

TAZOCIN EF[®]

piperacillin/tazobactam

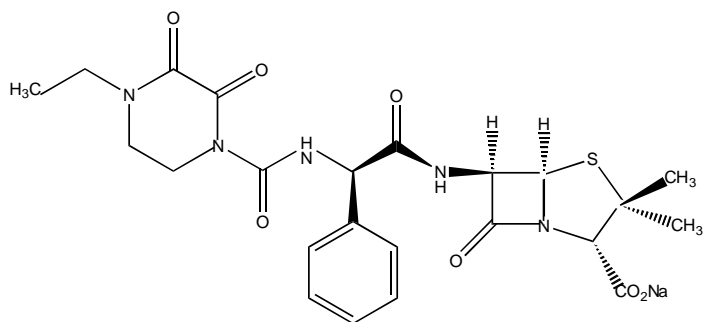
NAME OF THE DRUG

TAZOCIN EF; Piperacillin sodium + Tazobactam sodium

DESCRIPTION

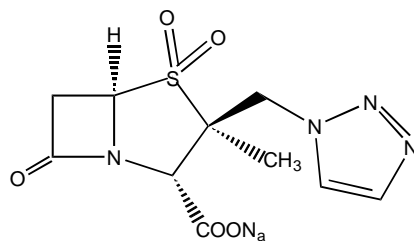
TAZOCIN EF is an injectable antibacterial combination, consisting of the semisynthetic antibiotic piperacillin sodium and the β -lactamase inhibitor tazobactam sodium, for intravenous administration.

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. Its structural formula is



Piperacillin sodium

Tazobactam sodium is a derivative of the penicillin nucleus. Chemically, tazobactam is a penicillanic acid sulfone. Its chemical name is sodium (2S-(2 α ,3 β ,5 α)-3-methyl-7-oxo-3-(1H-1,2,3-triazol-1-ylmethyl)-4-thia-1-azabicyclo[3.2.0] heptane-2-carboxylic acid 4,4-dioxide. The chemical structure of tazobactam sodium is:



Tazobactam sodium

TAZOCIN EF is available as a white to off-white sterile, cryodesiccated powder of piperacillin and tazobactam as the sodium salts packaged in glass vials. The product contains citric acid 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 EF formulation enhances and extends the antibiotic spectrum of piperacillin to include many β -lactamase producing bacteria normally resistant to it. Thus, TAZOCIN EF combines the properties of a broad-spectrum antibiotic and a β -lactamase inhibitor.

Microbiology

TAZOCIN EF 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.

Susceptibility

Local information of 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 states¹.

Table 1 MIC 90 for 1,952 clinically significant isolates

Organism (number)	MIC90 (mg/L)
<i>E.coli</i> (528)	2.0
<i>Klebsiella</i> spp. (180)	4.0
<i>Klebsiella</i> spp. (ESBL 44)	64.0
<i>Enterobacter</i> spp. (142)	16.0
<i>Citrobacter/Serratia</i> spp. (84)	8.0
<i>Morganella/Proteus/Providencia</i> spp. (45)	2.0
<i>Proteus mirabilis</i> spp. (104)	2.0
<i>Pseudomonas aeruginosa</i> (88)	32.0
<i>Acinetobacter calcoaceticus</i> (40)	32.0
<i>Staphylococcus aureus</i> (433)	4.0
Coagulase-negative Staphylococcal (28)	16.0
<i>Streptococcus pneumoniae</i> (45)	0.015

<i>Enterococci (109)</i>	4.0
<i>Haemophilus influenzae (59)</i>	0.094
<i>Bacteroides fragilis</i> 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 M11-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. 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
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
4 g/500 mg	33.8	17.3	11.7	6.8	2.8	1.3

**Completion of 30 minute infusion*

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 3 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)	$T_{1/2}$ (h)
Piperacillin 100mg/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 12.5mg/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 hospitalized 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 EF) 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

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

1. Lower respiratory tract infections
2. Urinary tract infections (complicated and uncomplicated)
3. Intra-abdominal infections
4. Skin and skin structure infections
5. Bacterial septicaemia
6. Gynaecological infections
7. Bacterial infections in neutropenic patients. Full therapeutic doses of TAZOCIN EF plus an aminoglycoside should be used.
8. Bone and joint infections
9. Polymicrobial infections: TAZOCIN EF is indicated for polymicrobial infections including those where aerobic and anaerobic organisms are suspected (intra-abdominal, skin and skin structure, upper and lower respiratory tract, gynaecological).

While TAZOCIN EF is indicated only for the conditions listed above, infections caused by piperacillin susceptible organisms are also amenable to TAZOCIN EF 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 EF should not require the addition of another antibiotic.

Appropriate culture and susceptibility tests should be performed before treatment in order to identify organisms causing infections and to determine their susceptibilities to TAZOCIN EF. Because of its broad-spectrum of activity against Gram-positive and Gram-negative aerobic and anaerobic organisms as listed above, TAZOCIN EF is particularly useful in the treatment of mixed infections and in presumptive therapy prior to the availability of the results of sensitivity tests. Therapy with TAZOCIN EF may, however, be initiated before results of such tests are known. Modification of the treatment may be required once these results become available or if there is no clinical response.

In serious infections, presumptive therapy with TAZOCIN EF may be initiated before susceptibility test results are available.

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

susceptibility tests become available, antimicrobial therapy should be adjusted.

Children under the age of 12 years

In hospitalised children aged 2 to 12 years, TAZOCIN EF is indicated for the treatment of serious intra-abdominal infections. It has not been evaluated in this indication for paediatric patients below the age of 2 years.

CONTRAINDICATIONS

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

PRECAUTIONS

Serious and occasionally fatal hypersensitivity (anaphylactic/anaphylactoid [including shock]) reactions have been reported in patients on penicillin/cephalosporin therapy. 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 EF. 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 EF should be discontinued and the appropriate therapy instituted. Serious anaphylactoid reactions require immediate emergency treatment with adrenaline. Oxygen, intravenous steroids and airway management, including intubation, should also be administered as indicated.

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 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 EF 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 EF.

Check the following before use

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

For patients with renal impairment and/or hepatic insufficiency, measurement of serum levels of piperacillin will provide guidance for adjusting dosage.

The theoretical sodium content of each vial of TAZOCIN EF

2.25 g vial: 128 mg sodium (5.58mmol)

4.5 g vial: 256 mg sodium (11.16 mmol)

which may increase a patient's overall sodium intake.

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 darkfield 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

Pregnancy Category B1.

Adequate human studies on the use of TAZOCIN EF 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 3000 mg/kg IV) or tazobactam and piperacillin (doses up to 750 mg/kg and 3000 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 has been found to cross the placenta in rats. 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 EF during pregnancy are not available. Piperacillin is excreted in low concentrations in milk. 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 EF 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 EF 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 $\mu\text{g/mL}$ and 2500 $\mu\text{g/mL}$, respectively. Piperacillin and tazobactam did not affect the fertility of male or female rats.

Interactions with other drugs

Concurrent administration of probenecid and TAZOCIN EF produced a longer half-life and lower renal clearance for both piperacillin and tazobactam. However, peak plasma concentrations of neither drug are affected. No kinetic interaction is found between TAZOCIN EF and vancomycin.

Concurrent administration of piperacillin and tobramycin in patients with severe renal dysfunction (ie 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.

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.

Piperacillin when used concomitantly with vecuronium has been implicated in the prolongation of the neuromuscular blockade of vecuronium. TAZOCIN EF (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.

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

If TAZOCIN EF is used concurrently with another antibiotic, especially an aminoglycoside, the drugs must not be mixed in intravenous solutions or administered concurrently due to physical incompatibility.

During simultaneous administration of high doses of heparin, oral anticoagulants and other drugs that may affect the blood coagulation system and/or the thrombocyte function, the coagulation parameters should be tested 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 TAZOCIN EF 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 EF should be interpreted cautiously and confirmed by other diagnostic methods.

ADVERSE REACTIONS

TAZOCIN EF 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, pruritis, vomiting, allergic reactions, nausea, urticaria, superinfection, phlebitis, thrombophlebitis, dyspepsia, and insomnia.

Adverse reactions are listed in the Table in CIOMS frequency categories:

Very Common:	≥ 10%
Common:	≥ 1%
Uncommon:	≥ 0.1% and < 1%
Rare:	≥ 0.01% and < 0.1%
Very rare:	< 0.01%
Not known:	frequency could not be accurately estimated from clinical studies

The following table of suspected undesirable effects is based on clinical trials and/or spontaneous postmarketing reporting rates:

Body System ***Adverse Reaction***

Infections and infestations

Uncommon: Candidal superinfection

Blood and lymphatic system

Uncommon: Leucopenia, neutropenia, thrombocytopenia

Rare: Anaemia, bleeding manifestations (including purpura, epistaxis, bleeding time prolonged), eosinophilia, haemolytic anaemia

Very rare: Agranulocytosis, Coombs direct test positive, Pancytopenia, prolonged partial thromboplastin time, prothrombin time prolonged, disturbed thrombocyte function, thrombocytosis

Immune system disorders

Uncommon: Hypersensitivity reaction

Rare: Anaphylactic/anaphylactoid reaction (including shock)

Metabolism and Nutrition Disorders

Very rare: Blood albumin decreased, blood glucose decreased, blood total protein decreased, hypokalaemia

Nervous system disorders

Uncommon: Headache, insomnia

Frequency
unknown: Hallucination, dizziness, dry mouth

Vascular disorders

Uncommon: Hypotension, phlebitis, thrombophlebitis

Rare: Flushing

Gastrointestinal

Body System Adverse Reaction

Common: Diarrhoea, nausea, vomiting

Uncommon: Constipation, dyspepsia, jaundice, stomatitis

Rare: Abdominal pain, pseudomembranous colitis

Frequency
unknown: Bloody diarrhoea

Hepatobiliary

Uncommon: Alanine aminotransferase increased, aspartate aminotransferase increased

Rare: Bilirubin increased, blood alkaline phosphatase increased, gamma-glutamyltransferase increased, hepatitis

Skin and subcutaneous tissue disorders

Common: Rash

Uncommon: Pruritis, urticaria

Rare: Bullous dermatitis, erythema multiforme

Very Rare: Stevens-Johnson Syndrome, toxic epidermal necrolysis

Frequency
unknown: Increased sweating, eczema, exanthema

Musculoskeletal, Connective tissue and bone disorders

Rare: Arthralgia

Frequency
unknown: Myalgia, Muscular weakness, prolonged muscle relaxation

Renal and urinary disorders

Body System ***Adverse Reaction***

Uncommon:	Blood creatinine increased
Rare:	Interstitial nephritis, renal failure
Very rare:	Blood urea nitrogen increased

General disorders and administration site conditions

Uncommon:	Fever, injection site reaction
Rare:	Rigors
Frequency unknown:	Oedema, tiredness, fatigue

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

DOSAGE AND ADMINISTRATION

Dosage

TAZOCIN EF may be given by slow intravenous injection, by infusion (20-30 minutes).

Adults and children 12 years and older

The usual intravenous dosage for adults and children with normal renal function is 4 g piperacillin/0.5 g tazobactam (TAZOCIN EF) given every eight hours.

The total daily dose depends on the severity and localisation of the infection and can vary from 2 g piperacillin/0.25 g tazobactam to 4g piperacillin /0.5g tazobactam (TAZOCIN EF) administered every six, eight or twelve hours.

Use in neutropenic patients -adults and children over the age of 12:

In neutropenic patients, the usual intravenous dosage for adults and children with normal renal function is 4.5 g TAZOCIN EF given every eight hours as a 30 minute infusion, in conjunction with an aminoglycoside. 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 EF administered every six or eight hours.

Tazocin EF has been shown to have a synergistic effect with an aminoglycoside against Pseudomonas infection. Therefore combination therapy is recommended for use in neutropenic patients, in whom infection is attributed predominantly to Pseudomonas organisms.

Children under the age of 12 years:

Recommended Intravenous Dosage

Hospitalised children with intra-abdominal infection

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

For children aged 2 to 12 years, weighing over 40 kg, and with normal renal function, follow the adult dose guidance, ie 4 g piperacillin/0.5 g tazobactam every 8 hours.

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

Renal insufficiency:

In patients with renal insufficiency, the intravenous dose should be adjusted to the degree of actual renal function impairment. The suggested daily doses are as follows:

Intravenous dosage schedule for adults with impaired renal function

Creatinine Clearance (mL/min)	Recommended Piperacillin/Tazobactam Dosage
> 40	NO DOSAGE ADJUSTMENT NECESSARY
20-40	12 g/1.5 g/day Divided Dose 4 g piperacillin/0.5 g tazobactam q 8 hr
< 20	8 g/1 g/day Divided Doses 4 g piperacillin/0.5 g tazobactam q 12 hr

For patients on haemodialysis, the maximum daily dose is 8 g/1 g/day TAZOCIN EF. In addition, because haemodialysis removes 30%-50% of piperacillin in 4 hours, one additional dose of 2 g piperacillin/0.25 g tazobactam (TAZOCIN EF) should be administered following each dialysis period. For patients with renal failure and hepatic insufficiency, measurement of serum levels of TAZOCIN EF will provide additional guidance for adjusting dosage.

Children aged 2 to 12 years:

The pharmacokinetics of piperacillin/tazobactam have not been studied in paediatric patients with renal impairment. Each patient must be monitored closely for signs of drug toxicity. Drug dose and interval should be adjusted accordingly.

Duration of therapy:

In acute infections, treatment with TAZOCIN EF should be for a minimum of five days and continued for 48 hours beyond resolution of clinical symptoms or the fever.

Co-administration of piperacillin/tazobactam with aminoglycosides

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

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

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

Aminoglycoside	Piperacillin / tazobactam (grams) dose	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	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 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 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 piperacillin/tazobactam.

Administration

Reconstitution Directions

For intravenous use

Diluents for Reconstitution: Sterile Water for Injections
 Sodium Chloride Injection
 Dextrose 5% in Water

When swirled constantly, reconstitution generally occurs within 5 to 10 minutes. The reconstituted

solution should be withdrawn from the vial by syringe. When reconstituted as directed, the vial contents withdrawn by syringe will provide the labelled amount of TAZOCIN EF. Solutions of TAZOCIN EF prepared in this manner appear clear to slightly yellow in colour.

Reconstitute each vial with the volume of diluent shown in the table below, using one of the above diluents.

Vial Size (piperacillin/tazobactam)	Minimum volume of diluent to be added to vial
4.50 g (4 g/0.5 g)	20 mL

Administration Directions

For intravenous use:

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

Compatible Intravenous Diluents:

1. 0.9% Sodium Chloride for Injection.
2. Sterile Water for Injection.*
3. Dextrose 5%.
4. Dextran 6% in Saline.
5. Lactated Ringer's Solution (Only compatible with piperacillin/tazobactam EDTA reformulation and is compatible for co-administration via a Y-site).

*Maximum recommended volume of Sterile Water for Injection per dose is 50 mL.

Pharmaceutical Incompatibilities

TAZOCIN EF should not be mixed with other drugs in a syringe or infusion bottle since compatibility has not been established. Whenever TAZOCIN EF is used concurrently with another antibiotic, the drugs must be administered separately. The mixing of TAZOCIN EF with an aminoglycoside can result in substantial inactivation of the aminoglycoside. However, amikacin and gentamicin were determined to be compatible with TAZOCIN EF in certain diluents at specific concentrations (see DOSAGE AND ADMINISTRATION: **Co-administration of piperacillin/tazobactam with Aminoglycosides**)

Because of chemical instability, TAZOCIN EF should not be used with solutions containing only sodium bicarbonate or having a pH in the basic range.

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

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. 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.

PRESENTATION

2.25 g vial containing piperacillin sodium 2.085 g equivalent to 2 g piperacillin and tazobactam sodium 0.2683 g equivalent to 250 mg tazobactam.

4.5 g vial containing piperacillin sodium 4.170 g equivalent to 4 g piperacillin and tazobactam sodium 0.5366 g equivalent to 500 mg tazobactam.

STORAGE AND STABILITY

Lyophilized powder:

Vials containing sterile TAZOCIN EF lyophilized powder may be stored below 30°C for up to 2 years.

Solutions:

Diluted solutions should be used immediately.

NAME AND ADDRESS

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DATE OF PREPARATION

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Reference

1. Daley, D., Mulgrave, L., Munro, S., Smith, H. and Dimech, W. An evaluation of the *in vitro* activity of piperacillin/tazobactam. Pathology 28: 167-172, 1996.