PROFESSIONAL INFORMATION

SCHEDULING STATUS S4

1 NAME OF THE MEDICINE

TIPERABEX 4 g/0,5 g; 4,5 g powder for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains piperacillin sodium equivalent to 4,0 g piperacillin base and tazobactam sodium equivalent to 0,5 g tazobactam base.

Excipients with known effect:

Each vial of TIPERABEX 4 g/0,5 g contains 9,39 mmol (216 mg) of sodium.

Sugar free.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for infusion.

Off-white to white cake or powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

TIPERABEX 4 g/0,5 g is indicated for the treatment of the following systemic and/or local bacterial infections in which susceptible organisms have been detected or are suspected:

Adults

1. Community acquired pneumonia due to *Haemophilus influenzae*.

2. Intra-abdominal infections caused by piperacillin resistant beta-lactamase producing strains of *Escherichia coli* and *Bacteroides fragilis*.
3. Skin and skin structure infections caused by piperacillin resistant beta-lactamase producing strains of *Staphylococcus aureus*.
4. Gynaecologic infections including endometritis caused by piperacillin resistant beta-lactamase producing strains of *E coli*.
5. TIPERABEX 4 g/0,5 g plus an aminoglycoside is indicated for bacterial infections in neutropenic patients.

Children

CHILDREN UNDER THE AGE OF 12 YEARS:

TIPERABEX 4 g/0,5 g plus an aminoglycoside is indicated for bacterial infections in neutropenic patients.

CHILDREN 2 - 12 YEARS:

In hospitalised children aged 2 to 12 years, TIPERABEX 4 g/0,5 g 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 TIPERABEX 4 g/0,5 g is indicated only for the conditions listed above, infections caused by piperacillin susceptible organisms are also amenable to TIPERABEX 4 g/0,5 g treatment due to its piperacillin content. Therefore, the treatment of mixed infections caused by piperacillin susceptible organisms and ß-lactamase producing organisms susceptible to TIPERABEX 4 g/0,5 g should not require the addition of another antibiotic.

TIPERABEX 4 g/0,5 g 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

The dose and frequency of TIPERABEX 4 g/0,5 g depends on the severity and localisation of the infection and expected pathogens.

Adults and adolescent patients 12 years and older

The usual dosage for adults and adolescents with normal renal function is 4 g/0,5 g TIPERABEX 4 g/0,5 g given every eight hours.

For immunocompromised patients and neutropenic patients with infection, the dosage is 4 g/0,5 g TIPERABEX 4 g/0,5 g every 6 hours in combination with an aminoglycoside.

Neutropenic patients

In treating neutropenic patients, full therapeutic doses of TIPERABEX 4 g/0,5 g 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 TIPERABEX 4 g/0,5 g 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

TIPERABEX 4 g/0,5 g may be used at the same dose levels as adults except in cases of renal impairment (see below).

Renal Impairment

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 (each patient must be monitored closely for signs of substance toxicity; medicine dose and interval should be adjusted accordingly):

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 every 8 hours. In addition, because haemodialysis removes 30 % - 40 % of piperacillin in 4 hours, one additional dose of 0,75 g TIPERABEX 4 g/0,5 g 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

Use in children aged below 2 years

The safety and efficacy of TIPERABEX 4 g/0,5 g in children 0-2 years of age has not been established.

No data from controlled clinical studies are available.

Children under the age of 12 years

TIPERABEX 4 g/0,5 g 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 to 12 years with renal insufficiency

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

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

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

The intravenous dose should be adjusted to the degree of actual renal impairment. 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

TIPERABEX 4 g/0,5 g is administered by slow intravenous infusion (30 minutes).

For instructions on reconstitution of the medicine before administration, see section 6.6.

4.3 Contraindications

TIPERABEX 4 g/0,5 g is contraindicated in:

- patients with known hypersensitivity to the piperacillin / tazobactam or to any of the excipients listed in section 6.1.
- patients with a history of allergic reactions to any of the penicillins and/or cephalosporins or ß-lactamase inhibitors.

4.4 Special warnings and precautions for use

The selection of TIPERABEX 4 g/0,5 g 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 medicines.

Before initiating therapy with TIPERABEX 4 g/0,5 g, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, other beta-lactam medicines (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 likely to occur in persons with a history of penicillin hypersensitivity or sensitivity to multiple allergens.

TIPERABEX 4 g/0,5 g may cause severe cutaneous adverse reactions, such as Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms, and acute generalised exanthematous pustulosis (see section 4.8). If patients develop a skin rash they should be monitored closely and TIPERABEX 4 g/0,5 g discontinued if lesions progress.

If an allergic reaction occurs during therapy with TIPERABEX 4 g/0,5 g, the antibiotic should be discontinued. Serious hypersensitivity reactions require immediate emergency measures, with adrenaline, corticosteroids and antihistamines. An open airway must be maintained.

Hemophagocytic lymphohistiocytosis (HLH)

Cases of haemophagocytic lympohistiocytosis (HLH) have been reported in patients treated with piperacillin / tazobactam, often following treatment longer than 10 days. HLH is a life-threatening syndrome of pathologic immune activation characterised by clinical signs and symptoms of an excessive systemic inflammation (e.g., fever, hepatosplenomegaly, hypertriglyceridaemia, hypofibrinogenaemia, high serum ferritin, cytopenias and haemophagocytosis). Patients who develop early manifestations of pathologic immune activation

should be evaluated immediately. If diagnosis of HLH is established piperacillin / tazobactam treatment should be discontinued.

Pseudomembranous colitis has been reported with nearly all antibacterial medicines, including piperacillin. Antibiotic-induced pseudomembranous colitis may be manifested by severe, persistent diarrhoea which may be life-threatening. The onset of pseudomembranous colitis may occur during or after antibacterial treatment. In these cases, TIPERABEX 4 g/0,5 g should be discontinued.

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, TIPERABEX 4 g/0,5 g 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.

While TIPERABEX 4 g/0,5 g 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.

Bleeding manifestations have occurred in some patients receiving ß-lactam antibiotics. These reactions have sometimes been associated with abnormalities of coagulation tests such as clotting time, platelet aggregation and prothrombin time and are more likely to oc-

cur in patients with renal failure. If bleeding manifestations occur, the antibiotic should be discontinued, and appropriate therapy instituted.

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

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).

The possibility of the emergence of resistant or non-susceptible organisms, including fungi, which might cause superinfections, should be kept in mind, particularly during prolonged treatment. If this occurs, appropriate measures should be taken.

This product contains 216 mg (9,39 mmol) of sodium per vial, which may increase a patient's overall sodium intake. This is equivalent to 10,8 % of the WHO recommended daily intake of 2 g sodium for an adult.

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.

Renal impairment

Due to its potential nephrotoxicity (see section 4.8), TIPERABEX 4 g/0,5 g should be used with care in patients with renal impairment or in haemodialysis patients. Intravenous dosages and administration intervals should be adjusted to the degree of renal function impairment (see section 4.2).

In a study where 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. This analysis concluded that piperacillin / tazobactam was a cause of delayed renal recovery in these patients.

Combined use of TIPERABEX 4 g/0,5 g and vancomycin may be associated with an increased incidence of acute kidney injury (see section 4.5).

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

4.5 Interaction with other medicines and other forms of interaction

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.

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 TIPERABEX 4 g/0,5 g 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.

The inactivation of tobramycin and gentamicin by piperacillin has been demonstrated in patients with severe renal impairment.

For information related to the administration of piperacillin / tazobactam with aminoglycosides please refer to sections 6.2 and 6.6.

Methotrexate

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

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

Probenecid

Concurrent administration of probenecid and TIPERABEX 4 g/0,5 g produces a longer half-life and lower renal clearance for both piperacillin and tazobactam; however, peak plasma concentrations of either substances are unaffected.

Vancomycin

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.

No pharmacokinetic interactions have been noted between piperacillin / tazobactam and vancomycin.

Effects on laboratory tests

Non-enzymatic methods of measuring urinary glucose may lead to false-positive results. Therefore, enzymatic urinary glucose measurement is required under TIPERABEX 4 g/0,5 g 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 Coombs test may be positive.

There have been reports of positive test results using the Bio-Rad Laboratories *Platelia Aspergillus* EIA test in patients receiving piperacillin / tazobactam injection who were subsequently found to be free of *Aspergillus* infection. Cross-reactions with non-*Aspergillus* polysaccharides and polyfuranoses with Bio-Rad Laboratories *Platelia Aspergillus* EIA test have been reported. Therefore, positive test results in patients receiving TIPERABEX 4 g/0,5 g should be interpreted cautiously and confirmed by other diagnostic methods.

Paediatric population

It is not known if the extent of interactions is similar in the paediatric age group to that in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety in pregnancy and lactation has not been established.

Piperacillin and tazobactam cross the placenta.

Breastfeeding

Piperacillin is excreted in human milk.

Women receiving TIPERABEX 4 g/0,5 g should not breastfeed their infants.

Fertility

A fertility study in rats showed no effect on fertility and mating after intraperitoneal administration of tazobactam or the combination piperacillin / tazobactam.

No data on male and female fertility is available.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

a. Summary of the safety profile

The most frequently reported adverse reaction is diarrhoea.

Among the most serious adverse reactions were pseudo-membranous colitis and toxic epidermal necrolysis. Pancytopenia, anaphylactic shock and Stevens-Johnson syndrome have also been reported.

b. Tabulated list of adverse reactions

MedDRA System organ class:	
Frequencies	**Adverse reactions**
Infections and Infestations	
Frequent:	Candida infections
Less frequent:	Pseudomembranous colitis
Blood and lymphatic system disorders	
Frequent:	Thrombocytopenia, anaemia
Less frequent:	Leukopenia, bleeding manifestations (including purpura, epistaxis), agranulocytosis

Frequency unknown: Pancytopenia, neutropenia, haemolytic anaemia, thrombocytosis, eosinophilia

Immune system disorders

Frequency unknown: Anaphylactic / anaphylactoid reaction (including anaphylactic / anaphylactoid shock), hypersensitivity reaction

Metabolism and nutrition disorders

Less frequent: Hypokalaemia

Psychiatric disorders

Frequent: Insomnia

Frequency unknown: Delirium

Nervous system disorders

Frequent: Headache

Less frequent: Seizure

Vascular disorders

Less frequent: Hypotension, phlebitis, thrombophlebitis, flushing

Respiratory, thoracic and mediastinal disorders

Less frequent: Epistaxis

Frequency unknown: Eosinophilic pneumonia

Gastrointestinal disorders

Frequent: Diarrhoea, nausea, vomiting, constipation, dyspepsia, abdominal pain

Less frequent: Pseudomembranous colitis, stomatitis

Hepatobiliary disorders

Frequency unknown: Hepatitis, jaundice

Skin and subcutaneous tissue disorders

Frequent:	Rash, pruritus
Less frequent:	Urticaria, erythema multiforme, rash maculo-papular
Frequency unknown:	Bullous dermatitis, dermatitis exfoliative, Stevens-Johnson Syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalised exanthematous pustulosis (AGEP), purpura

Musculoskeletal and connective tissue disorders

Less frequent:	Arthralgia, myalgia

Renal and urinary disorders

Frequency unknown:	Renal failure, tubulointerstitial nephritis

General disorders and administrative site conditions

Frequent:	Pyrexia, injection site reaction
Less frequent:	Chills

Investigations

Frequent:	Alanine 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
Less frequent:	Blood glucose decreased, blood bilirubin increased, prothrombin time prolonged
Frequency unknown:	Bleeding time prolonged, gamma glutamyl transferase 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) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

The majority of events experienced during overdosage including nausea, vomiting and diarrhoea have also been reported with the usual recommended dosages. Patients may experience neuromuscular excitability or convulsions if higher than recommended doses are given intravenously (particularly in the presence of renal failure).

Treatment should be supportive and symptomatic according to the patient's clinical presentation. No specific antidote is known. Excessive serum concentrations of either piperacillin or tazobactam may be reduced by haemodialysis.

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

In case of motor excitability or convulsions, anticonvulsive 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

Pharmacotherapeutic group: Antibacterials for systemic use; Combinations of penicillins including beta-lactamase inhibitors.

ATC code: J01CR05

Mechanism of action

Piperacillin, a broad spectrum, semi-synthetic penicillin active against many Gram-positive and Gram-negative aerobic and anaerobic bacteria, exerts bactericidal activity by inhibition of both septum and cell wall synthesis.

Tazobactam, a triazolylmethyl penicillanic acid sulfone (a beta-lactam structurally related to penicillins), is an inhibitor of many ß-lactamases (which commonly cause resistance to penicillins and cephalosporins but do not inhibit AmpC enzymes or metallo beta-lactamases), including the plasmid and chromosomally mediated enzymes. The presence of tazobactam in the TIPERABEX 4 g/0,5 g formulation enhances and extends the antibiotic spectrum of piperacillin to include many beta-lactamase-producing bacteria that have acquired resistance to piperacillin alone.

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.

Pharmacodynamic effects

The time above the minimum inhibitory concentration (T > MIC) is considered to be the major pharmacodynamic determinant of efficacy for piperacillin.

TIPERABEX 4 g/0,5 g is highly active against piperacillin-sensitive micro-organisms as well as ß-lactamase producing, piperacillin-resistant micro-organisms.

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

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

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

Mechanism of resistance

The two main mechanisms of resistance to TIPERABEX 4 g/0,5 g are:

- Inactivation of the piperacillin component by those beta-lactamases that are not inhibited by tazobactam: beta-lactamases in the Molecular class B, C and D. In addition, tazobactam does not provide protection against extended-spectrum beta-lactamases (ESBLs) in the Molecular class A and D enzyme groups.
- Alteration of penicillin-binding proteins (PBPs), which results in the reduction of the affinity of piperacillin for the molecular target in bacteria.

Additionally, alterations in bacterial membrane permeability, as well as expression of multi-drug efflux pumps, may cause or contribute to bacterial resistance to TIPERABEX 4 g/0,5 g, especially in gram-negative bacteria.

5.2 Pharmacokinetic properties

Absorption

The peak piperacillin and tazobactam concentrations after 4 g/0,5 g administered over 30 minutes by intravenous infusion are 298 µg/ml and 34 µg/ml respectively.

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 into cerebrospinal fluid is low in subjects with non-inflamed meninges, as with other penicillins.

Biotransformation

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 substance, with 68 % of the administered dose appearing in the urine. Tazobactam and its metabolite are eliminated primarily by re-

nal excretion, with 80% of the administered dose appearing as unchanged substance 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. Piperacillin appears to slightly reduce the clearance of tazobactam.

Special populations

Hepatic impairment

The half-life of piperacillin and of tazobactam increases by approximately 25 % and 18 %, respectively, in patients with hepatic cirrhosis compared to healthy subjects. Dosage adjustment of piperacillin is not warranted in patients with hepatic cirrhosis.

Renal impairment

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.

Paediatric population

In a population PK analysis, estimated clearance for 9-month-old to 12-year-old patients was comparable to adults, with population mean (SE) value of 5,64 (0,34) ml/min/kg. The piperacillin clearance estimate is 80 % of this value for paediatric patients 2-9 months of age. The population mean (SE) for piperacillin volume of distribution is 0,243 (0,011) l/kg and is independent of age.

Elderly patients

The mean half-life for piperacillin and tazobactam were 32 % and 55 % longer, respectively, in the elderly compared with younger subjects. This difference may be due to age-related changes in creatinine clearance.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None.

6.2 Incompatibilities

This medicine must not be mixed with other medicines except those mentioned in section 6.6.

Whenever TIPERABEX 4 g/0,5 g is used concurrently with another antibiotic (e.g., aminoglycosides), the substances must be administered separately. The mixing of beta-lactam antibiotics with an aminoglycoside *in vitro* can result in substantial inactivation of the aminoglycoside.

TIPERABEX 4 g/0,5 g should not be mixed with other substances in a syringe or infusion bottle since compatibility has not been established.

Due to chemical instability, TIPERABEX 4 g/0,5 g should not be used in solutions containing only sodium bicarbonate.

TIPERABEX 4 g/0,5 g should not be added to blood products or albumin hydrolysates.

TIPERABEX 4 g/0,5 g is not compatible with Ringer's Lactate.

6.3 Shelf life

Storage of the product before reconstitution

24 months

Storage of the reconstituted and diluted solution

From a microbiological point of view, TIPERABEX 4 g/0,5 g should be used immediately.

If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user. Chemical and physical in-use stability has been demonstrated for 24 hours when stored at or below 25 °C or for 48 hours when stored in the refrigerator at 2 to 8 °C.

6.4 Special precautions for storage

This medicine does not require any special storage conditions.

For storage instructions after reconstitution, see section 6.3.

6.5 Nature and contents of container

TIPERABEX 4 g/0,5 g is packaged in a 50 ml clear, borosilicate, type I glass vial, with a type I, halogenated bromobutyl rubber stopper and an aluminium plastic combined cap.

Available in pack sizes of 1, 10 or 12 vials, in a carton box with a package leaflet. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The reconstitution and dilution are to be made under aseptic conditions. The solution is to be inspected visually for particulate matter and discolouration prior to administration. The solution should only be used if the solution is clear and free from particles.

Reconstituted solutions and storage conditions

Reconstituted diluents	Compatible intravenous solutions	Storage Conditions
0,9 % sodium chloride for injection	0,9 % sodium chloride for injection	0h, < 25 °C
Sterile water for injection	Sterile water for injection	24h, < 25 °C
Dextrose 5 %	Dextrose 5 %	48h, 2 - 8 °C
Bacteriostatic water for injection	Dextran 6 % in saline	-
Bacteriostatic saline	-	-

Each vial of TIPERABEX 4 g/0,5 g 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.

Co-administration of TIPERABEX 4 g/0,5 g with aminoglycosides

Due to in vitro inactivation of the aminoglycoside by the beta-lactam antibiotics, TIPERABEX 4 g/0,5 g and the aminoglycoside are recommended for separate administration. TIPERABEX 4 g/0,5 g and the aminoglycoside should be reconstituted and diluted separately when concomitant therapy with aminoglycosides is indicated (see section 4.5).

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

No special requirements.

7 HOLDER OF THE CERTIFICATE OF REGISTRATION

Abex Pharmaceutica (Pty) Ltd

Suite C, Rubenstein Ridge

617 Rubenstein Drive

Moreleta Park, 0181

South Africa

Tel.: +27 (0)12 997 6974

8 REGISTRATION NUMBER(S)

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9 DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

18 February 2025

10 DATE OF REVISION OF THE TEXT

Not applicable.