PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

TAZOBAX 4 g/ 0,5 g Powder for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial TAZOBAX contains 4 g piperacillin and 0,50 g tazobactam as sodium salts.

Sugar free

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Glass vials containing a white to off-white powder.

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

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

TAZOBAX 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 methicillin-sensitive *Staphylococcus aureus.*

4. Gynaecological infections including endometritis caused by piperacillin resistant beta-lactamase producing strains of *Escherichia coli.*

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

patients.

Children

Children under the age of 12 years

TAZOBAX plus an aminoglycoside is indicated for bacterial infections in neutropenic patients.

Children 2 - 12 years

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

TAZOBAX may be 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

The dose and frequency of TAZOBAX depends on the severity and localisation of the infection and expected pathogens.

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 8 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.

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 48 hours beyond resolution of clinical symptoms or the fever. The usual duration of treatment is 7 to 10 days.

Special Populations

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 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 piperacillin/tazobactam every 8 hours. In addition, because haemodialysis removes 30 to 40 % of piperacillin in 4 hours, one additional dose of 6 g/0,75 g TAZOBAX 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.

Paediatric population

Children under the age of 12 years:

TAZOBAX 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 TAZOBAX 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 TAZOBAX 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.

Use in children aged below 2 years

The safety and efficacy of TAZOBAX in children 0- 2 years of age has not been established.

No data from controlled clinical studies are available.

Method of administration

For intravenous infusion.

TAZOBAX must be given by slow intravenous infusion (30 minutes).

4.3 Contraindications

TAZOBAX is contraindicated:

- in patients with known hypersensitivity to piperacillin, tazobactam or any of the excipients of TAZOBAX (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

The selection of piperacillin / tazobactam to treat an individual patient should take into account the appropriateness of using a broad-spectrum semi-synthetic penicillin based on factors such as the severity of the infection and the prevalence of resistance to other suitable antibacterial agents.
Before initiating therapy with TAZOBAX, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, other beta-lactam
agents (e.g. cephalosporin, monobactam or carbapenem) and other allergens. 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 a sensitivity to multiple allergens.
There have been reports of patients with a history of penicillin hypersensitivity who have experienced severe hypersensitivity reactions when treated with a cephalosporin. Before initiating therapy with TAZOBAX, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, and other allergens.

If an allergic reaction occurs during therapy with TAZOBAX, the antibiotic should be discontinued. Serious hypersensitivity reactions require the discontinuation of the antibiotic, and may require administration of epinephrine and immediate emergency measures, with adrenalin, 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 TAZOBAX (see section 4.8). If patients develop a skin rash they should be monitored closely and TAZOBAX discontinued if lesions progress.

Haemophagocytic lymphohistiocytosis (haemophagocytic syndrome):

Haemophagocytic lymphohistiocytosis may occur following treatment with piperacillin/tazobactam longer than 10 days. Patients should be carefully monitored, and if any abnormalities such as pyrexia, rash, neurological symptoms, splenomegaly, swollen lymph nodes, cytopenia, increased LDH, hyperferritinaemia, hypertriglyceridaemia, hepatic impairment, or coagulation abnormalities are observed, administration of this drug should be discontinued, and appropriate measures should be taken.

Pseudomembranous colitis has been reported with piperacillin. 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 TAZOBAX.

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 agent against *C. difficile.*

In case of severe, persistent diarrhoea, the possibility of antibiotic-induced life-threatening pseudomembranous colitis must be taken into consideration. Therefore, TAZOBAX 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 some 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 and are more likely to occur in patients with renal failure. If bleeding manifestations occur, the antibiotic should be discontinued and appropriate therapy instituted.

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 with TAZOBAX. Therefore, periodic assessment of haematopoietic function should be performed.

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

Some patients with syphilis and other spirochaete infections may experience a Jarisch-Herxheimer reaction shortly after starting treatment. Symptoms include fever, chills, headache, and reactions at the site of the lesions. The reaction can be dangerous in cardiovascular syphilis or where there is a serious risk of increased local damage such as with optic atrophy.

The use of TAZOBAX may result in overgrowth of non-susceptible organisms, including fungi. The possibility of the emergence of resistant organisms, which might cause superinfections, should be kept in mind, particularly during prolonged treatment with TAZOBAX.

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).

TAZOBAX contains sodium.

TAZOBAX contains 783,99 mg/vial of sodium bicarbonate which may increase a patient’s overall sodium intake.

Hypokalaemia may occur in patients with low potassium reserves or those receiving concomitant medicinal products that may lower potassium levels. 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 (see section 4.8).

4.5 Interaction with other medicines and other forms of interaction

Interactions with other medicines

Probenecid

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.

Vancomycin

No interaction is found between piperacillin/tazobactam 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. Renal clearance, urinary recovery and the Area Under the Curve (AUC) are decreased when co-administrated with tobramycin.

Whenever piperacillin/tazobactam 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 which 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.

Oral contraceptives

Effectiveness of oral contraceptives may be decreased by concomitant antibiotic therapy, including TAZOBAX.

Laboratory tests

- Non-enzymatic methods of measuring urinary glucose may lead to false-positive results, as with other penicillins. Therefore, enzymatic urinary glucose measurement is required under TAZOBAX therapy.
- A number of chemical urine protein measurement methods may lead to false-positive results. Protein measurement with dip sticks is not affected.
- The direct antiglobulin test may be positive.
- Bio-Rad Laboratories Platelia Aspergillus EIA tests may lead to false-positive results for patients receiving TAZOBAX. Cross-reactions with non-Aspergillus polysaccharides and polyfuranoses with Bio-Rad Laboratories Platelia Aspergillus EIA test have been reported.

Positive test results for the assays listed above in patients receiving TAZOBAX should be confirmed by other diagnostic methods.

4.6 Fertility, pregnancy and lactation

The safety in pregnancy and lactation has not been established.

Pregnancy

Piperacillin and tazobactam cross the placenta.

Lactation

Piperacillin is excreted in human milk. Women receiving TAZOBAX 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.

TAZOBAX has no or a negligible influence on driving or operating machines.

Patients should be advised not to drive or handle machinery or tools if they feel

dizzy, or do not feel well.

4.8 Undesirable effects

a. Summary of the safety profile

Local reactions reported include phlebitis, thrombophlebitis, pain, inflammation and oedema.

The most frequently reported systemic side-effects include: Diarrhoea, rash, erythema, pruritus, vomiting, allergic reactions, nausea, urticaria and super-infection.

b. Tabulated list of adverse reactions

Other systemic side-effects reported as possibly, probably, or definitely drug related occurring in less than 0,1 % of the patients are listed within each body system in order of decreasing severity:

MedDRA System Organ Class	***Frequency***	***Undesirable Effects***
Infections and Infestations	*Less frequent*	Candida-superinfections, vaginitis
Blood and lymphatic system disorders	Frequent	Thrombocytopenia, anaemia, positive direct Coombs (positive antiglobulin) test, prolonged activated partial thromboplastin time
	Less frequent	Leukopenia, agranulocytosis, prolonged prothrombin time/NR, epistaxis
	Unknown	Pancytopenia, neutropenia, haemolytic anaemia, thrombocytosis, eosinophilia, purpura, prolonged bleeding time, Mesenteric embolism, pulmonary embolism.
Immune system disorders	Unknown	Anaphylactoid shock, anaphylactic shock, anaphylactoid reaction, anaphylactic reaction, hypersensitivity
Metabolism and nutrition disorders	Frequent	Hypoalbuminaemia, decreased total protein
	Less frequent	Hypokalaemia, hypoglycaemia, thirst, taste perversion
Psychiatric disorders	Frequent	Insomnia, agitation, confusion, anxiety, hallucination, depression.
	Unknown	Delirium
Nervous system disorders	Frequent	Headache, dizziness, tremor, convulsions, dry mouth, hypotension, syncope, tinnitus.
	Less frequent	Seizure
Eye disorders	Frequent	Photophobia

Cardiac disorders	Frequent	Tachycardia including ventricular and supraventricular bradycardia, arrhythmia, including atrial fibrillation, ventricular fibrillation, cardiac arrest, cardiac failure, circulatory failure, myocardial infarction.
Vascular disorders	Less frequent	Hypotension, superficial phlebitis, thrombophlebitis, flushing
Respiratory, thoracic and mediastinal disorders	Frequent	Rhinitis, dyspnoea, pharyngitis, bronchospasm, coughing.
	Less frequent	Eosinophilic pneumonia
Gastrointestinal disorders	Frequent	Diarrhoea, abdominal pain, flatulence, nausea, vomiting, constipation, melena, dyspepsia
	Less frequent	Stomatitis, haemorrhage, gastritis, hiccough
Hepato-biliary disorders	Less frequent	Hyperbilirubinaemia
	Unknown	Jaundice, hepatitis, increased gamma-glutamyltransferase
Skin and subcutaneous tissue disorders	Frequent	Rash, pruritus, eruption, increased sweating,
	Less frequent	Erythema multiforme, urticaria, eczema, rash maculo-papular, genital pruritus, toxic epidermal necrolysis, diaphoresis
	Unknown	Stevens-Johnson syndrome, dermatitis exfoliative, drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalised exanthematous pustulosis (AGEP), dermatitis bullous purpura
Musculoskeletal, connective tissue and bone disorders	Less frequent	Arthralgia, myalgia, muscle pain
Renal and urinary disorders	Frequent	Increased blood creatinine, increased blood urea, retention, dysuria, haematuria, incontinence.

	Unknown	Renal failure, tubulointerstitial nephritis
General disorders and administration site conditions	Frequent	Pyrexia, injection site reaction, chills, injection site pain when solution was not prepared according to recommendations (see section 4.2). fever, hot flushes, oedema, tiredness, pain, rigors, malaise
Investigations	Frequent	Aspartate aminotransferase increased, protein total decreased, blood albumin decreased, blood alkaline phosphatase increased

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

Beta-lactam antibiotic class effects

Beta-lactam antibiotics, including piperacillin tazobactam, may lead to manifestations of encephalopathy and convulsions (see section 4.4).

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 Med Safety APP (Medsafety X SAHPRA) or via the eReporting platform (who-umc.org) found on the SAHPRA website. Alternatively use the "**Adverse Drug Reactions (ADR)/Product Quality Problem Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/document/adverse-drug-reactions-and-quality-problem-reporting-form/.

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 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, sympathomimetic medicines 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 (eg. oral teicoplanin or oral vancomycin).

Preparations which inhibit peristalsis are contra-indicated.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 20.1.1 Broad and medium spectrum antibiotics.

Pharmacotherapeutic group: Antibacterials for systemic use, Combinations of penicillins including beta-lactamase inhibitors; ATC code: J01C R05

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 in vivo 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.

5.3 Preclinical safety data

Not Applicable

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium bicarbonate

Water for injection

6.2 Incompatibilities

TAZOBAX should not be mixed with other medicines in a syringe or infusion bottle since compatibility has not been established. It may only be mixed with those solutions mentioned under **Reconstitution directions.** TAZOBAX should be administered through an infusion set separately from any other medicines, unless compatibility is proven.

Whenever TAZOBAX is used concurrently with another antibiotic, especially an aminoglycoside, the medication should not be mixed in intravenous solutions or administered together, because of possible incompatibility. The mixing of beta-lactam antibiotics with an aminoglycoside in vitro can result in

substantial inactivation of the aminoglycoside.

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

Lactated Ringer's injection is not compatible as an initial diluent with piperacillin and tazobactam combination.

TAZOBAX should not be added to blood products or albumin hydrolysates.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Dry Powder: Vials containing sterile piperacillin/tazobactam dry powder may be stored at controlled room temperature (at or below 25 ºC).

Solutions: Vials containing reconstituted solutions for intravenous use are stable for 24 hours at room temperature (at or below 25 ºC) and 48 hours under refrigeration (2 to 8 ºC).

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

DO NOT FREEZE.

6.5 Nature and contents of container

Type I clear borosilicate 50 mL glass vials sealed by type 1 butyl rubber stoppers and aluminium plastic cap. The product is packed a carton with a package insert.

6.6 Special precautions for disposal and other handling

Reconstitution directions:

Dilutions for reconstitution:

Sterile water for injection

Bacteriostatic water for injection

Sodium chloride injection

Each vial of 4 g/0,5 g TAZOBAX 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 TAZOBAX with aminoglycosides

Due to in vitro inactivation of the aminoglycoside by the beta-lactam antibiotics, TAZOBAX and the aminoglycoside are recommended for separate administration. TAZOBAX 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 TAZOBAX 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	**TAZOBAX (grams) dose**	**TAZOBAX 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	2,2,5 3,3,75 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 TAZOBAX with other aminoglycosides has not been established. Only the concentration and diluents for amikacin and gentamicin with the dosages of TAZOBAX 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 TAZOBAX.

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

For single use only. Discard any unused solution.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Acino Pharma (Pty) Ltd

106, 16th Road

Midrand

1686

087 742 1860

8 REGISTRATION NUMBER(S)

37/20.1.1/0454

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

5 September 2003

10 DATE OF REVISION OF THE TEXT

22 May 2025