# APPROVED PACKAGE INSERT

**SCHEDULING STATUS:**

S4

**PROPRIETARY NAME AND DOSAGE FORM:**

TAZOCIN® 4 EF Injection

**COMPOSITION:**

Piperacillin/Tazobactam is an injectable antibacterial combination consisting of the semi-synthetic antibiotic piperacillin sodium and the beta-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-l-piperazinecarboxamido)-2-phenylaceta-mido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid.

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

TAZOCIN 4 EF Injection contains piperacillin sodium equivalent to piperacillin 4 g and tazobactam sodium equivalent to tazobactam 500 mg.

**PHARMACOLOGICAL CLASSIFICATION:**

A 20.1.1 Broad and Medium Spectrum Antibiotics

**PHARMACOLOGICAL ACTION:**

Piperacillin, a broad spectrum, semi-synthetic 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 an inhibitor of many ß-lactamases, including the plasmid and chromosomally mediated enzymes. The presence of tazobactam in the piperacillin/tazobactam formulation enhances and extends the antibiotic spectrum of piperacillin.

Microbiology

Piperacillin/tazobactam is highly active against piperacillin-sensitive micro-organisms as well as ß-lactamase producing, piperacillin-resistant micro-organisms.

Gram-negative bacteria: Most plasmid mediated ß-lactamase producing and non-producing strains of *Escherichia coli, Klebsiella* spp (including *K. oxytoca, K. pneumoniae*), *Proteus vulgaris, Proteus mirabilis, Morganella morganii, Serratia* spp. (including *S. marcescens), Neisseria gonorrhoeae, Neisseria meningitidis, Moraxella* spp. (including *Branhamella catarrhalis), Haemophilus influenzae, H. parainfluenzae*.

Gram-positive bacteria: ß-lactamase producing and non-producing strains of streptococci (*S. pneumoniae, S. pyogenes, S. agalactiae, S. viridans,* Group C, Group G), *Enterococcus faecalis, Staphylococcus aureus, S. epidermidis* (coagulase-negative staphylococci).

Anaerobic bacteria: ß-lactamase producing and non-producing anaerobes such as *Bacteroides* spp. (including *B. melaninogenicus*) the *Bacteroides fragilis* group including *B. fragilis, B. distasonis,* as well as, *Peptostreptococcus* spp., *Fusobacterium* spp., *Clostridia* spp. (including *C. difficile, C. perfringens*).

Susceptibility

The following minimum inhibitory concentration (MIC) interpretative criteria breakpoints are suggested:

MINIMUM INHIBITORY CONCENTRATION (MIC) BREAKPOINTS

| | Susceptible | Intermediate | Resistant |
|---|---|---|---|
| Enterobacteriaciae | ≤ 16 mg/L | 32 - 64 mg/L | ≥ 128 mg/L |
| Pseudomonas | ≤ 64 mg/L | - | ≥ 128 mg/L |
| Staphylococcus | ≤ 8 mg/L | - | ≥ 16 mg/L |
| *Streptococcus | ≤ 1 mg/L | - | ≥ 2 mg/L |
| Anaerobes | ≤ 32 mg/L | 64 mg/L | ≥ 128 mg/L |

The prevalence of acquired resistance may vary geographically and with time for selected species. Local information of resistance is desirable, particularly when treating severe infections. This information provides guidance on micro-organisms susceptible to piperacillin/tazobactam.

*There are no formal recommendations for Streptococcus, therefore, the above breakpoints are those recommended by Pfizer.

*In vitro* sensitivity does not necessarily imply clinical efficacy.

**INDICATIONS:**

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

**Adults:**

1. Community acquired pneumonia due to *Haemophilus influenzae.*
2. Intra-abdominal Infections caused by piperacillin resistant beta-lactamase producing strains of *Escherichia coli* and *Bacteroides fragilis*.
3. Skin and Skin Structure Infections caused by piperacillin resistant beta-lactamase producing strains of *Staphylococcus aureus*.
4. Gynaecologic Infections including endometritis caused by piperacillin resistant beta-lactamase producing strains of *E coli*.
5. Piperacillin/tazobactam plus an aminoglycoside is indicated for Bacterial infections in Neutropenic patients.

**Children:**

CHILDREN UNDER THE AGE OF 12 YEARS:

Piperacillin/tazobactam plus an aminoglycoside is indicated for bacterial infections in neutropenic patients.

CHILDREN 2 - 12 YEARS:

In hospitalised children aged 2 to 12 years, piperacillin/tazobactam is indicated for the treatment of serious intra-abdominal infections, caused by *E. coli* or *Bacteroides* species.

It has not been evaluated in this indication for paediatric patients below the age of 2 years.

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

Piperacillin/Tazobactam is useful in the treatment of mixed infections and in presumptive therapy prior to the availability of the results of sensitivity tests.

**CONTRAINDICATIONS:**

The use of piperacillin/tazobactam is contraindicated in patients with a history of allergic reactions to any of the penicillins and/or cephalosporins or ß-lactamase inhibitors, or any of the constituents.

**WARNINGS AND SPECIAL PRECAUTIONS:**

Serious and occasionally fatal hypersensitivity (anaphylactic/anaphylactoid including shock) reactions have been reported in patients receiving therapy with penicillins. These reactions are more apt to occur in persons with a history of penicillin hypersensitivity or sensitivity to multiple allergens.

There have been reports of patients with a history of penicillin hypersensitivity that have experienced severe hypersensitivity reactions when treated with a cephalosporin. Before initiating therapy with piperacillin/tazobactam, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, and other allergens.

If an allergic reaction occurs during therapy with piperacillin/tazobactam, the antibiotic should be discontinued. Serious hypersensitivity reactions require immediate emergency measures, with adrenaline, corticosteroids and antihistamines. An open airway must be maintained.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including piperacillin. Antibiotic-induced pseudomembranous colitis may be manifested by severe, persistent diarrhoea which

may be life-threatening. The onset of pseudomembranous colitis may occur during or after antibacterial treatment.

Therefore it is important to consider this diagnosis in patients who present with diarrhoea subsequent to the administration of antibacterial agents.

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation and treatment with an oral antibacterial drug effective against *C. difficile.*

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

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

Bleeding manifestations have occurred in some patients receiving ß-lactam antibiotics. 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, which 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.

This product contains 2,79 mEq (64 mg) of sodium per gram of piperacillin which may increase a patient's overall sodium intake. Periodic 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. Modest elevation of indices of liver function may be observed.

In patients with renal insufficiency or haemodialysis patients, the intravenous dose should be adjusted to the degree of renal function impairment.

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

**INTERACTIONS:**

Interactions with other medicines:

Concurrent administration of probenecid and piperacillin/ tazobactam produced a longer half-life and lower renal clearance for both piperacillin and tazobactam; however, peak plasma concentrations of either medicine are unaffected.

No interaction is found between piperacillin/tazobactam and vancomycin.

Piperacillin either alone or with tazobactam did not significantly alter the pharmacokinetics of tobramycin in subjects with normal renal function and with mild or moderate renal impairment. The pharmacokinetics of piperacillin, tazobactam, and the M1 metabolite were also not significantly altered by tobramycin administration.

Whenever piperacillin/tazobactam 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.

Piperacillin, when given concomitantly with vecuronium has been implicated in the prolongation of the neuromuscular blockage of vecuronium.
Due to their similar mechanism of action, it is expected that the neuromuscular blockade produced by any of the non-depolarizing muscle relaxants could be prolonged in the presence of piperacillin.

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

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

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 DIRECTIONS FOR USE).

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

Lactated Ringer's solution is only compatible with TAZOCIN 4 EF formulation.

Piperacillin/tazobactam should not be added to blood products or albumin hydrolysates.

Laboratory tests:

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 the 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 piperacillin/tazobactam should be interpreted cautiously and confirmed by other diagnostic methods.

**PREGNANCY AND LACTATION:**

Adequate studies on the use of piperacillin/tazobactam during pregnancy and the period of breast feeding are not yet available. Piperacillin/tazobactam did not affect fertility in rats and was not teratogenic in mice or rats. Piperacillin and tazobactam cross the placenta. Piperacillin is excreted in low concentrations in human milk; tazobactam concentrations in human milk have not been studied. Until further experience is available, however, pregnant or nursing women should be treated only if the therapeutic benefit outweighs the risk to the patient and the foetus.

**DOSAGE AND DIRECTIONS FOR USE:**

Piperacillin/tazobactam must be given by slow intravenous infusion (30 minutes).

*Adults and juveniles 12 years and older*

The usual dosage for adults and juveniles with normal renal function is 4/0,5 g piperacillin/tazobactam given every eight hours. The dosage in immunocompromised and neutropenic patients with infection is 4/0,5 g piperacillin/tazobactam every 6 hours in combination with an aminoglycoside.

*Children under the age of 12 years*

TAZOCIN 4 EF is only recommended for the treatment of children with neutropenia.

For children weighing over 50 kg, follow the adult dosing guidance, including the aminoglycoside.

For children with normal renal function and weighing less than 50 kg the dose should be adjusted to 90 mg/kg (80 mg piperacillin/10 mg tazobactam) administered every 6 hours, in combination with an aminoglycoside.

*Elderly*

Piperacillin/tazobactam may be used at the same dose levels as adults except in cases of renal impairment (see below).

*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 |
|---|---|
| 90 – 40 | 12 g/1,5 g / day in divided doses of 4 g/0,5 g q8h or 3 g/0,375 g q6h |
| 20 – 40 | 8 g/1,0 g / day in divided doses of 2 g/0,25 g q6h |
| < 20 | 6 g/0,75 g / day in divided doses of 2 g/0,25 g q8h |

For patients on haemodialysis, the maximum daily dose is 2 g/0,25 g every 8 hours piperacillin/tazobactam. In addition, because haemodialysis removes 30 % - 40 % of piperacillin in 4 hours, one additional dose of 0,75 g piperacillin/tazobactam should be administered following each dialysis period. For patients with renal failure and hepatic insufficiency, measurement of serum levels of piperacillin/tazobactam will provide additional guidance for adjusting dosage.

*Neutropenic patients*

In treating neutropenic patients, full therapeutic doses of piperacillin/tazobactam and an aminoglycoside should be used. The possibility of hypokalaemia should be kept in mind in patients who have low potassium reserves, and periodic electrolyte determinations should be made in these patients.

*Duration of therapy*

In acute infections, treatment with piperacillin/tazobactam should be for a minimum of five days and continued for forty-eight hours beyond resolution of clinical symptoms or the fever. The usual duration of treatment is 7 - 10 days.

*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 112,5 mg/kg (100 mg piperacillin/12,5 mg tazobactam) every 8 hours.

For children aged 2 to 12 years, weighing over 40 kg, and with normal renal function, follow the adult dose guidance, i.e. 4,5 g (4 g piperacillin/0,5 g tazobactam) every 8 hours.

The duration of therapy should be guided by the severity of the infection and the patient's clinical and bacteriological progress. Therapy is recommended to be a minimum of 5 days and a maximum of 14 days, considering the dose administration should continue at least 48 hours after the resolution of clinical signs and symptoms.

*Children aged 2 – 12 years with renal insufficiency*

The pharmacokinetics of piperacillin/tazobactam have not been studied in paediatric patients with renal impairment. The following dosage adjustment for paediatric patients aged 2 to 12 years with renal impairment is recommended.

INTRAVENOUS DOSAGE SCHEDULE FOR CHILDREN AGED 2 – 12 YEARS WITH IMPAIRED RENAL FUNCTION

| Creatinine Clearance (ml/min) | Recommended Piperacillin/Tazobactam Dosage |
|---|---|
| > 50 | 112,5 mg/kg (100 mg/12,5 mg) q8h |
| ≤ 50 | 78,75 mg/kg (70 mg/8,75 mg) q8h |

The dosage modification is only an approximation. Each patient must be monitored closely for signs of drug toxicity. Drug dose and interval should be adjusted accordingly.

**Reconstitution directions**

Diluents for Reconstitution:

Sterile Water for Injection

Bacteriostatic Water for Injection

Sodium Chloride Injection

Each vial of 4 g/0,5 g TAZOCIN 4 EF should be reconstituted with at least 20 ml of one of the above diluents. Shake until dissolved.

For intravenous infusion

The reconstituted solution may be further diluted to the desired volume (e.g. 50 ml or 100 ml) with one of the reconstitution diluents or with:

Dextrose 5 % in Water

**Co-Administration of piperacillin/tazobactam with aminoglycosides**

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

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

| Aminoglycoside | Piperacillin/ tazobactam (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).

Compatiblity 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 the Y-site. Simultaneous co-administration via Y-site in any other manner than listed above may result in inactivation of the aminoglycoside by piperacillin/tazobactam.

**SIDE EFFECTS**:

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

| | |
|---|---|
| Very Common | ≥ 10 % |
| Common | ≥ 1 % and < 10 % |
| Uncommon | ≥ 0,1 % and < 1% |
| Rare | ≥ 0,01 % and < 0,1 % |
| Very rare | < 0,01 % |

**Infections and infestations:**

| | |
|---|---|
| Uncommon: | Candidal superinfections |

**Blood and lymphatic system:**

| | |
|---|---|
| Uncommon: | Leukopenia, 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, thrombocytosis |

**Immune system disorders:**

Uncommon: Hypersensitivity reaction

Rare: Anaphylactic/anaphylactoid reaction (including shock)

**Metabolism and nutritional disorders:**

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

**Nervous system disorders:**

Uncommon: Headache, insomnia

**Vascular disorders:**

Uncommon: Hypotension, phlebitis, thrombophlebitis

Rare: Flushing

**Gastro-intestinal:**

Common: Diarrhoea, nausea, vomiting

Uncommon: Constipation, dyspepsia, jaundice, stomatitis

Rare: Abdominal pain, pseudomembranous colitis

**Hepatobiliary system:**

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: | Pruritus, urticaria |
| Rare: | Bullous dermatitis, erythema multiforme |
| Very rare: | Stevens-Johnson Syndrome, toxic epidermal necrolysis |

**Musculoskeletal, connective tissue and bone disorders:**

| | |
|---|---|
| Rare: | Arthralgia |

**Renal and urinary disorders:**

| | |
|---|---|
| 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 |

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

**KNOWN SYMPTOMS OF OVERDOSE AND PARTICULARS OF ITS TREATMENT:**

See SIDE EFFECTS. The majority of events experienced during overdosage 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).

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 haemodialysis.

In the event of an emergency, all required intensive medical measures are indicated as in the case of piperacillin.

In case of motor excitability or convulsions, anticonvulsive agents (e.g. diazepam or barbiturates) may be indicated.

In case of severe, hyperallergic (anaphylactic) reactions, the usual countermeasures are to be initiated (antihistamines, corticosteroids, sympathicomimetic drugs and, if required, oxygen and airway management).

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

**IDENTIFICATION:**

4/0,5 g: 70 ml Glass vials containing a white to off-white caked mass or powder

Constituted solution: Clear colourless to pale yellow liquid free from foreign matter.

**PRESENTATION:**

TAZOCIN 4 EF is available as a white to off-white sterile, cryodesiccated powder of piperacillin and tazobactam as the sodium salts packaged in 70 ml glass vials.

4/0,5 g TAZOCIN 4 EF: Each 70 ml vial contains sterile piperacillin sodium equivalent to 4 grams and sterile tazobactam sodium equivalent to 500 milligrams. Product code 8455.

**STORAGE INSTRUCTIONS**:

Dry Powder: Vials containing sterile piperacillin/tazobactam dry powder may be stored at controlled room temperature (up to 25 °C).

Solutions: Vials containing reconstituted solutions for intravenous and intramuscular use are stable for 24 hours at room temperature (below 25 °C) and 48 hours under refrigeration (2 - 8 °C).

Diluted solutions prepared for intravenous use are stable for 24 hours at room temperature (below 25 °C) and 48 hours under refrigeration (2 - 8 °C) in I.V. bags or syringes. Unused solution should be discarded.

**REGISTRATION NUMBER:**

TAZOCIN 4 EF Injection: Z/20.1.1/201

**NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:**

Pfizer Laboratories (Pty) Ltd.

85 Bute Lane

Sandton

2196

**DATE OF PUBLICATION OF THIS PACKAGE INSERT:**

02 May 2002