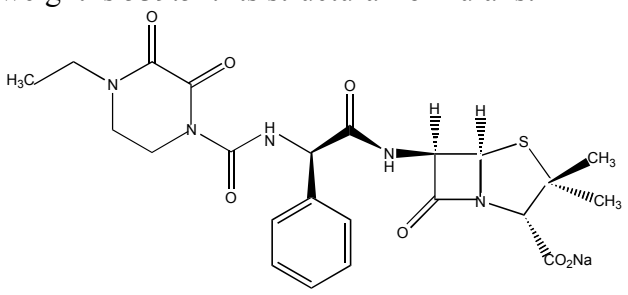
TAZOCIN*
Piperacillin Sodium/Tazobactam Sodium

NAME OF THE MEDICINE
TAZOCIN*

QUALITATIVE AND QUANTITATIVE COMPOSITION
Piperacillin sodium/tazobactam sodium Injection 4.0 g/0.5 g

Each vial contains a total of 2.79 mEq (64 mg) of sodium per gram of piperacillin.
The product contains no preservatives.

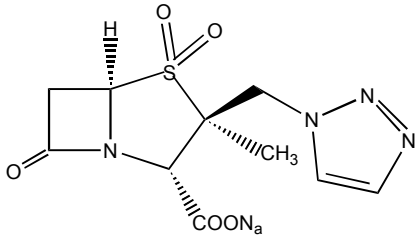
Piperacillin sodium is derived from D(-)-α-aminobenzylpenicillin. The chemical name of piperacillin sodium is sodium (2S,5R,6R)-6-[(R)-2-(4-ethyl-2,3-dioxo-1-piperazine-carboxamido)-2-phenylacetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid. The empirical formula is $C_{23}H_{26}N_5NaO_7S$ and the molecular weight is 539.54. Its structural formula is:



Piperacillin sodium

CAS Registry Number: 59703-84-3

Tazobactam sodium is a derivative of the penicillin nucleus. Chemically, tazobactam is a penicillanic acid sulfone. Its chemical name is sodium (2S-(2α,3β,5α)-3-methyl-7-oxo-3-(lH-l,2,3-triazol-1-ylmethyl)-4-thia-1-azabicyclo[3.2.0] heptane-2-carboxylic acid-4,4-dioxide. The empirical formula is $C_{10}H_{11}N_4NaO_5S$ and the molecular weight is 322.28. The chemical structure of tazobactam sodium is:



Tazobactam sodium

CAS Registry Number: 89785-84-2

DESCRIPTION
TAZOCIN is an injectable antibacterial combination, consisting of the semisynthetic antibiotic piperacillin sodium and the β-lactamase inhibitor tazobactam sodium, for intravenous administration.

TAZOCIN is available as a white to off-white sterile, cryodesiccated powder of piperacillin and tazobactam as the sodium salts packaged in glass vials. Each vial of TAZOCIN contains a total of 2.79 mEq (64 mg) of sodium per gram of piperacillin. The formulation also contains citric acid monohydrate and disodium edetate (EDTA).

PHARMACOLOGY

Piperacillin, a broad spectrum, semisynthetic penicillin active against many gram-positive and gram-negative aerobic and anaerobic bacteria, exerts bactericidal activity by inhibition of both septum and cell wall synthesis. Tazobactam, a triazolylmethyl penicillanic acid sulfone, is a potent inhibitor of many β-lactamases, including the plasmid and chromosomally mediated enzymes that commonly cause resistance to penicillins. The presence of tazobactam in the TAZOCIN formulation enhances and extends the antibiotic spectrum of piperacillin to include many β-lactamase producing bacteria normally resistant to it. Thus, TAZOCIN combines the properties of a broad-spectrum antibiotic and a β-lactamase inhibitor.

Microbiology

TAZOCIN is active against most strains of the following β-lactamase producing and non β-lactamase producing microorganisms:

Gram-negative bacteria

Escherichia coli, *Citrobacter* spp., *Klebsiella* spp. (including *K. pneumoniae*), *Enterobacter* spp. (including *E. cloacae*), *Proteus vulgaris*, *Proteus mirabilis, Serratia* spp. (including *S. marcescens*), *Pseudomonas aeruginosa* and other *Pseudomonas* spp., *Neisseria gonorrhoeae*, *Neisseria meningitidis, Moraxella catarrhalis, Acinetobacter* spp., *Haemophilus influenza*.

Gram-positive bacteria

Streptococci (*S. pneumoniae*, *S. pyogenes*, *S. agalactiae*, *S. viridans*), Enterococci (*E. faecalis*, *E. faecium*), *Staphylococcus aureus* (not methicillin-resistant *S. aureus*), *S. epidermidis* (coagulase-negative Staphylococci).

Anaerobic bacteria

Bacteroides spp. including *Bacteroides fragilis* group, *Peptostreptococcus* spp., *Fusobacterium* spp., *Eubacterium* group, *Clostridia* spp., *Veillonella* spp.

Disc susceptibility test

Dilution or diffusion techniques – either quantitative (MIC) or breakpoint, should be used following a regularly updated, recognised and standardised method (eg., NCCLS). Standardised susceptibility test procedures require the use of laboratory control micro-organisms to control the technical aspects of the laboratory procedures.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and if the micro-organism is not fully susceptible to alternative, clinically feasible medicines, the test should be repeated. This category implies possible clinical applicability in body sites where the medicine is physiologically concentrated or in situations where high dosage of the medicine can be used. This category also provides a buffer zone, which prevents small-uncontrolled technical factors from causing major

discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Note: The prevalence of resistance may vary geographically for selected species and local information on resistance is desirable, particularly when treating severe infections. This information provides guidance on micro-organisms susceptible to piperacillin/tazobactam. The following MIC 90 values were reported in 1996 for clinical isolates collected in 3 Australian states.

Table 1: MIC 90 for 1,952 clinically significant isolates

Organism (number)	**MIC90 (mg/L)**
E.coli (528)	*2.0*
Klebsiella spp. *(180)*	*4.0*
Klebsiella spp. *(ESBL 44)*	*64.0*
Enterobacter spp. *(142)*	*16.0*
Citrobacter/Serratia spp. *(84)*	*8.0*
Morganella/Proteus/Providencia spp. *(45)*	*2.0*
Proteus mirabilis spp. *(104)*	*2.0*
Pseudomonas aeruginosa (88)	*32.0*
Acinetobacter calcoaceticus (40)	*32.0*
Staphylococcus aureus (433)	*4.0*
Coagulase-negative Staphylococcal (28)	*16.0*
Streptococcus pneumoniae (45)	*0.015*
Enterococci (109)	*4.0*
Haemophilus influenzae (59)	*0.094*
Bacteroides fragilis gp (23)	*4.0*

The latest NCCL references are:
Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard-Seventh Edition, NCCLS document M7-A5, 2006. NCCLS, Wayne, PA

For anaerobes:
Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria; Approved Standard-Sixth Edition. NCCLS document M1l-A, 2006. NCCLS, Wayne, PA

Pharmacokinetics
Distribution and plasma levels
Mean plasma concentrations of piperacillin and tazobactam at steady-state of the combination appear in Tables 2 and 3. Peak piperacillin and tazobactam plasma concentrations are attained immediately after completion of an intravenous infusion. When given with tazobactam, piperacillin plasma levels are similar to those attained when equivalent doses of piperacillin are administered alone.
Table 2: Plasma levels in adults after a thirty-minute intravenous infusion of piperacillin/tazobactam (steady-state)

PIPERACILLIN PLASMA LEVELS (μg/mL)						
Piperacillin/Tazobactam Dose	30*min	1 hr	1.5 hr	2 hr	3 hr	4 hr
2 g/250 mg	134	57	29	17	5	2

4 g/500 mg	298	141	87	47	16	7
TAZOBACTAM PLASMA LEVELS (μg/mL)						
Piperacillin/Tazobactam Dose	30*min	1 hr	1.5 hr	2 hr	3 hr	4 hr
2 g/250 mg	14.8	7.2	4.2	2.6	1.1	0.7
4 g/500 mg	33.8	17.3	11.7	6.8	2.8	1.3

*Completion of 30-minute infusion

Table 3: Plasma levels in adults after an intramuscular injection of piperacillin/tazobactam (steady-state)

PIPERACILLIN PLASMA LEVELS (μg/mL)						
Piperacillin/Tazobactam Dose	30 min	1 hr	1.5 hr	2 hr	3 hr	4 hr
2 g/250 mg	55	45	31	19	8	4
TAZOBACTAM PLASMA LEVELS (μg/mL)						
Piperacillin/Tazobactam Dose	30 min	1 hr	1.5 hr	2 hr	3 hr	4 hr
2 g/250 mg	10.5	7.4	4.9	3.2	1.4	0.9

In healthy subjects piperacillin/tazobactam plasma elimination half-lives range from 0.7 to 1.2 hours following single or multiple doses. These half-lives are unaffected by dose or duration of infusion. Piperacillin and tazobactam are 21% and 23% respectively, bound to plasma proteins. The protein binding of either piperacillin or tazobactam is unaffected by the presence of either compound. Piperacillin and tazobactam are widely distributed in tissues and body fluids including intestinal mucosa, gall bladder, lung and bile.

Biotransformation

Piperacillin does not undergo biotransformation in humans. Approximately 20% of a dose of tazobactam is metabolised to a single metabolite that has been found to be microbiologically inactive.

Excretion

Piperacillin and tazobactam are eliminated by the kidney via glomerular filtration and tubular secretion. Piperacillin is excreted rapidly as unchanged drug, with 69% of the dose appearing in the urine. Piperacillin is also secreted into bile. Tazobactam and its metabolite are eliminated primarily by renal excretion, with 80% of the dose appearing as unchanged drug and the remainder of the dose appearing as the metabolite.

Impaired renal function

The half-life of piperacillin and tazobactam increases with decreasing creatinine clearance. The increase 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. Dosage adjustments are recommended when creatinine clearance is below 40 mL/min, see DOSAGE AND ADMINISTRATION.

Piperacillin and tazobactam are removed from the body during haemodialysis with 31% and 39% of the doses of piperacillin and tazobactam, respectively, recovered in the dialysis fluid. Piperacillin and tazobactam are removed from the body by peritoneal dialysis with 5% and 12% of the dose, respectively, appearing in the dialysate. For dosage recommendations in patients undergoing haemodialysis, see DOSAGE AND ADMINISTRATION.

Impaired liver function
Piperacillin half-life and AUC were increased by 25% and 40% respectively and tazobactam half-life and AUC by 18% and 23% respectively in patients with hepatic impairment. However, dosage adjustments in patients with hepatic impairment are not necessary.

Children
The pharmacokinetics of piperacillin and tazobactam have been examined in 24 paediatric patients aged 2 months to 12 years receiving 100 mg/kg piperacillin/12.5 mg/kg tazobactam (Table 4). The maximum concentration (C_{max}) for both piperacillin and tazobactam is increased relative to the maximum adult dose but the predicted time above the minimum inhibitory concentration is slightly decreased. The dosage of 100 mg/kg piperacillin/12.5 mg/kg tazobactam administered every 8 hours is predicted to provide coverage 31% to 61% of the time for the range of MIC values of 2 μg/mL to 16 μg/mL commonly found in intra-abdominal infections in children.

Table 4: Piperacillin and tazobactam pharmacokinetics in children (cv%) following single doses.

Dose	Patient age	C_{max} (mg/L)	AUC (mg.h/L)	CL (mL/min/kg)	V_{ss} (L/kg)	$T_{½}$ (h)
Piperacillin 100 mg/kg	2-5 mo	382(15)	539(29)	3.3(24)	0.28(32)	1.3(16)
	6-23 mo	344(15)	373(27)	4.8(29)	0.25(27)	1.0(24)
	2-5 y	408(80)	331(21)	5.2(19)	0.23(36)	0.9(26)
	6-12 y	394(24)	404(17)	4.2(21)	0.24(42)	0.8(27)
Tazobactam 12.5 mg/kg	2-5 mo	43(49)	63(32)	3.6(28)	0.32(31)	1.3(15)
	6-23 mo	35(22)	42(23)	5.2(24)	0.33(29)	1.1(23)
	2-5 y	45(42)	37(24)	5.8(19)	0.27(33)	0.9(29)
	6-12 y	45(25)	57(27)	3.9(36)	0.28(36)	1.3(57)

CLINICAL TRIALS
Paediatric
A study was performed to compare the safety, tolerance, and efficacy of 100 mg/kg piperacillin/12.5 mg/kg tazobactam with those of 50 mg/kg cefotaxime plus 7.5 mg/kg metronidazole administered intravenously (IV) every 8 hours for the treatment of hospitalised paediatric patients (aged 2 to 12 years of age) with clinically or bacteriologically diagnosed intra-abdominal infection (IAI). The cure rates in the efficacy evaluable (EE) population at the follow-up visit were 90% and 91% for piperacillin/tazobactam and cefotaxime plus metronidazole, respectively. The results of the clinical and microbiological analyses in 521 patients showed that piperacillin/tazobactam (TAZOCIN) administered intravenously was at least as effective as cefotaxime plus metronidazole in the treatment of children aged 2 to 12 years with severe IAIs.

INDICATIONS
Piperacillin, a broad spectrum, semisynthetic penicillin active against many

gram-positive and gram-negative aerobic and anaerobic bacteria, exerts bactericidal activity by inhibition of both septum and cell wall synthesis.

Tazobactam, a triazolylmethyl penicillanic acid sulphone, is a potent inhibitor of many β-lactamases, in particular the plasmid mediated enzymes which commonly cause resistance to penicillins and cephalosporins including third-generation cephalosporins. The presence of tazobactam in the TAZOCIN formulation enhances and extends the antibiotic spectrum of piperacillin to include many β-lactamase producing bacteria normally resistant to it and other β-lactam antibiotics. Thus, TAZOCIN combines the properties of a broad spectrum antibiotic and a β-lactamase inhibitor.

TAZOCIN is highly active against piperacillin-sensitive micro-organisms as well as many β-lactamase producing, piperacillin-resistant microorganisms.

Gram-negative bacteria: most plasmid mediated β-lactamase producing and non-β-lactamase producing strains of *Escherichia coli, Klebsiella* spp. (including *K. oxytoca, K. pneumoniae), Proteus* spp. (including *Proteus vulgaris, Proteus mirabilis*), *Salmonella* spp*., Shigella* spp., *Neisseria gonorrhoeae, Neisseria meningitidis, Moraxella* spp. (including *M. catarrhalis*), *Haemophilus* spp. (including *H. influenzae, H. parainfluenzae*), *Pasteurella multocida, Yersinia* spp., *Campylobacter spp., Gardnerella vaginalis*. Many chromosomally mediated β-lactamase producing and non-β-lactamase producing strains of *Enterobacter* spp. (including *E. cloacae, E. aerogenes*), *Citrobacter* spp. (including *C. freundii, C. diversus*), *Providencia* spp*., Morganella morganii, Serratia* spp. (including *S. marcescens, S. liquefaciens*), *Pseudomonas aeruginosa* and other *Pseudomonas* spp. (including *P. cepacia, P. fluorescens*), *Xanthomonas maltophilia, Acinetobacter* spp.

Gram-positive bacteria: β-lactamase producing and non-β-lactamase producing strains of *streptococci (S. pneumoniae, S. pyogenes, S. bovis, S. agalactiae, S. viridans,* Group *C,* Group *G), enterococci (E. faecalis), Staphylococcus aureus* (not methicillin-resistant *S. aureus), S. saprophyticus, S. epidermidis* (coagulase-negative *staphylococci*), *corynebacteria*, *Listeria monocytogenes, Nocardia* spp. Anaerobic bacteria: β-lactamase producing and non-β-lactamase producing anaerobes, such as *Bacteroides* spp. (including *B. bivius, B. disiens, B. capillosus, B. melaninogenicus, B. oralis*), the *Bacteroides fragilis* group (including *B. fragilis, B. vulgatus, B. distasonis, B. ovatus, B. thetaiotaomicron, B. uniformis, B. asaccharolyticus*), as well as *Peptostreptococcus* spp., *Fusobacterium* spp., *Eubacterium* group*, Clostridia* spp. (including *C. difficile, C. perfringens), Veillonella* spp., and *Actinomyces* spp.

TAZOCIN is indicated for treatment of the following systemic and/or local bacterial infections in which susceptible organisms have been detected or are suspected: Lower respiratory tract infections; urinary tract infections (complicated and uncomplicated); intra-abdominal infections; skin and skin structure infections; bacterial septicaemia. Polymicrobic infections: TAZOCIN is indicated for polymicrobic infections including those where gram-positive and gram-negative aerobic and/or anaerobic organisms are suspected (intra-abdominal, skin and skin structure, lower respiratory tract).

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

TAZOCIN is also used for appendicitis complicated by rupture with peritonitis and/or abscess formation in children aged 2-12 years.

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

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

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

CONTRAINDICATIONS
The use of TAZOCIN is contraindicated in patients with a history of allergic reactions to any of the penicillins and/or cephalosporins or β-lactamase inhibitors or any of its excipients.

PRECAUTIONS
Serious and occasionally fatal hypersensitivity (anaphylactic/anaphylactoid [including shock]) reactions have been reported in patients on penicillin/cephalosporin therapy including piperacillin/tazobactam. Although anaphylaxis is more frequent following parenteral therapy, it has occurred in patients on oral penicillins/cephalosporins. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity and/or a history of sensitivity to multiple allergens. There have been reports of individuals with a history of penicillin/cephalosporin hypersensitivity who have experienced severe reactions when treated with either a penicillin or cephalosporin. Past history of a severe allergic reaction to penicillin/cephalosporin is a contraindication to the use of TAZOCIN. Before initiating therapy with any penicillin/cephalosporin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, or other allergens. If an allergic reaction occurs, TAZOCIN should be discontinued and the appropriate therapy instituted. Serious anaphylactic/anaphylactoid reactions (including shock) require immediate emergency treatment with adrenaline. Oxygen, intravenous steroids and airway management, including intubation, should also be administered as indicated.

TAZOCIN 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. If patients develop a skin rash they should be monitored closely and TAZOCIN discontinued if lesions progress.

Antibiotic-associated pseudomembranous colitis has been reported with many

antibiotics including piperacillin. A toxin produced by *Clostridium difficile* appears to be the primary cause. The severity of the colitis may range from mild to life-threatening. It is important to consider this diagnosis in patients who develop diarrhoea or colitis in association with antibiotic use (this may occur up to several weeks after cessation of antibiotic therapy). Mild cases usually respond to drug discontinuation alone. However, in moderate to severe cases appropriate therapy with a suitable oral antibacterial agent effective against *C. difficile* should be considered. Fluids, electrolytes and protein replacement should be provided when indicated. Drugs that delay peristalsis eg: opiates and diphenoxylate with atropine (Lomotil) may prolong and/or worsen the condition and should not be used.

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

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

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 renal impairment**

In patients with renal insufficiency or dialysis patients (haemodialysis and CAPD), the intravenous dose should be adjusted to the degree of renal impairment. Measurement of serum levels of piperacillin will provide guidance for adjusting dosage (see DOSAGE AND ADMINISTRATION).

- **Use with caution in the following circumstances**

Bleeding manifestations have occurred in some patients receiving piperacillin. These reactions have sometimes been associated with abnormalities of coagulation tests, such as clotting time, platelet aggregation and prothrombin time and are more likely to occur in patients with renal failure. If bleeding manifestations occur, the antibiotic should be discontinued and appropriate therapy instituted.

The possibility of the emergence of resistant organisms that might cause superinfections should be kept in mind, particularly during prolonged treatment. If this occurs, appropriate measures should be taken.
As with other penicillins, patients may experience neuromuscular excitability or convulsions if higher than recommended doses are given intravenously.

Repeated use of lignocaine as diluent should be avoided in patients with severe liver disease or decreased hepatic blood flow due to the possibility of lignocaine toxicity (resulting from decreased metabolism and accumulation).

Combined administration of β-lactamase inhibitors and β-lactam antibiotics may be associated with a slightly increased risk of hepatic adverse reactions. The incidence of increased liver enzymes in patients treated with TAZOCIN was slightly higher than has been reported previously with the use of piperacillin alone. The potential for increased hepatic adverse reactions should be borne in mind when using TAZOCIN.

- **Check the following before use**

Periodical assessment of organ system functions including renal, hepatic and haematopoietic during prolonged therapy (≥21 days*)* is advisable.

This product contains 2.79 mEq (64 mg) of sodium per gram of piperacillin which may increase a patient's overall sodium intake. The theoretical sodium content of each vial of TAZOCIN is:

4.5 g vial: 256 mg sodium

Periodical electrolyte determinations should be made in patients with low potassium reserves and the possibility of hypokalaemia should be kept in mind with patients who have potentially low potassium reserves and who are receiving cytotoxic therapy or diuretics.

Because of its poor penetration into the CSF, piperacillin is not advised in the treatment of meningitis and brain abscess.

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

- **Use in pregnancy**

Adequate human studies on the use of TAZOCIN during pregnancy are not available. Limited studies with piperacillin alone in rats and mice revealed no teratogenic effects or harm to the foetus. Studies with tazobactam (doses up to 3,000 mg/kg IV) or tazobactam and piperacillin (doses up to 750 mg/kg and 3,000 mg/kg IV) in mice showed no evidence of teratogenicity or harm to the foetus. Studies in rats at these dose levels showed no evidence of teratogenicity though maternal toxicity, in the form of decreased weight gain, was noted at the dose levels tested. Piperacillin and tazobactam cross the placenta in humans. Pregnant women should be treated only if the expected benefit outweighs the possible risks to the pregnant woman and foetus.

- **Use in lactation**

Adequate clinical studies on the use of TAZOCIN during lactation are not available. Piperacillin is excreted in low concentrations in human milk; tazobactam concentrations in human milk have not been studied. In animal studies, both piperacillin and tazobactam were excreted in the milk of lactating rats. Women who are breast-feeding should be treated only if the expected benefit outweighs the possible risks to the woman and child.

- **Use in children**

Safety and efficacy of the use of TAZOCIN in children under the age of 2 years has not yet been established.

- **Carcinogenicity, mutagenicity and impairment of fertility**

Long-term carcinogenicity studies of TAZOCIN in animals have not been performed. Mutagenicity studies with piperacillin and tazobactam showed no evidence of

genotoxicity in assays for chromosomal and DNA damage. One assay for gene mutations (Mouse lymphoma assay) was weakly positive at tazobactam and piperacillin concentrations ≥3200 μg/mL and 2500 μg/mL, respectively. Piperacillin and tazobactam did not affect the fertility of male or female rats.

INTERACTIONS WITH OTHER MEDICINES

- **Aminoglycosides**

The mixing of beta-lactam antibiotics with aminoglycosides *in-vitro* can result in substantial inactivation of the aminoglycoside. However, amikacin and gentamicin were determined to be compatible *in-vitro* with TAZOCIN in certain diluents at specific concentrations for a simultaneous Y-site infusion (See DOSAGE AND ADMINISTRATION).

The inactivation of aminoglycosides in the presence of penicillin class drugs has been recognised. It has been postulated that penicillin-aminoglycoside complexes form; these complexes are microbiologically inactive and of unknown toxicity.

Concurrent administration of piperacillin and tobramycin in patients with severe renal dysfunction (i.e. chronic haemodialysis patients) has been reported to reduce the elimination half-life and significantly increase the total body clearance of tobramycin.

The alteration of tobramycin pharmacokinetics in patients with mild to moderate renal dysfunction who are taking piperacillin concomitantly is unknown. However, reports suggest that the aminoglycoside inactivation in patients concomitantly taking an aminoglycoside with a broad-spectrum beta-lactam penicillin is only clinically significant in patients with severe renal dysfunction.

- **Probenecid**

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 neither drug are affected.

- **Vancomycin**

No pharmacokinetic interactions have been found between TAZOCIN and vancomycin.

- **Non-depolarizing muscle relaxants**

Piperacillin when used concomitantly with vecuronium has been implicated in the prolongation of the neuromuscular blockade of vecuronium. TAZOCIN (piperacillin/tazobactam) could produce the same phenomenon if given along with vecuronium. Due to their similar mechanism of action, it is expected that the neuromuscular blockade produced by any of the non-depolarising muscle relaxants could be prolonged in the presence of piperacillin.

- **Methotrexate**

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

- **Anticoagulants**

During simultaneous administration of heparin, oral anticoagulants and other

medicines that may affect the blood coagulation system including the thrombocyte function, appropriate coagulation tests should be performed more frequently and monitored regularly.

- **Effects on laboratory tests**

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

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

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

ADVERSE EFFECTS

TAZOCIN is generally well tolerated. The overall incidence of adverse events was 15.7% although a cause/effect relationship was not established in all cases. This incidence was comparable to that observed with other agents used in the clinical studies. Treatment had to be discontinued in only 2.9% of cases due to adverse reactions.

The most frequently reported adverse clinical reactions were diarrhoea, rash, erythema, pruritus, vomiting, allergic reactions, nausea, urticaria, superinfection, phlebitis, thrombophlebitis, dyspepsia, and insomnia.

The following adverse reactions have been reported in clinical trials and are listed in CIOMS frequency categories as follows:

Very common: ≥10%
Common: ≥1%
Uncommon: ≥0.1% and <1%
Rare: ≥0.01% and <0.1%
Very rare: <0.01%
Unknown Cannot be estimated from available data

Skin and subcutaneous tissue disorders

Common: Rash
Uncommon: Pruritis, urticaria
Rare: Eruption (including bullous dermatitis)
Unknown: Increased sweating, eczema, exanthema.

Gastrointestinal

Common: Diarrhoea, including soft/loose stools, nausea, vomiting
Uncommon: Constipation, dyspepsia, stomatitis
Rare: Abdominal pain, pseudomembranous colitis

Nervous system disorders
Uncommon: Headache, insomnia
Unknown: Hallucination, dizziness, dry mouth

Musculoskeletal, connective tissue and bone disorders
Rare: Arthralgia.
Unknown: Muscular weakness, muscle pain, prolonged muscle relaxation

Vascular disorders
Uncommon: Phlebitis, hypotension, thrombophlebitis
Rare: Flushing
Unknown: Tachycardia, including supraventricular and ventricular; bradycardia; arrhythmia, including atrial fibrillation, ventricular fibrillation, cardiac arrest, cardiac failure, circulatory failure, myocardial infarction

Blood and lymphatic system
Uncommon: Leucopenia, neutropenia, thrombocytopenia
Rare: Anaemia, bleeding manifestations (including purpura, epistaxis and bleeding time prolonged), eosinophilia
Very rare: Coombs direct test positive, disturbed thrombocyte function, prolonged partial thromboplastin time, prothrombin time prolonged

Hepatobiliary
Uncommon: Alanine aminotransferase increased, aspartate aminotransferase increased
Rare: Bilirubin increased, blood alkaline phosphatase increased, gamma glutamyltransferase increased. The incidence of such rises is higher than with piperacillin alone.

Renal and urinary disorders
Uncommon: Blood creatinine increased
Rare: Interstitial nephritis, renal failure
Very rare: Blood urea nitrogen increased.

Metabolism and nutrition disorders
Very rare: Blood albumin decreased, blood glucose decreased, blood total protein decreased, hypokalaemia.

Hypokalaemia was reported in patients with liver disease and those receiving cytotoxic therapy or diuretics when given high doses of piperacillin.

General disorders and administration site conditions
Uncommon: Fever, injection site reaction (pain, inflammation)
Rare: Rigors
Unknown: Hot flushes, oedema, tiredness.

Post-marketing Experience
Additional adverse events reported from worldwide marketing experience with TAZOCIN, occurring under circumstances where causal relationship with TAZOCIN

is uncertain.

Blood and lymphatic system
Rare: Haemolytic anaemia
Very rare: Agranulocytosis, pancytopenia, thrombocytosis

Immune system disorders
Uncommon: Hypersensitivity reaction
Rare: Anaphylactic/anaphylactoid reaction (including shock)

Infections and infestations
Uncommon: Candidal superinfection, especially with prolonged treatment

Renal and urinary disorders
Rare: Interstitial nephritis, renal failure

Skin and subcutaneous tissue disorders
Uncommon: Maculopapular rash
Rare: Erythema multiforme
Very rare: Stevens-Johnson syndrome, toxic epidermal necrolysis
Unknown: Drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalised exanthematous pustulosis (AGEP)

Hepatobiliary
Uncommon: Cholestatic jaundice
Rare: Hepatitis

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

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

Adults and Children Over 12 Years, Each with Normal Renal Function
The usual dosage for adults and children over 12 years with normal renal function is 4.5 g TAZOCIN given every eight hours. The total daily dose depends on the severity and localisation of the infection and can vary from 2.25 g to 4.5 g TAZOCIN administered every six or eight hours.

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

Children Aged 12 Years or Under with Normal Renal Function
TAZOCIN is only recommended for the treatment of children with neutropenia or complicated appendicitis. For neutropenic children with normal renal function the dose should be adjusted to 90 mg/kg (80 mg piperacillin/10 mg tazobactam) administered every six hours in combination with an aminoglycoside, not exceeding 4.5 g TAZOCIN every six hours. In children aged 2-12 years with complicated

appendicitis, the dose should be adjusted to 112.5 mg/kg (100 mg piperacillin/12.5 mg tazobactam) administered every eight hours, not exceeding 4.5 g TAZOCIN every eight hours.

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

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

Renal Insufficiency in Adults, the Elderly and Children Receiving the Adult Dose
In patients receiving the adult dose with renal insufficiency, the intravenous dosages and administration intervals should be adjusted to the degree of actual renal impairment. The suggested daily doses are as follows:

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

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

Renal Insufficiency in Children Aged 12 Years and Under
In children with renal insufficiency the intravenous dosages and administration intervals should be adjusted to the degree of actual renal impairment as follows:

Creatinine Clearance (mL/min)	Recommended Piperacillin/Tazobactam Dosage
≥40	No adjustment
20 – 39	90 mg (80 mg piperacillin/10 mg tazobactam)/kg q 8H, not exceeding 13.5 g/day
<20	90 mg (80 mg piperacillin/10 mg tazobactam)/kg q 12H, not exceeding 9 g/day

For children weighing <50 kg on haemodialysis, the recommended dose is 45 mg (40 mg piperacillin/5 mg tazobactam)/kg q 8H.

The above dosage modifications are only an approximation. Each patient must be monitored closely for signs of drug toxicity. Drug dose and interval should be adjusted accordingly. In patients with hepatic impairment, no dose adjustment is

necessary.

Co-administration of TAZOCIN with Aminoglycosides
Due to the *in vitro* inactivation of the aminoglycoside by beta-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 INTERACTIONS WITH OTHER MEDICINES).

In circumstances where co-administration is preferred, 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 Dose (grams)**	**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

‡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 above table have been established as compatible for co-administration via Y-site infusion. Simultaneous co-administration via Y-site in any manner other than listed above may result in inactivation of the aminoglycoside by TAZOCIN.

Duration of Therapy
In acute infections, treatment with TAZOCIN should be continued for 48 hours beyond the resolution of clinical symptoms or the fever. In paediatric complicated appendicitis treatment is recommended for a minimum of 5 days and a maximum of 14 days.

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).

Reconstitution Directions:
Intravenous Injection: Each vial of TAZOCIN 4.5 g should be reconstituted with 20 mL of one of the following diluents.
Solutions known to be compatible with TAZOCIN 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
- Lactated Ringer's Solution (Only compatible with reformulated TAZOCIN containing EDTA).

Swirl until dissolved. Intravenous injection should be given over at least 3-5 minutes. Intravenous Infusion: Each vial of TAZOCIN 4.5 g should be reconstituted with at least 20 mL of one of the reconstitution diluents.

The reconstituted solution 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

[†]Maximum recommended volume of Sterile Water for Injection per dose is 50 mL.

OVERDOSAGE

There have been post-marketing reports of overdose with piperacillin/tazobactam. The majority of those events experienced including nausea, vomiting, and diarrhoea have also been reported with the usual recommended dosages. Patients may experience neuromuscular excitability or convulsions if higher than recommended doses are given intravenously (particularly in the presence of renal failure).

No specific antidote is known. Treatment should be supportive and symptomatic according to the patient's clinical presentation. In the event of an emergency, all required intensive medical measures are indicated as in the case of piperacillin. In cases of motor excitability or convulsions, anticonvulsive agents (e.g., diazepam or barbiturates) may be indicated. In cases of anaphylactic reactions, the usual counter measures are to be initiated (adrenaline, antihistamines, corticosteroids and, if required, oxygen and airway management).

Excessive serum concentrations of either piperacillin or tazobactam may be reduced by haemodialysis.

PHARMACEUTICAL PARTICULARS

Incompatibilities

See DOSAGE AND ADMINISTRATION for Reconstitution Directions.

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.

The mixing of beta-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 DOSAGE AND 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.

Shelf-life
Please refer to the outer carton.

Special precautions for storage
Lyophilised Powder: Vials containing sterile TAZOCIN powder for injection should be stored at controlled room temperature (15°C - 25°C) in the original container.

Solution: Vials containing reconstituted solutions for intravenous use are stable for 24 hours when stored under refrigeration (2°C - 8°C).

Diluted solutions prepared for intravenous use are stable for 24 hours when stored under refrigeration (2°C - 8°C) in I.V. bags or syringes.

Nature and contents of container
Vials

*Trademark

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