141]

The half-lives of piperacillin and tazobactam increase with decreasing creatinine clearance.[6,136,137] 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.[136]

Hemodialysis removes 30% to 50% of piperacillin/tazobactam with an additional 5% of the tazobactam dose removed as the tazobactam metabolite.[114,142,143] 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.[143]

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.[39,40,41,42,43]

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.[44] Peri/post-natal development was impaired (reduced pup weights, increase in still birth, increase in pup mortality), concurrent with maternal toxicity.[45]

Impairment of Fertility

Reproduction studies in rats revealed no evidence of impaired fertility due to tazobactam or piperacillin/tazobactam when administered intraperitoneally.[44]

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS

Sodium Hydrogen Carbonate
Citric Acid (monohydrate)
Edetate Disodium (dihydrate)
Water for Injections
Nitrogen

6.2. INCOMPATIBILITIES

Solutions known to be compatible with piperacillin/tazobactam 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 piperacillin/tazobactam 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[144]
- Lactated Ringer's Injection[145]
- Hartmann's solution[146]
- Ringer's acetate[147]
- Ringer's acetate/malate[147]

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

Whenever piperacillin/tazobactam is used concurrently with another antibiotic (e.g., aminoglycosides), the drugs must be administered separately. The mixing of piperacillin/tazobactam with an aminoglycoside *in vitro* can result in substantial inactivation of the aminoglycoside.[148,149]

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 piperacillin/tazobactam *in vitro* in certain diluents at specific concentrations (see section **4.2. Posology and method of administration**).

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

Because of chemical instability, piperacillin/tazobactam should not be used with solutions containing only sodium bicarbonate. Piperacillin/tazobactam should not be added to blood products or albumin hydrolysates.

6.3. SHELF-LIFE

36 months

6.4. SPECIAL PRECAUTIONS FOR STORAGE

Lyophilized Powder: Vials containing sterile Tazocin® EF lyophilized powder may be stored at controlled room temperature (15°C – 25°C) for up to 3 years.

Solutions: When reconstituted as directed, solutions are stable for 24 hours when stored under refrigeration (2°C – 8°C) in I.V. bags or syringes. Unused solution should be discarded.

6.5. NATURE AND CONTENTS OF CONTAINER

Tazocin® EF is available as lyophilized powder for reconstituation in clear glass Vials along with 20 mL sterile water for injection.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER 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.[150]

Vial Size (Piperacillin/Tazobactam)	**Volume of Compatible Solvent to be Added to Vial**
4.50 g	20 mL

Tazocin® EF/LPD/PK-11
According to CDS V 31 dated: 23 March, 2020; Supersedes CDS V 30 dated: 28 August, 2019

Marketed by:
Wyeth Pakistan Limited.

*Please visit our website **www.pfizerpro.com.pk** for latest version of Product leaflet.*

7. REFERENCES

2. Serra P. Piperacillin/tazobactam in patients with exacerbated chronic bronchitis – Final Report of the Trial 1991 (Wyeth Data on file).
3. Serra P. A multi-center, open-label, non comparative, safety, tolerance, and efficacy study of parenteral piperacillin/tazobactam in the treatment of hospitalized patients with either uncomplicated or complicated but mild urinary tract infection – Ministerial Report 1989 (Study D68 P526 – Wyeth Data on file).
4. Froessler B, Girbes ARJ: Pharmacokinetics of piperacillin/tazobactam in septic ICU-patients with acute renal function loss. Intensive Care Med 1997;23(1):S112 Abs 636.
5. Johnson CA, Halstenson CE, Kelloway JS, Shapiro BE, Zimmerman SW, Tonelli A, *et al*: Single-dose pharmacokinetics of piperacillin and tazobactam in patients with renal disease. Clin Pharmacol Ther 1992;51:32-41.
6. Wu WH, Greene DS, Kuye O, Ruffner A, Hoffler D, Haynes J, *et al*: Pharmacokinetics of piperacillin/tazobactam (4/1) after a single infusion in renal impaired patients. Pharm Res 1991;8(10):S315 (PPDM 8357).
7. Lathia C, Sia L, Greene D, Kuye O, Batra V, Tonelli A, *et al*: Pharmacokinetics of piperacillin/tazobactam combination IV in normal and cirrhotic subjects. Pharm Res 1991;8:S303 (Abs PPDM 8309).
8. Reformulated Zosyn (EDTA Formulation) Y-Site Compatibility (Concurrent or Sequential Administration with Flushing) Study with Aminoglycosides. RPT-58383 dated May 3, 2005.
9. Desai N, Gong Y, Dalal H, Akcan O, Cohen J. Zosyn Label Expansion: Simulated Clinical Infusion Compatibility Study for Y-Site Co-Administration of Zosyn® (Vials or Galaxy Containers) with Gentamicin Drug Product Diluted with 5% Dextrose or 0.9% Sodium Chloride. Wyeth Research RPT-76099, 2009.
10. Dutta A, Greene D, McAteer J, Sia L, Kuye O, Faulkner R, *et al*: Comparison of pharmacokinetics (PK) of piperacillin (pip)/tazobactam (taz) in young vs. elderly healthy adult males. J Clin Pharmacol 1990;30(9):859 (Abs 114).
11. Blum M: Justification document - Piperacillin/Tazobactam: Incorporation of Anaphylactic/Anaphylactoid Reaction (Including Shock) as suspected adverse reaction in piperacillin/tazobactam labeling.
12. Delage C, Irey NS: Anaphylactic deaths: a clinicopathologic study of 43 cases. J Forensic Sci 1972;17(4):525-40.
13. Spontaneous Adverse Events Reporting System. (Wyeth-Ayerst Data on file).
14. Smith JW, Johnson JE, Cluff LE: Studies on the epidemiology of adverse drug reactions. II. An evaluation of penicillin allergy. N Engl J Med 1966;274(18):998-1002.
15. Ahmad SH, Kumar P, Fakhir S, Ahmad KN, Rattan A, Channa RS, *et al*: Antibiotic associated colitis. Indian J Pediatr 1993:60:591-4.
16. Roddis MJ: Antibiotic-associated colitis: a retrospective study of fifteen cases. Age Ageing 1978;7:182-8.
17. Lee M, Stobnicki M, Sharifi R: Hemorrhagic complications of piperacillin therapy. J Urol 1986;136(2):454-5.
18. Moore M, McNamara TR, Johnson J: Elevated bleeding time and epistaxis with piperacillin therapy. South Med J 1985;78(3):363.

19. Rye PJ, Roberts G, Staugas REM, Martin AJ: Coagulopathy with piperacillin administration in cystic fibrosis: two case reports. J Pediatr 1994;30:278-9.

20. Fass RJ, Copelan EA, Brandt JT, Moeschberger ML, Ashton JJ: Platelet-mediated bleeding caused by broad-spectrum penicillins. J Infect Dis 1987;155(6):1242-8.

21. Olivera E, Lakhani P, Watanakunakorn C: Isolated severe thrombocytopenia and bleeding caused by piperacillin. Scand J Infect Dis 1992;24:815-7.

22. Andrassy K, Ritz E, Hasper B, Scherz M, Walter E, Storch H, *et al*: Penicillin-induced coagulation disorder. Lancet 1976;2(7994):1039-41.

23. Gentry LO, Jemsek JG, Natelson EA: Effects of sodium piperacillin on platelet function in normal volunteers. Antimicrob Agents Chemother 1981;19(4):532-3.

24. Brown CH, Bradshaw MW, Natelson EA, Alfrey CP, Williams TW: Defective platelet function following the administration of penicillin compounds. Blood 1976;47(6):949-56.

25. Justification document - Piperacillin/Tazobactam Injection: Leukopenia and Neutropenia.

26. Justification for a Safety Labeling Decision for Piperacillin/Tazobactam: Convulsions. 14-August-2008.

27. Mackie K, Pavlin EG: Recurrent paralysis following piperacillin administration. Anesthesiology 1990;72:561-3.

28. Condon RE, Munshi CA, Arfman RC: Interaction of vecuronium with piperacillin or cefoxitin evaluated in a prospective, randomized, double-blind clinical trial. Am Surg 1995;61(5):403-6.

29. Bloom EJ, Ignoffo RJ, Reis CA, Cadman E: Delayed clearance of methotrexate associated with antibiotics and antiinflammatory agents. Clin Res 1986;34(2):560A.

30. Yamamoto K, Sawada Y, Matsushita Y, Moriwaki K, Bessho F, Iga T: Delayed elimination of methotrexate associated with piperacillin administration. Ann Pharmacol 1997;31:1261-2.

31. Ganes D, Batra V, Faulkner R, Greene D, Haynes J, Kuye O, *et al*: Effect of probenecid on the pharmacokinetics of piperacillin and tazobactam in healthy volunteers. Pharm Res 1991;8(10):S-299 (Abs PPDM 8293).

32. Halstenson CE, Schwartz SL: Single-dose, open label, randomized, crossover, pharmacokinetic interaction study between ZOSYN or piperacillin and tobramycin in subjects with normal renal function and subjects with mild or moderate renal impairment: Final Report (protocol 0910A1-101-US). Wyeth-Ayerst GMR-30552, 1998.

33. Vechlekar D, Sia L, Lanc R, Kuye O, Yacobi A, Faulkner R: Pharmacokinetics of piperacillin/tazobactam IV with and without vancomycin IV in healthy adult male volunteers. Pharm Res 1992;9(10):S322.

34. LeBel M, Paone RP, Lewis GP: Effect of ten new β-lactam antibiotics on urine glucose test methods. Drug Intell Clin Pharm 1984;18:617-20.

35. Sulahian A, Touratier S, Leblanc T, Rousselot P, Derouin F, Ribaud P. False positive aspergillus antigenemia related to concomitant administration of tazocillin. Abstract M-2062a. Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), 2003 Sep14-17; Chicago Illinois.

36. Viscoli C, Machetti M, Cappellano P, Bucci B, Bruzzi A, Bacigalupo A. False-positive Platelia *Aspergillus* (PA) test in patients (pts) receiving piperacillin-tazobactam (p/t). Abstract M-2062b. Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), 2003 Sep 14-17, Chicago Illinois.

37. Swanink CMA, Meis JFGM, Rijs AJMM, Donnelly JP, Verweij PE. Specificity of a sandwich enzyme-linked immunosorbent assay for detecting *Aspergillus* galactomannan. J Clin Microbiol,1997 Jan, 35(1):257-260.

38. Pinel C, Fricker-Hidalgo H, Lebeau B, *et al*. Detection of circulating *Aspergillus* galactomannan: value and limits of the Platelia test for diagnosing invasive aspergillosis. J Clin Microbiol 2003 May; 45(5): 2184-2186.

39. MIRACL-22477: Embryo-fetal toxicity and teratogenic potential study of CL 298,741 alone or CL 227,193 in combination with CL 298,741 administered intravenously to CRL:CD™-1(ICR)BR mice. Argus protocol 612-006. 16-Jan-1989.

40. MIRACL-21610: Dosage-range developmental toxicity (embryo-fetal toxicity and teratogenic potential) study of CL 298,741 alone or CL 227,193 in combination with CL 298,741 administered intravenously to Crl:CD®-1(ICR)BR mice. Argus protocol 612-006P, 20-Dec-1988.

41. MIRACL-22865: Embryo-fetal toxicity and teratogenic potential study (including a "behavioral" post-natal evaluation) of CL 298,741 alone or CL 277,193 in combination with CL 298,741 administered intravenously to Crl:CD®(SD)BR rats. Argus protocol 612-007. 12-Apr-1990.

42. Lochry EA, Hoberman AM, Filler R, Dougherty WJ, Traitor CE. Developmental toxicity of tazobactam alone and in combination with piperacillin in mice [abstract]. *Teratol Soc Abs*. 1991:453 (Abs 119).

43. Lochry EA, Hoberman AM, Filler R, Dougherty WJ, Traitor CE. Embryo-fetal toxicity and teratogenic potential of Tazobactam alone and in combination with Piperacillin in rats [abstract]. Teratol Soc Abs. 1991:453 (Abs 120).

44. Sato T, Lochry EA, Hoberman AM, Christian MS. Reproductive and developmental toxicity studies of tazobactam/piperacillin or tazobactam(1)-Fertility and general reproduction study in rats with intraperitoneal administration. J Toxicol Sci. 1994;19 Suppl 2:199-24. Japanese.

45. Sato T, Hoberman AM, Christian MS. Reproductive and developmental toxicity studies of tazobactam/piperacillin or tazobactam (3)-perinatal and postnatal study in rats with intraperitoneal administration. *J Toxicol Sci*. 1994;19 Suppl 2:233-47. Japanese.

46. MIRACL-22953: Transfer of tazobactam into breast milk of rats after an intravenous dose of ^{14}C-tazobactam in combination with piperacillin (SN A8928). Cyanamid project number 17178. 20-Jul-1990.

47. MIRACL-22955: Placental transfer of Tazobactam (CL 298,741) after a single intravenous dose given alone or in combination with Piperacillin to pregnant rats (SN A8908). Cyanamid project number 17176. 20-Jul-1990.

48. Bourget P, Sertin A, Lesne-Hulin A, Fernandez H, Ville Y, Peborgh PV: Influence of pregnancy on the pharmacokinetic behavior and the trans-placental transfer of the piperacillin-tazobactam combination. Eur J Obstet Gynecol Reprod Biol 1998;76(1):21-7.

49. Brown CEL, Christmas JT, Bawdon RE: Placental transfer of cefazolin and piperacillin in pregnancies remote from term complicated by Rh isoimmunization. Am J Obstet Gynecol 1990;163:938-43.

50. Baier R, Puppel H: Piperacillin concentrations in the milk and serum of puerperae at the beginning of lactation. [Translation from German]. Antimikrob Antineoplast Chemother 1984;1(1-2):23-6.

51. Baier R, Wolnik L, Puppel H, Mohr C, Ochs U: Piperacillin concentrations in milk and serum from lactating women. Abstracts of the 22nd ICAAC 1982:203 (Abs 779).

52. Blum M: Justification document - Candidal Superinfection.

53. Blum M: Justification document - Leukopenia.

54. Blum M: Justification document - Neutropenia.
55. Blum M: Justification document - Thrombocytopenia.
56. Blum M: Justification document - Anemia.
57. Blum M: Justification document - Bleeding Manifestations.
58. Blum M: Justification document - Eosinophilia.
59. Blum M: Justification document - Haemolytic Anemia.
60. Blum M: Justification document - Agranulocytosis.
61. Blum M: Justification document - Coombs Direct Test Positive.
62. Blum M: Justification document - Pancytopenia.
63. Blum M: Justification document - Prolonged Partial Thromboplastin Time.
64. Blum M: Justification document - Prothrombin Time Prolonged.
65. Blum M: Justification document - Thrombocytosis.
66. Blum M: Justification document - Hypersensitivity Reaction.
67. Blum M: Justification document - Blood Albumin Decreased.
68. Blum M: Justification document - Blood Glucose Decreased.
69. Blum M: Justification document - Blood Total Protein Decreased.
70. Blum M: Justification document - Hypokalemia.
71. Blum M: Justification document - Headache.
72. Blum M: Justification document - Insomnia.
73. Blum M: Justification document - Hypotension.
74. Blum M: Justification document - Phlebitis.
75. Blum M: Justification document - Thrombophlebitis.
76. Blum M: Justification document - Flushing.
77. Blum M : Justification document - Diarrhea.
78. Blum M: Justification document - Nausea.
79. Blum M: Justification document - Vomiting.
80. Blum M: Justification document - Constipation.
81. Blum M: Justification document - Dyspepsia.
82. Blum M: Justification document - Jaundice.
83. Blum M: Justification document - Stomatitis.
84. Blum M: Justification document - Abdominal Pain.
85. Blum M: Justification document - Pseudomembranous Colitis.
86. Blum M: Justification document - Alanine Aminotransferase Increased.
87. Blum M: Justification document - Aspartate Aminotransferase Increased.
88. Blum M: Justification document - Bilirubin Increased.
89. Blum M: Justification document - Blood Alkaline Phosphatase Increased.

90. Blum M: Justification document - Gamma-glutamyltransferase Increased.
91. Justification document: Piperacillin/Tazobactam: Hepatitis.
92. Blum M: Justification document - Rash.
93. Blum M: Justification document - Pruritis
94. Blum M: Justification document - Urticaria.
95. Blum M: Justification document - Bullous Dermatitis.
96. Killion L, Mariano D: Justification document - Erythema Multiforme.
97. Killion L, Mariano D: Justification document - Stevens-Johnson Syndrome.
98. Killion L, Mariano D: Justification document - Toxic Epidermal Necrolysis.
99. Blum M: Justification document - Arthralgia.
100. Justification for a safety labeling decision: Piperacillin/Tazobactam: Myalgia dated 05-Apr-2010.
101. Blum M: Justification document - Blood Creatinine Increased.
102. Killion L, Mariano D: Justification document - Interstitial Nephritis.
103. Killion L, Mariano D: Justification document - Renal Failure.
104. Blum M: Justification document - Blood Urea Nitrogen Increased.
105. Blum M: Justification document - Fever.
106. Blum M: Justification document - Injection Site Reaction.
107. Blum M: Justification document - Rigors.
108. Wills R, Henry RL, Francis JL: Antibiotic hypersensitivity reactions in cystic fibrosis. J Pediatr Child Health 1998;34:325-9.
109. Mallon P, Murphy P, Elborn S: Fever associated with intravenous antibiotics in adults with cystic fibrosis. Lancet 1997;350(9092):1676-7.
110. Moss RB, Babin S, Hsu Y, Blessing-Moore J, Lewiston NJ: Allergy to semisynthetic penicillins in cystic fibrosis. J Pediatr 1984;104(3):460-6.
111. Malanga CJ, Kokonitis L, Mauzy S: Piperacillin-induces seizures. Clin Ped 1997;36(8):475-8.
112. Bloomer HA, Baxton LJ, Maddock RK: Penicillin-induced encephalopathy in uremic patients. JAMA 1967;200(2):121-3.
113. Barrons RW, Murray KM, Richey RM: Populations at risk for penicillin-induced seizures. Ann Pharmacother 1992;26:26-9.
114. Heim-Duthoy KL, Halstenson CE, Abraham PA, Matzke GR: The effect of hemodialysis on piperacillin pharmacokinetics. Int J Clin Pharmacol Ther Toxicol 1986;(12):680-4.
115. Halstenson CE, Kelloway JS, Shapiro BE, Greene DS, Faulkner R, Heim-Duthoy KL: Disposition of piperacillin/tazobactam in hemodialysis patients. Pharmacother 1991;11(1):106.
116. Holmes B, Richards, DM, Brogden RN, Heel RC: Piperacillin: a review of its antibacterial activity, pharmacokinetic properties and therapeutic use. Drugs 1984;28:375-425.
117. ~~Bryson HM, Brogden RN: Piperacillin/tazobactam: a review of its antibacterial activity, pharmacokinetic properties and therapeutic potential. Drugs 1994;47(3):506-35.~~ Reference superceded by Reference 152, updated in CDS version 30.0.

~~118. Acar JF, Goldstein FW, Kitzis MD: Susceptibility survey of piperacillin alone and in the presence of tazobactam. J Antimicrob Chemother 1993;31(Suppl A):23-8.~~ Reference superceded by Reference 152, updated in CDS version 30.0.

~~119. Higashitani F, Hyodo I, Ishida N, Inoue M, Mitsuhashi S: Inhibition of β-lactamases by tazobactam and in vitro antibacterial activity of tazobactam combined with piperacillin. J Antimicrob Chemother 1990;25:567-74.~~ Reference no longer applicable, removed in CDS version 30.0.

120. ~~Sorgel F, Kinzig M: The chemistry, pharmacokinetics and tissue distribution of piperacillin/tazobactam. J Antimicrob Chemother 1993;31(A):39-60~~. Reference no longer applicable, removed in CDS version 30.0.

121. Sorgel F, Kinzig M: Pharmacokinetics and tissue penetration of piperacillin/tazobactam with particular reference to its potential in abdominal and soft tissue infections. Eur J Surg 1994;Suppl 573:39-44.

122. Schoonover LL, Occhipinti DJ, Rodvold KA, Danziger LH: Piperacillin/tazobactam: a new beta-lactam/beta-lactamase inhibitor combination. Ann Pharmacother 1995;29:501-14.

123. Nord CE, Kinzig M, Sorgel F, Brismar B: Pharmacokinetics and tissue penetration of tazobactam and piperacillin in patients undergoing colorectal surgery. Abs 17th Int Chemother Abs 950, Berlin, June 23-38, 1991.

124. Kinzig M, Sorgel F, Brismar B, Nord CE: Pharmacokinetics and tissue penetration of tazobactam and piperacillin in patients undergoing colorectal surgery. Antimicrob Agents Chemother 1992;36(9):1997-2004.

125. Daschner FD, Just M, Spillner G, Schlosser V: Penetration of piperacillin into cardiac valves, subcutaneous and muscle tissue of patients undergoing open-heart surgery. J Antimicrob Chemother 1982;9:482-92.

126. Incavo SJ, Ronchetti PJ, Choi JH, Wu H, Kinzig M, Sorgel F: Penetration of piperacillin-tazobactam into cancellous and cortical bone tissues. Antimicrob Agents Chemother 1994;38(4):905-7.

127. Baier R, Puppel H, Zelder O, Zehner R, Marburg : Piperacillin concentrations in bile. Antibacterial Chemotherapy Piperacillin Symposium 1908:246-57.

128. Marlin GE, Burgess KR, Burgoyne J, Funnell GR, Guinness MDG: Penetration of piperacillin into bronchial mucosa and sputum. Thorax 1981:36;774-80.

129. Sunder-Plasman L, Halter G, Kinzig M, Sorgel F: Penetration of piperacillin/tazobactam into the respiratory tract. Pharm Res 1996;13(Suppl. 9):S119 (Abs S3018).

130. Kinzig M, Sorgel F, Naber KG, Kujath P, Nord CE, Brismar B, *et al*: Tissue penetration of piperacillin/tazobactam. Progr Abstr 31st Intersci Conf Antimicrob Agents Chemother 1991:242 (Abs 862).

131. Minami Y, Komuro M, Sakawa K, Ishida N, Shindo T, Matsumoto K, *et al*: Human-specific metabolite of piperacillin (PIPC), desethyl-PIPC, newly found after 10-year clinical usage. Progr Abstr 31st Intersci Conf Antimicrob Agents Chemother 1991:125 (Abs 159).

132. Yatsu JS, Kinzig M, Bansal S, Tonelli F, Sorgel F: Biliary concentrations of tazobactam and piperacillin in humans. Abs 18th Int Congr Chemother 1993:257 (Abs 805).

133. Tanimura H, Uchiyama K, Ishimoto K: Bile excretion of piperacillin in combination with tazobactam. Abs 18th Int Congr Chemother 1993:257 (Abs 806).

134. Aronoff GR, Sloan RS, Brier ME, Luft FC: The effect of piperacillin dose on elimination kinetics in renal impairment. Eur J Clin Pharmacol 1983;24:543-7.

135. Occhipinti DJ, Pendland SL, Schoonover LL, Rypins EB, Danziger LH, Rodvold KA: Pharmacokinetics and pharmacodynamics of two multiple-dose piperacillin-tazobactam regimens. Antimicrob Agents Chemother 1997;41(11):2511-17.

136. Derendorf H, Dalla Costa T: Pharmacokinetics of piperacillin, tazobactam, and its metabolite in renal impairment. Inter J Clin Pharm Ther 1996;34(11):482-8.

137. Johnson CA, Halstenson CE, Shepard JH, Oxton L, Shapiro BE, Zimmerman SW, *et al*: Piperacillin/tazobactam disposition in patients with various degrees of renal function. Clin Pharmacol Therap 1990;47(2):175 (Abst P11-108).

138. Thompson MIB, Russo ME, Matsen JM, Atkin-Thor E: Piperacillin pharmacokinetics in subjects with chronic renal failure. Antimicrob Agents Chemother 1981;19(3):450-3.

139. Cyanamid: Single dose, mass balance study of C^{14} tazobactam when administered in combination with piperacillin as a 30 minute intravenous infusion in healthy adult male volunteers. Cyanamid D68-35.

140. Cyanamid: Cyanamid D68-510.

141. Cyanamid: Single-dose, open-label, parallel, pharmacokinetic study of piperacillin and tazobactam after intravenous infusion in normal subjects and subjects with liver cirrhosis. Cyanamid D68-31.

142. Francke EL, Appel GB, Neu HC: Pharmacokinetics of intravenous piperacillin in patients undergoing chronic hemodialysis. Antimicrob Agents Chemother 1979;16(6):788-791.

143. Lathia CD, Halstenson C, Keane W, Johnson C, Zimmerman CD, Doepner M, *et al*: Pharmacokinetics of tazobactam metabolite M1 after administration of piperacillin 3 g/tazobactam 0.375 g in subjects with renal impairment. Clin Pharmacol Ther 1992:132 (PI-46).

144. RPT-60684. Version 1.0. Zosyn® (sterile piperacillin sodium and tazobactam sodium) EDTA formulation's admixture with Dextran 6% in 0.9% Sodium Chloride Injection, USP. 29-Sep-2005.

145. RPT-58381. Version 2.0. Compatibility of reformulated Zosyn (EDTA formulation) in admixture with various diluents. 11-May-2005.

146. RPT-65972. Version 1.0. Reformulated Tazocin® EF: Strength and degradation profiles of reconstituted solutions and commercial solvent (including Hartmann's Solution) admixture plus simulated Y-site studies with amikacin or gentamicin. 29-Aug-2006.

147. RPT-74066. Version 1.0. Confirmation of compatibility of reformulated Tazocin® EF with Ringer's Acetate and Ringer's Acetate/Malate used in Nordic countries. 06-Jun-2008.

148. Hale DC, Jenkins R, Matsen JM: *In-vitro* inactivation of aminoglycoside antibiotics by piperacillin and carbenicillin. Am J Clin Pathol 1980;74:316-9.

149. Doepner DA, Yacobi A, Doepner MD, McAteer J, Tantillo K, Faulkner RD, *et al*: *In-vitro* interaction of tobramycin and piperacillin/tazobactam in human plasma, urine, and distilled water. Pharm Res 1992;9(10):S-353.

150. Cohen J, Desai N: Additional Statement in Label Instructions for Reformulated Zosyn Regarding Reconstitution Time. RPT-66202 dated 01 September, 2006.

151. (Clinical Overview) Piperacillin-tazobactam 2011 CDS update.

152. (Clinical Overview) Piperacillin-tazobactam 2012 CDS MIC update.

153. 2.5 Clinical Overview for Piperacillin-Tazobactam: Combination treatment with an aminoglycoside, February-2013.

154. Report of CIOMS Working Groups III and V, Guidelines for Preparing Core Clinical-Safety Information on Drugs, Second Edition

155. 2.5 Clinical Overview to update ADR frequencies to Core Data Sheet April 2015.

156. 2.5 Clinical Overview to add ADRs, “drug reaction with eosinophilia and systemic symptoms” and “acute generalized exanthematous pustulosis” to Core Data Sheet March 2015.

157. 2.5 Clinical Overview for the addition of text regarding vancomycin to section 4.5 Interaction with Other Medicinal Products and Other Forms of Interaction of the CDS July 2015.

158. Memo: Calculation of sodium content of piperacillin/tazobactam, September 2015.

159. 2.5 Clinical Overview to Support Updates to Adverse Drug Reaction Frequency Category Tables of the Core Data Sheet, to Add Eosinophilic Pneumonia and Dermatitis Exfoliative January 2016

160. 2.5 Clinical Overview to Support the Addition of Adverse Drug Reactions, Eosinophilic Pneumonia and Dermatitis Exfoliative to Section 4.8 Undesirable Effects, of the Core Data Sheet, January 2016

161. Protocol 68-23. Single doses, open label, parallel, multi-center pharmacokinetic study of piperacillin and tazobactam in subjects with various degrees of renal impairment. Aug 1990.

162. Jensen J-US, Hein L, Lundgren B, *et al.* Kidney failure related to broad-spectrum antibiotics in critically ill patients: Secondary end point results from a 1200 patients randomized trial. BMJ Open 2012;2:e000635

163. 2.5 Clinical Overview to Support Update of Text to Section 4.2 Posology and Method of Administration of the Core Date Sheet, July 2016

164. 2.5 Clinical Overview to support updates to section 4.4 special warnings and precautions for use of the core data sheet, July 2016.

165. American Thoracic Society and the Infectious Disease Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med 2005;171:388-416.

166. Rybak M, Lomaestro B, Rotschafer JC, *et al*. Therapeutic monitoring of vancomycin in adult patients: A consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. Am J Health-Syst Pharm 2009;66:82-98.

167. 2.5 Clinical Overview to support updates to section 4.4 special warnings and precautions for use and section 4.5 interaction with other medicinal products and other forms of interaction of the core data sheet, November 2016.

168. 2.5 Clinical Overview to support updates to section 4.5 interaction with other medicinal products and other forms of interaction and section 4.8 undesirable effects of the Core Data Sheet, September 2018.

170. 2.5 Clinical Overview To Support the Addition of Adverse Drug Reaction Seizure to Section 4.8 Undesirable Effects, March 2019.

171. Adverse Drug Reaction Frequency Justification Document (ADR FJD), March 2019.

172. Gin A, Dilay L, Karlowsky JA, Walkty A, Rubinstein E, Zhanel G. Piperacillin-tazobactam: a β lactam/β lactamase inhibitor combination. Expert Rev Anti Infect Ther 2007;5:365-383.

173. Drawz SM, Bonomo RA. Three decades of β lactamase inhibitors. Clin Microbiol Rev 2010;23:160-201.

174. Wright AJ. The Penicillins. Mayo Clin Prac 1999;74:290-307.

175. Higgins PG, Wisplinghoff D, Stefanik D, Seifert H. In vitro activities of the β lactamase inhibitors clavulanic acid, sulbactam, and tazobactam alone or in combination with β lactams against

epidemiologically characterized multidrug-resistant *Acinetobacter baumannii* strains. Antimicrob Agents Chemother 2004;48:1586-2592.

176. Bush K, Jacoby GA. Updated functional classification of β lactamases. Antimicrob Agents Chemother 2010;54:969-976.

177. Lodise TP, Lomaestro B, Rodvold KA, Danziger LH, Drusano GL. Pharmacodynamic profiling of piperacillin in the presence of tazobactam in patients through the use of population pharmacokinetic models and Monte Carlo simulation. Antimicrob Agents Chemother 2004; 48:4718-24.

178. Rice LB. Mechanisms of resistance and clinical relevance of resistance to β-lactams, glycopeptides and fluoroquinolones. Mayo Clin Proc. 2012; 87:198-208.

179. Georgopapadakou NH. Penicillin-binding proteins and bacterial resistance to β lactams. Antimicrob Agents Chemother 1993;37:2045-2053.

180. 2.5 Clinical Overview To Support Updates to Section 5.1 Pharmacodynamic Properties, August 2019.

181. 2.5 Clinical Overview To Support Updates to Section 4.1 Therapeutic Indications and 5.1 Pharmacodynamic Properties of the core data sheet, March 2020.