NEW ZEALAND DATA SHEET

1. PRODUCT NAME

TAZOCIN EF® 2.25 g piperacillin/tazobactam 2.0 g/0.25 g powder for injection

TAZOCIN EF® 4.5 g piperacillin/tazobactam 4.0 g/0.5 g powder for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of TAZOCIN EF 2.25 g contains piperacillin sodium 2.085 g equivalent to 2 g piperacillin and tazobactam sodium 0.2683 g equivalent to 250 mg tazobactam.

Each vial of TAZOCIN EF 4.5 g contains piperacillin sodium 4.170 g equivalent to 4 g piperacillin and tazobactam sodium 0.5366 g equivalent to 500 mg tazobactam.

Excipient(s) with known effect:

- Disodium edetate dihydrate (EDTA).

The theoretical sodium content of each vial of TAZOCIN EF is 2.84 mEq (65 mg) of sodium per gram of piperacillin which may increase a patient's overall sodium intake.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for injection

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.

4. CLINICAL PARTICULARS

4.1 Therapeutic 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. Polymicrobic infections: TAZOCIN EF is indicated for polymicrobic 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.

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

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.

4.2 Dose and method of administration

Dose

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 4 g piperacillin/0.5 g 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, i.e. 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 impairment

In patients with renal impairment or in haemodialysis patients, the intravenous dose and administration interval 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 Doses 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 Dose (grams)**	**Piperacillin/ Tazobactam Diluent Volume (mL)**	**Aminoglycoside Concentration Range‡ (mg/mL)**	**Acceptable Diluents**
Amikacin	2.25,4.5	50,150	1.75 – 7.5	0.9% sodium chloride or 5% dextrose
Gentamicin	2.25,4.5	50,150	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.

Method of 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.

4.3 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.

- Patients with hypersensitivity to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

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.

TAZOCIN EF should be given with caution to patients who have previously experienced signs and symptoms of allergy associated with a cephalosporin or penicillin treatment. 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.

Severe cutaneous adverse reactions (SCAR), such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalised exanthematous pustulosis (AGEP) have been reported in patients taking beta-lactam antibiotics. When SCAR is suspected, TAZOCIN EF should be discontinued immediately and an alternative treatment should be considered.

Antibiotic-associated pseudomembranous colitis has been reported with many antibiotics including piperacillin. A toxin produced by *Clostridiodes 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 e.g. 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 (seizures) may occur when high doses are administered, especially in patients with impaired renal function (see section 4.8).

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 renal impairment

Due to its potential nephrotoxicity (see section 4.8), piperacillin/tazobactam should be used with care in patients with renal impairment or in hemodialysis patients. The intravenous dose and administration interval should be adjusted to the degree of renal function impairment (see section 4.2).

In a secondary analysis using data from a large multicenter, randomised-controlled trial when glomerular filtration rate (GFR) was examined after administration of frequently used antibiotics in critically ill patients, the use of piperacillin/tazobactam was associated with a lower rate of reversible GFR improvement compared with the other antibiotics. This secondary analysis concluded that piperacillin/tazobactam was a cause of delayed renal recovery in these patients.

Combined use of piperacillin/tazobactam and vancomycin may be associated with an increased incidence of acute kidney injury (see section 4.5).

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 is 2.84 mEq (65 mg) of sodium per gram of piperacillin which may increase a patient's overall sodium intake.

2.25 g vial:	130 mg	sodium (5.65 mmol)
4.5 g vial:	260 mg	sodium (11.31 mmol)

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.

Massive doses of TAZOCIN EF can cause hypokalaemia and sometimes hypernatraemia. In patients undergoing high-dose treatment for more than 5 days, electrolyte balance, blood counts, and renal function should be monitored. Additionally, use of a potassium-sparing diuretic may be helpful.

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.

Paediatric Population

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

Effects on laboratory tests

Penicillins may interfere with:

- Urinary glucose test
- Coomb's tests
- Tests for urinary or serum proteins
- Tests which use bacteria e.g. Guthrie test.

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* enzyme immunoassay (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.

4.5 Interaction with other medicines and other forms of interaction

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.

Studies have detected an increased incidence of acute kidney injury in patients concomitantly administered piperacillin/tazobactam and vancomycin as compared to vancomycin alone (see section 4.4). Some of these studies have reported that the interaction is vancomycin dose-dependent. Expert guidelines recommend intensive vancomycin dosing and maintenance of trough levels between 15 mg/L and 20 mg/L which is an increase from previously published recommendations of target trough concentrations of 5-10 mg/L. Attaining these trough concentrations often requires practitioners to prescribe vancomycin doses which exceed manufacturers' recommendations. Therefore, it is possible that in addition to the increased risk of vancomycin-induced nephrotoxicity reported with adherence to these guidelines the risk of nephrotoxicity may also increase due to an interaction with piperacillin/tazobactam.

No kinetic interaction is found between TAZOCIN EF and vancomycin.

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.

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.

4.6 Fertility, pregnancy and lactation

Fertility

Piperacillin and tazobactam did not affect the fertility of male or female rats.

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 fetus. 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 fetus. 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 fetus.

Lactation

Adequate clinical studies on the use of TAZOCIN EF during lactation or in breastfeeding women are not available. Low quantities of TAZOCIN EF can be detected in breast milk with the potential for hypersensitivity reactions (e.g. drug rashes) or gastrointestinal disorders (e.g. diarrhoea or candidosis) in the breast-fed infant. Consequently, breastfeeding might have to be discontinued.

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.

4.7 Effects on ability to drive and use machines

No studies on the effect on the ability to drive or use machines have been performed.

4.8 Undesirable effects

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% and < 10%
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	
Common:	Candida infection†
Rare:	Pseudomembranous colitis
Blood and lymphatic system disorders	
Common:	Thrombocytopenia, anaemia†
Uncommon:	Leucopenia
Rare:	Agranulocytosis
Not known:	Pancytopenia†, neutropenia, haemolytic anaemia†, thrombocytosis†, eosinophilia†
Immune system disorders	
Not known:	Anaphylactoid shock†, anaphylactic shock†, anaphylactoid reaction†, anaphylactic reaction†, hypersensitivity†
Metabolism and nutrition disorders	
Uncommon:	Hypokalaemia
Nervous system disorders	
Common:	Headache
Uncommon:	Seizure†
Not known:	Dizziness
Vascular disorders	
Uncommon:	Hypotension, phlebitis, thrombophlebitis, flushing
Respiratory, thoracic and mediastinal disorders	

Body System	Adverse Reaction
Rare:	Epistaxis
Not known:	Eosinophilic pneumonia†
Gastrointestinal disorders	
Very common:	Diarrhoea
Common:	Abdominal pain, vomiting, constipation, nausea, dyspepsia
Rare:	Stomatitis
Not known:	Bloody diarrhoea, dry mouth
Hepatobiliary disorders	
Not known:	Hepatitis†, jaundice
Skin and subcutaneous tissue disorders	
Common:	Rash, pruritus
Uncommon:	Erythema multiforme†, urticaria, rash maculopapular†
Rare:	Toxic epidermal necrolysis (TEN)†
Not known:	Stevens-Johnson syndrome (SJS)†, drug reaction with eosinophilia and systemic symptoms (DRESS)†, acute generalised exanthematous pustulosis (AGEP)†, dermatitis exfoliative†, dermatitis bullous, purpura, eczema, hyperhidrosis, cutaneous vasculitis
Musculoskeletal and connective tissue disorders	
Uncommon:	Arthralgia, myalgia
Not known:	Muscular weakness, prolonged muscle relaxation
Renal and urinary disorders	
Not known:	Renal failure, tubulointerstitial nephritis†
General disorders and administration site conditions	
Common:	Pyrexia, injection site reaction
Uncommon:	Chills
Not known:	Oedema, fatigue

Body System	Adverse Reaction
Psychiatric disorders	
Common:	Insomnia
Not known:	Hallucinations, delirium†
Investigations	
Common:	Alanine aminotransferase increased, aspartate aminotransferase increased, protein total decreased, blood albumin decreased, Coombs direct test positive, blood creatinine increased, blood alkaline phosphatase increased, blood urea increased, activated partial thromboplastin time prolonged
Uncommon:	Blood glucose decreased, blood bilirubin increased, prothrombin time prolonged
Not known:	Bleeding time prolonged, gamma-glutamyltransferase increased

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

† Adverse event identified post-marketing.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

4.9 Overdose

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.

For advice on the management of overdose, please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

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.

Piperacillin and other β-lactam antibiotics block the terminal transpeptidation step of cell wall peptidoglycan biosynthesis in susceptible bacteria by interacting with penicillin-binding proteins (PBPs), the bacterial enzymes that carry out this reaction. *In vitro*, piperacillin is active against a variety of gram-positive and gram-negative aerobic and anaerobic bacteria.

Piperacillin has reduced activity against bacteria harboring certain β-lactamase enzymes, which chemically inactivate piperacillin and other β-lactam antibiotics. Tazobactam sodium, which has very little intrinsic antimicrobial activity, due to its low affinity for PBPs, can restore or enhance the activity of piperacillin against many of these resistant organisms. Tazobactam is a potent inhibitor of many class A β-lactamases (penicillinases, cephalosporinases and extended spectrum enzymes). It has variable activity against class A carbapenemases and class D β-lactamases. It is not active against most class C cephalosporinases and inactive against Class B metallo-β-lactamases.

Two features of piperacillin/tazobactam lead to increased activity against some organisms harboring β-lactamases that, when tested as enzyme preparations, are less inhibited by tazobactam and other inhibitors: tazobactam does not induce chromosomally mediated β-lactamases at tazobactam levels achieved with the recommended dosing regimen and piperacillin is relatively refractory to the action of some β-lactamases.

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

Mechanism of resistance

There are three major mechanisms of resistance to β-lactam antibiotics: changes in the target penicillin-binding proteins (PBPs) resulting in reduced affinity for the antibiotics, destruction of the antibiotics by bacterial β-lactamases, and low intracellular antibiotic levels due to re2duced uptake or active efflux of the antibiotics.

In gram-positive bacteria, changes in PBPs are a major mechanism of resistance to β-lactam antibiotics, including piperacillin/tazobactam. This mechanism is responsible for methicillin resistance in staphylococci and penicillin resistance in *Streptococcus pneumoniae* as well as viridans group streptococci and enterococci. Resistance caused by changes in PBPs also occurs to a lesser extent in fastidious gram-negative species such as *Haemophilus influenzae* and *Neisseria gonorrhoeae*. Piperacillin/tazobactam is not active against strains in which

resistance to β-lactam antibiotics is determined by altered PBPs . As indicated above, there are some β-lactamases that are not inhibited by tazobactam.

Antibacterial spectrum (Groupings of relevant species according to piperacillin/tazobactam susceptibility)

Commonly susceptible species

Aerobic gram-negative bacteria

Citrobacter koseri
Haemophilus influenzae
Moraxella catarrhalis
Proteus mirabilis

Aerobic gram-positive bacteria

Enterococcus faecalis (ampicillin-or penicillin-susceptible isolates only)
Listeria monocytogenes
Staphylococcus aureus (methicillin-susceptible isolates only)
Staphylococcus spp., coagulase-negative (methicillin-susceptible isolates only)
Streptococcus agalactiae (Group B streptococci)†
Streptococcus pyogenes (Group A streptococci)†

Anaerobic gram-positive bacteria

Clostridium spp.
Eubacterium spp.
Anaerobic gram-positive cocci††

Anaerobic gram-negative bacteria

Bacteroides fragilis group
Fusobacterium spp.
Porphyromonas spp.
Prevotella spp.

Species for which acquired resistance may be a problem

Aerobic gram-positive bacteria

Enterococcus faecium
Streptococcus pneumoniae††
Viridans group streptococci††

Aerobic gram-negative bacteria

Acinetobacter baumannii
Citrobacter freundii
Enterobacter spp.
Escherichia coli
Klebsiella pneumoniae

Morganella morganii
Proteus vulgaris
Providencia spp.
Pseudomonas aeruginosa
Serratia spp.

Anaerobic gram-positive bacteria

Clostridium perfringens

Anaerobic gram-negative bacteria

Bacteroides distasonis
Prevotella melaninogenica

Inherently resistant organisms

Aerobic gram-positive bacteria

Corynebacterium jeikeium

Aerobic gram-negative bacteria

Burkholderia cepacia
Legionella spp.
Stenotrophomonas maltophilia

Others

Chlamydophila pneumoniae
Mycoplasma pneumoniae

† Streptococci are not β-lactamase producing bacteria; resistance in these organisms is due to alterations in PBPs and, therefore, piperacillin/tazobactam-susceptible isolates are susceptible to piperacillin alone. Penicillin resistance has not been reported in *S. pyogenes*.

†† Including *Anaerococcus*, *Finegoldia*, *Peptococcus*, *Peptoniphilus*, and *Peptostreptococcus* spp. (CLSI M100 Ed. 29, 2019).

Susceptibility

Susceptibility testing should be conducted using standardised laboratory methods such as those described by the Clinical and Laboratory Standards Institute (CLSI). These include dilution methods (minimal inhibitory concentration [MIC] determination) and disk susceptibility methods.

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 states[1].

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 CLSI interpretive criteria for susceptibility testing of piperacillin/tazobactam are listed in the following table:

CLSI Susceptibility Interpretive Criteria for Piperacillin/Tazobactam

Pathogen	**Minimal Inhibitory Concentration (mg/L of Piperacillin)[a]**			**Disk[b] Diffusion Inhibition Zone (mm Diameter)**		
	S	I	R	S	I	R
Enterobacteriaceae	≤16	32-64	≥128	≥21	18-20	≤17
Acinetobacter spp.	≤16	32-64	≥128	≥21	18-20	≤17
Pseudomonas aeruginosa	≤16	32-64	≥128	≥21	15-20	≤14
Certain other non-fastidious gram-negative bacilli[c]	-	-	-	≥21	18-20	≤17
Haemophilus influenzae and *Haemophilus parainfluenzae*	≤1	-	≥2	≥21	-	-
Anaerobes[d]	≤32	64	≥128	-	-	-

Source: Clinical and Laboratory Standards Institute. *Performance Standards for Antimicrobial Susceptibility Testing;* . CLSI document M100:ED29. CLSI, Wayne, PA, 2019. This document is updated annually and may be accessed at http://clsi-m100.com/.
S = Susceptible. I = Intermediate. R = Resistant.
[a] MICs are determined using a fixed concentration of 4 mg/L tazobactam and by varying the concentration of piperacillin.
[b] CLSI interpretive criteria are based on disks containing 100 µg of piperacillin and 10 µg of tazobactam.
[c] Refer to CLSI Document M100 Table 2B-5 for the list of organisms included.
[d] With the exception of *Bacteroides fragilis*, MICs are determined by agar dilution only.

Standardised susceptibility test procedures require the use of quality control microorganisms to control the technical aspects of the test procedures. Quality control microorganisms are specific strains with intrinsic biological properties relating to resistance mechanisms and their genetic expression within the microorganism; the specific strains used for susceptibility test quality control are not clinically significant.

Organisms and quality control ranges for piperacillin/tazobactam to be utilized with CLSI methodology and susceptibility test interpretive criteria are listed in the following table:

Quality Control Ranges for Piperacillin/Tazobactam to be Used in Conjunction with CLSI Susceptibility Test Interpretive Criteria

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

Source: Clinical and Laboratory Standards Institute. *Performance Standards for Antimicrobial Susceptibility Testing.* CLSI document M100ED29. CLSI, Wayne, PA, 2019.
[a] Agar dilution only.

Clinical efficacy and safety

MERINO trial (blood stream infections due to ESBL producing organisms)

In a prospective, randomised non-inferiority clinical trial, definitive (i.e. based on susceptibility confirmed *in-vitro*) treatment with piperacillin/tazobactam did not meet non-inferiority in

regard to 30-day mortality in the treatment of blood stream infections due to ESBL producing *E. coli* or *Klebsiella pneumoniae* in critically ill adult patients. A total of 23 of 187 patients (12.3%) randomised to piperacillin/tazobactam met the primary outcome of mortality at 30 days compared with 7 of 191 (3.7%) randomized to meropenem (risk difference, 8.6% [1-sided 97.5% CI − ∞ to 14.5%]; P = 0.90 for non-inferiority). Clinical and microbiological resolution by day 4 occurred in 121 of 177 patients (68.4%) in the piperacillin/tazobactam group compared with 138 of 185 (74.6%), randomized to meropenem (risk difference, −6.2% [95% CI, −15.5 to 3.1%]; P = 0.19). The cause of the mortality imbalance is not clear. This study was not sponsored by Pfizer.

Paediatric population

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.

5.2 Pharmacokinetic properties

Distribution

Mean plasma concentrations of piperacillin and tazobactam at steady state of the combination appear in Table 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.

Elimination

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 section 4.2.

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 section 4.2.

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.

Paediatric population

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

5.3 Preclinical safety data

Genotoxicity

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.

Carcinogenicity

Long term carcinogenicity studies of TAZOCIN EF in animals have not been performed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Citric acid monohydrate
- Disodium edetate dihydrate (EDTA).

6.2 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 section 4.2, 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.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Lyophilized powder:

TAZOCIN EF 2.25 g vial - Store at or below 25°C

TAZOCIN EF 4.5 g vial – Store below 30°C

Solutions:

48 hours reconstituted stored at 2° to 8°C (Refrigerate, do not freeze).

6 hours reconstituted stored at or below 25°C.

6.5 Nature and contents of container

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

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

Not all pack sizes may be marketed.

The medicinal product is supplied in packs of 1 or 10 vials.

6.6 Special precautions for disposal and other handling

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription

8. SPONSOR

Pfizer New Zealand Limited
P O Box 3998
Auckland, New Zealand, 1140.
Toll Free Number: 0800 736 363

9. DATE OF FIRST APPROVAL

23 September 1993

10. DATE OF REVISION OF THE TEXT

27 August 2020

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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.

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.1	Addition of cross-referencing to Section 5.1 for associated bacteraemia due to extended-beta-lactamase (ESBL) producing organisms
4.2	Minor editorial changes, deletion of dose and diluent volume not relevant to registered strengths.
4.4	Minor editorial changes; update to *Clostridium difficile* nomenclature.
4.8	Minor editorial changes.
5.1	Addition of information to Mechanism of Action; addition of mechanism of resistance; revision to antibacterial spectrum; updates to CLSI information according to current guidance; inclusion of MERINO trial data; minor editorial changes.
5.2	Minor editorial changes.