SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

TAZOCIN® 4 EF Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for infusion

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.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

TAZOCIN 4 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:

Adults

- Community acquired pneumonia due to *Haemophilus influenzae.*

- Intra-abdominal infections caused by piperacillin resistant beta-lactamase producing strains of *Escherichia coli* and *Bacteroides fragilis*.
- Skin and skin structure infections caused by piperacillin resistant beta-lactamase producing strains of *Staphylococcus aureus*.
- Gynaecologic infections including endometritis caused by piperacillin resistant beta-lactamase producing strains of *E. coli*.
- TAZOCIN 4 EF plus an aminoglycoside is indicated for bacterial infections in neutropenic patients.

Children

Children under the age of 12 years

TAZOCIN 4 EF plus an aminoglycoside is indicated for bacterial infections in neutropenic patients.

Children 2 - 12 years

In hospitalised children aged 2 to 12 years, TAZOCIN 4 EF 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 TAZOCIN 4 EF is indicated only for the conditions listed above, infections caused by piperacillin susceptible organisms are also amenable to TAZOCIN 4 EF treatment due to its piperacillin content. Therefore, the treatment of mixed infections caused by piperacillin susceptible organisms and beta-lactamase producing organisms susceptible to TAZOCIN 4 EF should not require the addition of another antibiotic.

TAZOCIN 4 EF is useful in the treatment of mixed infections and in presumptive therapy prior to the availability of the results of sensitivity tests.

4.2 Posology and method of administration

Posology

Adults and juveniles 12 years and older

The usual dosage for adults and juveniles with normal renal function is 4 g/0,5 g TAZOCIN 4 EF given every eight

hours. The dosage in immunocompromised and neutropenic patients with infection is 4 g/0,5 g TAZOCIN 4 EF every 6 hours in combination with an aminoglycoside.

Neutropenic patients

In treating neutropenic patients, full therapeutic doses of TAZOCIN 4 EF 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 TAZOCIN 4 EF 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.

Special populations

Elderly

TAZOCIN 4 EF 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 TAZOCIN 4 EF dosage
90 - 40	12 g/1,5 g/day in divided doses of 4 g/0,5 g every 8 hours or 3 g/0,375 g every 6 hours
20 - 40	8 g/1,0 g/day in divided doses of 2 g/0,25 g every 6 hours
< 20	6 g/0,75 g/day in divided doses of 2 g/0,25 g every 8 hours

For patients on haemodialysis, the maximum daily dose is 2 g/0,25 g every 8 hours. In addition, because haemodialysis removes 30 % - 40 % of piperacillin in 4 hours, one additional dose of 0,75 g TAZOCIN 4 EF should be administered following each dialysis period.

For patients with renal failure and hepatic insufficiency, measurement of serum levels of TAZOCIN 4 EF will provide additional guidance for adjusting dosage.

Paediatric population

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.

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 TAZOCIN 4 EF has 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 TAZOCIN 4 EF dosage
> 50	112,5 mg/kg (100 mg/12,5 mg) every 8 hours
≤ 50	78,75 mg/kg (70 mg/8,75 mg) every 8 hours

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

Method of administration

For intravenous infusion.

TAZOCIN 4 EF must be given by slow intravenous infusion (30 minutes).

4.3 Contraindications

TAZOCIN 4 EF is contraindicated:

- in patients with known hypersensitivity to piperacillin, tazobactam or any of the excipients of TAZOCIN 4 EF (listed in section 6.1).
- in patients with a history of allergic reactions to any of the penicillins and/or cephalosporins or beta-lactamase inhibitors.

4.4 Special warnings and precautions for use

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 TAZOCIN 4 EF, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, and other allergens.

If an allergic reaction occurs during therapy with TAZOCIN 4 EF, the antibiotic should be discontinued. Serious hypersensitivity reactions require immediate emergency measures, with adrenaline, corticosteroids and antihistamines. An open airway must be maintained.

Serious skin reactions, such as Stevens-Johnson syndrome and toxic epidermal necrolysis, have been reported in patients receiving TAZOCIN 4 EF (see section 4.8). If patients develop a skin rash they should be monitored closely and TAZOCIN 4 EF discontinued if lesions progress.

Pseudomembranous colitis has been reported with nearly all antibacterial medicines, including TAZOCIN 4 EF. Antibiotic-induced pseudomembranous colitis may be manifested by severe, persistent diarrhoea which may be life-threatening. The onset of pseudomembranous colitis symptoms 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 medicines.

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to medicine 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 medicine effective against *C. difficile.*

In case of severe, persistent diarrhoea, the possibility of antibiotic-induced life-threatening pseudomembranous colitis must be taken into consideration. Therefore, TAZOCIN 4 EF 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.

Bleeding manifestations have occurred in patients receiving beta-lactam antibiotics. These reactions have sometimes been associated with abnormalities of coagulation tests such as clotting time, platelet aggregation and prothrombin time/international normalised ratio (INR) and are more likely to occur in patients with renal impairment. If bleeding manifestations occur, TAZOCIN 4 EF should be discontinued and appropriate therapy instituted.

While TAZOCIN 4 EF 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 with TAZOCIN 4 EF. Therefore, periodic assessment of haematopoietic function should be performed.

Neurological complications in the form of convulsions may occur when high doses are administered, especially in patients with impaired renal function.

The use of TAZOCIN 4 EF 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.

In patients with renal insufficiency or haemodialysis patients, the intravenous dose should be adjusted to the degree of renal function impairment (see section 4.2).

For patients over 65 years of age, the dosage should be adjusted in the presence of renal insufficiency (see section 4.2).

The possibility of the emergence of resistant organisms, which might cause superinfections, should be kept in mind, particularly during prolonged treatment with TAZOCIN 4 EF. If this occurs, appropriate measures should be taken.

TAZOCIN 4 EF contains sodium

TAZOCIN 4 EF contains 2,79 mmol (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.

4.5 Interaction with other medicines and other forms of interaction

Interactions with other medicines

Probenecid

Concurrent administration of probenecid and TAZOCIN 4 EF produced a longer half-life and lower renal clearance for both piperacillin and tazobactam; however, peak plasma concentrations of either medicine are unaffected.

Vancomycin

No interaction is found between TAZOCIN 4 EF and vancomycin.

Aminoglycosides

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

Whenever TAZOCIN 4 EF is used concurrently with another antibiotic, especially an aminoglycoside, the medicines must not be mixed in intravenous solutions or administered concurrently due to physical incompatibility.

Oral anticoagulants

During simultaneous administration of high doses of heparin, oral anticoagulants and other medicines that may affect the blood coagulation system and/or the thrombocyte function, the coagulation parameters should be tested more frequently and monitored regularly.

Non-depolarising muscle relaxants

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-depolarising muscle relaxants could be prolonged in the presence of piperacillin.

Methotrexate

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

Laboratory tests

The administration of TAZOCIN 4 EF 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 TAZOCIN 4 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 4 EF should be interpreted cautiously and confirmed by other diagnostic methods.

4.6 Fertility, pregnancy and lactation

Safety in pregnancy and lactation has not been established.

Piperacillin and tazobactam cross the placenta.

Piperacillin is excreted in human milk. Women receiving TAZOCIN 4 EF should not breastfeed their infants.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Tabulated summary of adverse reactions

The adverse event terms in clinical studies were categorised utilising the incidence rate as follows:

Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1

000); very rare (< 1/10 000).

MedDRA system organ class	**Frequency**	**Undesirable effects**
Blood and lymphatic system disorders	Common	Thrombocytopenia, positive direct Coombs (positive antiglobulin) test, prolonged activated partial thromboplastin time
	Uncommon	Leukopenia, prolonged prothrombin time/INR
	Rare	Agranulocytosis, epistaxis
	Unknown	Neutropenia, purpura, prolonged bleeding time
Metabolism and nutrition disorders	Common	Hypoalbuminaemia, decreased total protein
	Uncommon	Hypokalaemia, hypoglycaemia
Nervous system disorders	Common	Headache, insomnia
Vascular disorders	Uncommon	Hypotension, phlebitis, thrombophlebitis, flushing
Gastrointestinal disorders	Very common	Diarrhoea
	Common	Abdominal pain, nausea, vomiting, constipation, dyspepsia
	Rare	Pseudomembranous colitis, stomatitis
Hepato-biliary disorders	Common	Increased aspartate aminotransferase, increased

		alanine aminotransferase, increased blood alkaline phosphatase
	Uncommon	Hyperbilirubinaemia
	Unknown	Jaundice, increased gamma-glutamyltransferase
Skin and subcutaneous tissue disorders	Common	Rash, pruritus
	Uncommon	Urticaria
	Unknown	Bullous dermatitis
Musculoskeletal, connective tissue and bone disorders	Uncommon	Arthralgia, myalgia
Renal and urinary disorders	Common	Increased blood creatinine, increased blood urea
	Unknown	Renal failure
General disorders and administration site conditions	Common	Pyrexia, injection site reaction
	Uncommon	Chills

Unknown frequencies cannot be estimated from available data

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

Post-marketing

The following post-marketing adverse events have been reported with TAZOCIN 4 EF:

MedDRA system organ class	**Undesirable effects**
Infections and infestations	Candidiasis
Blood and	Anaemia

lymphatic system disorders	Pancytopenia, haemolytic anaemia, eosinophilia, thrombocytosis
Immune system disorders	Anaphylactoid reaction, anaphylactic reaction, anaphylactoid shock, anaphylactic shock, hypersensitivity
Hepatobiliary disorders	Hepatitis
Skin and subcutaneous tissue disorders	Erythema multiforme, maculopapular rash, toxic epidermal necrolysis
	Stevens-Johnson syndrome
Renal and urinary disorders	Tubulointerstitial nephritis

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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Symptoms

See sections 4.8 and 4.4. 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

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 medicines (e.g. diazepam or barbiturates) may be indicated.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 20.1.1 Broad and medium spectrum antibiotics

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 beta-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.

The organisms that are inherently resistant to piperacillin-tazobactam are those organisms in which beta-lactam resistance is due to a change in a penicillin-binding protein (PBP). These include all methicillin-resistant staphylococci, penicillin-resistant streptococci and enterococci, and some penicillin-resistant *Haemophilus* and *Neisseria* where resistance is not due to a beta-lactamase. It needs to be noted, though, that not all beta-lactamases in *Enterobacteriaceae*, including *Escherichia coli*, are inhibited by tazobactam.

In vitro sensitivity does not necessarily imply clinical efficacy.

5.2 Pharmacokinetic properties

Distribution

Both piperacillin and tazobactam are approximately 30 % bound to plasma proteins. The protein binding of either piperacillin or tazobactam is unaffected by the presence of the other compound. Protein binding of the tazobactam metabolite is negligible.

Piperacillin/tazobactam is widely distributed in tissues and body fluids including intestinal mucosa, gallbladder, lung, bile, and bone. Mean tissue concentrations are generally 50 % to 100 % of those in plasma.

Distribution of piperacillin and tazobactam into cerebrospinal fluid is low in subjects with non-inflamed meninges, as with other penicillins.

Metabolism

Piperacillin is metabolised to a minor microbiologically active desethyl metabolite. Tazobactam is metabolised to a single metabolite that has been found to be microbiologically inactive.

Elimination

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

Piperacillin is excreted rapidly as unchanged medicine with 68 % of the administered dose appearing in the urine. Tazobactam and its metabolite are eliminated primarily by renal excretion with 80 % of the administered dose appearing as unchanged medicine and the remainder as the single metabolite. Piperacillin, tazobactam, and desethyl piperacillin are also secreted into the bile.

Following single or multiple doses of piperacillin/tazobactam to healthy subjects, the plasma half-life of piperacillin and tazobactam ranged from 0,7 to 1,2 hours and was unaffected by dose or duration of infusion. The elimination half-lives of both piperacillin and tazobactam are increased with decreasing renal clearance.

There are no significant changes in piperacillin pharmacokinetics due to tazobactam. However, piperacillin reduces the rate of elimination of tazobactam.

Special populations

The half-life of piperacillin and of tazobactam is increased in patients with hepatic cirrhosis compared to healthy subjects. Dosage adjustment of piperacillin is not warranted in patients with hepatic cirrhosis.

The half-life of piperacillin and tazobactam increases with decreasing creatinine clearance. The increase in half-life is two-fold and four-fold for piperacillin and tazobactam, respectively, at creatinine clearance below 20 mL/min compared to patients with normal renal function.

Haemodialysis removes 30 % to 50 % of piperacillin/tazobactam with an additional 5 % of the tazobactam dose removed as the tazobactam metabolite. Peritoneal dialysis removes approximately 6 % and 21 % of the piperacillin and tazobactam doses, respectively, with up to 18 % of the tazobactam dose removed as the tazobactam metabolite.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid monohydrate

Disodium edetate dihydrate (EDTA)

Sodium hydrogen carbonate

6.2 Incompatibilities

Pharmaceutical incompatibilities

TAZOCIN 4 EF 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 TAZOCIN 4 EF *in vitro* in

certain diluents at specific concentrations (see section 6.6).

Because of chemical instability, TAZOCIN 4 EF should not be used with solutions containing only sodium bicarbonate.

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

TAZOCIN 4 EF should not be added to blood products or albumin hydrolysates.

6.3 Shelf life

36 months

Solutions

Vials containing reconstituted solutions for intravenous 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 IV bags or syringes. Unused solution should be discarded.

6.4 Special precautions for storage

Dry powder

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

6.5 Nature and contents of container

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.

Each 70 mL vial contains sterile piperacillin sodium equivalent to 4 grams and sterile tazobactam sodium equivalent to 500 milligrams.

6.6 Special instructions for disposal and other handling

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 TAZOCIN 4 EF with aminoglycosides

Due to *in vitro* inactivation of the aminoglycoside by the beta-lactam antibiotics, TAZOCIN 4 EF and the aminoglycoside are recommended for separate administration. TAZOCIN 4 EF and the aminoglycoside should be reconstituted and diluted separately when concomitant therapy with aminoglycosides is indicated (see sections 4.5 and 6.2).

In circumstances where co-administration is preferred, the reformulated TAZOCIN 4 EF containing EDTA supplied in vials is compatible for simultaneous co-administration via Y-site infusion only with the following aminoglycosides under the following conditions:

Aminoglycoside	TAZOCIN 4 EF (grams) dose	TAZOCIN 4 EF diluent volume (mL)	Aminoglycoside concentration range‡ (mg/mL)	Acceptable diluents
Amikacin	2,25	50	1,75 - 7,5	0,9 %

	3,375 4,5	100 150		sodium chloride or 5 % dextrose
Gentamicin	2,25 3,375 4,5	100 150	0,7 - 3,32	0,9 % sodium chloride

‡The dose of aminoglycoside should be based on patient weight, status of infection (serious or life-threatening) and renal function (creatinine clearance).

Compatibility of TAZOCIN 4 EF with other aminoglycosides has not been established. Only the concentration and diluents for amikacin and gentamicin with the dosages of TAZOCIN 4 EF 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 TAZOCIN 4 EF.

7. HOLDER OF CERTIFICATE OF REGISTRATION

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