Professional Information

SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

PIPERACILLIN/TAZOBACTAM 2 g/0,25 g FRESENIUS Powder for solution for infusion

PIPERACILLIN/TAZOBACTAM 4 g/0,5 g FRESENIUS Powder for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

PIPERACILLIN/TAZOBACTAM 2 g/0,25 g FRESENIUS: Each vial contains piperacillin sodium equivalent to 2 g piperacillin and tazobactam sodium equivalent to 0,25 g tazobactam.

Contains 4,9 mmol (or 112 mg) sodium per vial.

PIPERACILLIN/TAZOBACTAM 4 g/0,5 g FRESENIUS: Each vial contains piperacillin sodium equivalent to 4 g piperacillin and tazobactam sodium equivalent to 0,5 g tazobactam.

Contains 9,7 mmol (or 224 mg) sodium per vial.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for infusion.

PIPERACILLIN/TAZOBACTAM 2 g/0,25 g FRESENIUS: White or almost white hygroscopic powder.

PIPERACILLIN/TAZOBACTAM 4 g/0,5 g FRESENIUS: White or almost white hygroscopic powder.

Osmolality: 655 mOsm/kg

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PIPERACILLIN/TAZOBACTAM FRESENIUS 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-Iactamase producing strains of *Escherichia coli* and *Bacteroides fragilis*.
- Skin and skin structure infections caused by piperacillin resistant beta-Iactamase producing strains of methicillin-sensitive *Staphylococcus aureus*.
- Gynaecologic infections including endometritis caused by piperacillin resistant beta-Iactamase producing strains of *E coli*.
- PIPERACILLIN/TAZOBACTAM FRESENIUS plus an aminoglycoside is indicated for bacterial infections in neutropenic patients.

Children:

Children under the age of 12 years:

PIPERACILLIN/TAZOBACTAM FRESENIUS plus an aminoglycoside is indicated for bacterial infections in neutropenic patients.

Children 2-12 years:

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

PIPERACILLIN/TAZOBACTAM FRESENIUS has not been evaluated in this indication for paediatric patients below the age of 2 years.

While PIPERACILLIN/TAZOBACTAM FRESENIUS is indicated only for the conditions listed above, infections caused by piperacillin susceptible organisms are also amenable to PIPERACILLIN/TAZOBACTAM FRESENIUS 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 FRESENIUS should not require the addition of another antibiotic.

PIPERACILLIN/TAZOBACTAM FRESENIUS 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 PIPERACILLIN/TAZOBACTAM FRESENIUS given every eight hours. The dosage in immunocompromised and neutropenic patients with infection is 4 g/0,5 g PIPERACILLIN/TAZOBACTAM FRESENIUS every 6 hours in combination with an aminoglycoside.

Children under the age of 12 years:

PIPERACILLIN/TAZOBACTAM FRESENIUS is only recommended for the treatment of children with neutropenia.

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

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

Elderly:

PIPERACILLIN/TAZOBACTAM FRESENIUS 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 FRESENIUS dosage**
90 – 40	12 g/1,5 g/day in divided doses of 4 g/0,5 g eight hourly or 3 g/0,375 g six hourly
20 – 40	8 g/1,0 g/day in divided doses of 2 g/0,25 g six hourly
< 20	6 g/0,75 g/day in divided doses of 2 g/0,25 g eight hourly

For patients on haemodialysis, the maximum daily dose is 2 g/0,25 g every 8 hours of PIPERACILLIN/TAZOBACTAM FRESENIUS. In addition, because haemodialysis removes 30 % – 40 % of piperacillin in 4 hours, one additional dose of 6 g/0,75 g PIPERACILLIN/TAZOBACTAM FRESENIUS should be administered following each dialysis period. For patients with renal failure and hepatic insufficiency, measurement of serum levels

of PIPERACILLIN/TAZOBACTAM FRESENIUS will provide additional guidance for adjusting dosage.

Neutropenic patients:

In treating neutropenic patients, full therapeutic doses of PIPERACILLIN/TAZOBACTAM FRESENIUS 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 FRESENIUS should be for a minimum of five days and continued for forty-eight hours beyond resolution of clinical symptoms or the fever. The usual duration of treatment is 7 – 10 days.

Hospitalised children with intra-abdominal infection:

For children aged 2 to 12 years, weighing up to 40 kg, and with normal renal function, the recommended dosage is 112,5 mg/kg (100 mg piperacillin/12,5 mg tazobactam) every 8 hours.

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

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

Children aged 2 – 12 years with renal insufficiency:

The pharmacokinetics of PIPERACILLIN/TAZOBACTAM FRESENIUS 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 FRESENIUS dosage**
> 50	112,5 mg/kg (100 mg/12,5 mg) eight hourly
≤ 50	78,75 mg/kg (70 mg/8,75 mg) eight hourly

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

Method of administration

PIPERACILLIN/TAZOBACTAM FRESENIUS must be given by slow intravenous infusion (30 minutes).

Prior to administration, each vial of PIPERACILLIN/TAZOBACTAM FRESENIUS must be reconstituted and may be further diluted to the desired volume. For information on instructions for reconstitution and dilution, see section 6.6.

4.3 Contraindications

The use of PIPERACILLIN/TAZOBACTAM FRESENIUS is contraindicated in patients with a history of allergic reactions to piperacillin, tazobactam or any of the penicillins and/or

cephalosporins or beta-lactamase inhibitors, or any of the other ingredients of PIPERACILLIN/TAZOBACTAM FRESENIUS (listed in section 6.1).

4.4 Special warnings and precautions for use

Hypersensitivity reactions

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

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

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

Serious skin reactions

Serious skin reactions, such as erythema multiforme, bullous dermatitis, exanthema, toxic epidermal necrolysis, Stevens-Johnson syndrome, drug reaction with eosinophilia and systemic symptoms, and acute generalised exanthematous pustulosis have been reported (see section 4.8). Patients should be monitored closely if they develop a skin rash and PIPERACILLIN/TAZOBACTAM FRESENIUS should be discontinued if lesions progress.

***Clostridium difficile* associated diarrhoea, including colitis**

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.

Therefore, it is important to consider this diagnosis in patients who present with diarrhoea subsequent to the administration of PIPERACILLIN/TAZOBACTAM FRESENIUS.

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, PIPERACILLIN/TAZOBACTAM FRESENIUS 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.

Haematology

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

Bleeding manifestations have occurred in some patients receiving beta-Iactam 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.

Haemophagocytic lymphohistiocytosis (HLH)

Cases of HLH have been reported in patients treated with PIPERACILLIN/TAZOBACTAM FRESENIUS, 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 FRESENIUS treatment should be discontinued.

Resistance

The use of PIPERACILLIN/TAZOBACTAM FRESENIUS 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. If this occurs, appropriate measures should be taken.

Neurological effects

Patients may experience neuromuscular excitability or convulsions if higher than recommended doses are given intravenously, especially in patients with impaired renal function.

Hypokalaemia

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.

Liver function

Modest elevation of indices of liver function may be observed.

Renal impairment

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

Periodic assessment of renal and hepatic systems during prolonged therapy is advisable.

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

Age

In patients over 65 years dosage should be adjusted in the presence of renal insufficiency.

Sodium content

PIPERACILLIN/TAZOBACTAM 2 g / 0,25 g FRESENIUS:

This medicine contains 112 mg sodium per vial, equivalent to 5,6% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

PIPERACILLIN/TAZOBACTAM 4 g / 0,5 g FRESENIUS:

This medicine contains 224 mg sodium per vial, equivalent to 11,2% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicines and other forms of interaction

Probenecid

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

Oral anticoagulants

During simultaneous administration of high doses of heparin, warfarin, oral anticoagulants, NSAIDs 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.

Other antibiotics

PIPERACILLIN/TAZOBACTAM FRESENIUS may also interact with bacteriostatic antibacterial medicines such as chloramphenicol and tetracyclines.

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.

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

Whenever PIPERACILLIN/TAZOBACTAM FRESENIUS is used concurrently with another antibiotic, especially an aminoglycoside such as tobramycin, the medicines must not be mixed in intravenous solutions or administered concurrently due to physical incompatibility (see sections 6.2 and 6.6).

Oral contraceptives

Effectiveness of oral contraceptives may be decreased by piperacillin/tazobactam, including PIPERACILLIN/TAZOBACTAM FRESENIUS.

Laboratory tests

The administration of PIPERACILLIN/TAZOBACTAM FRESENIUS 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.
The direct antiglobulin (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 FRESENIUS injection who were subsequently found to be free of Aspergillus infection. Cross-reactions with non-Aspergillus polysaccharides and polyfuranoses with Bio-Rad laboratories Platelia Aspergillus EIA test have been reported. Therefore, positive test results in patients receiving PIPERACILLIN/TAZOBACTAM FRESENIUS 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.

Adequate studies on the use of PIPERACILLIN/TAZOBACTAM FRESENIUS during pregnancy and the period of breastfeeding are not yet available.

Pregnancy

Piperacillin and tazobactam cross the placenta.

Studies in animals have shown developmental toxicity, but no evidence of teratogenicity, at doses that are maternally toxic.

Breastfeeding

Safety has not been established. Piperacillin is excreted in low concentrations in human milk; tazobactam concentrations in human milk have not been studied. Woman receiving PIPERACILLIN/TAZOBACTAM FRESENIUS should not breastfeed their infants.

Fertility

PIPERACILLIN/TAZOBACTAM FRESENIUS did not affect fertility in rats.

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

Infections and infestations

Frequent : Candida infection

Less frequent: *Clostridium difficile* associated diarrhoea, pseudomembranous colitis

Blood and the lymphatic system disorders

Frequent: Thrombocytopenia, anaemia

Less frequent: Leukopenia, agranulocytosis

Frequency unknown: Neutropenia, pancytopenia, haemolytic anaemia, thrombocytosis, eosinophilia

Immune system disorders

Frequency unknown: Anaphylactoid reaction, anaphylactoid shock, anaphylactic shock, anaphylactic reaction, hypersensitivity

Metabolism and nutrition disorders

Frequent: Hypoalbuminaemia

Less frequent: Hypokalaemia, hypoglycaemia

Psychiatric disorders

Frequent: Insomnia

Frequency unknown: Delirium

Nervous system disorders

Frequent: Headache

Less frequent: Seizure

Cardiac disorders

Less frequent: Chest pain

Vascular disorders

Less frequent: Hypotension, phlebitis, thrombophlebitis, flushing

Respiratory, thoracic and mediastinal disorders:

Less frequent: Epistaxis

Frequency unknown: Eosinophilic pneumonia

Gastrointestinal disorders

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

Less frequent: Stomatitis

Hepato-biliary disorders

Less frequent: Hyperbilirubinaemia

Frequency unknown: Hepatitis, jaundice

Skin and subcutaneous tissue disorders

Frequent: Rash, pruritis

Less frequent: Urticaria, erythema multiforme, toxic epidermal necrolysis, maculopapular rash

Frequency unknown: Stevens-Johnson syndrome, exfoliative dermatitis, drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalised exanthematous pustulosis (AGEP), bullous dermatitis, purpura

Musculoskeletal, connective tissue and bone disorders

Less frequent: Arthralgia, myalgia

Renal and urinary disorders

Less frequent: Interstitial nephritis

Frequency unknown: Tubulointerstitial nephritis, renal failure

General disorders and administrative site conditions

Frequent: Fever, injection site reaction

Less frequent: Rigors, chills, fever and rash in cystic fibrosis patients

Investigations

Frequent: Increased alanine aminotransferase, increased aspartate aminotransferase, decreased total blood protein, decreased blood albumin, Positive direct Coombs (positive antiglobulin) test, increased blood creatinine, increased blood alkaline phosphatase, increased blood urea, prolonged activated partial thromboplastin time

Less frequent: Decreased blood glucose, increased blood bilirubin, prolonged prothrombin time

Frequency unknown: Prolonged bleeding time, increased gamma-glutamyltransferase

Unknown frequencies cannot be established from the available data.

Beta-lactam antibiotics class effects

Beta-lactam antibiotics, including piperacillin tazobactam, may led 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 requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

Healthcare providers are asked to report any suspected adverse drug reactions to the Holder of the Certificate of Registration at the following email address: safety.fksa@fresenius-kabi.com and to the relevant medicine's regulatory authority in the country where the product is marketed.

4.9 Overdose

Symptoms of overdose

See sections 4.4 and 4.8. The majority of events experienced during overdosage including nausea, vomiting and diarrhoea. Patients may experience neuromuscular excitability or convulsions if higher than recommended doses are given intravenously (particularly in the presence of renal failure).

Treatment of overdose

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, hypersensitivity (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: Combinations of penicillins, incl. 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, 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.

Microbiology:

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

Resistant organisms

Inherently resistant organisms:

Aerobic Gram-positive micro-organisms:	*Corynebacterium jeikeium*
Aerobic Gram-negative micro-organisms:	*Legionella* species *Stenotrophomonas maltophilia*[+,$]
Other micro-organisms:	*Chlamydophilia pneumonia* *Mycoplasma pneumonia*

Species for which acquired resistance may be a problem:

Aerobic Gram-positive micro-organisms:	**Aerobic Gram-negative micro-organisms:**
Enterococcus faecium[$,+] *Streptococcus pneumonia* *Streptococcus viridans group*	*Acinetobacter baumannii* [$] *Burkholderia cepacia* *Citrobacter freundii* *Enterobacter* species *Escherichia coli* *Klebsiella pneumonia* *Morganella morganii* *Proteus vulgaris* *Providencia ssp.* *Pseudomonas aeruginosa* *Serratia* species

[$] Species showing natural intermediate susceptibility.

[+] Species for which high-resistance rates (more than 50 %) have been observed in one or more areas/countries/regions.

The prevalence of acquired resistance may vary geographically and with time for selected species. Local information of resistance is desirable, particularly when treating severe

infections. This information provides guidance on micro-organisms susceptible to piperacillin/tazobactam.

In vitro sensitivity does not necessarily imply clinical efficacy.

5.2 Pharmacokinetic properties

Absorption

Peak concentrations of piperacillin and tazobactam are attained after completion of an intravenous infusion or injection.

Distribution

Both piperacillin and tazobactam are 20 - 30 % bound to plasma proteins.

Piperacillin/tazobactam is widely distributed in tissues and body fluids including intestinal mucosa, gallbladder, lung, bile and bone. Distribution into cerebrospinal fluid is low in subjects with non-inflamed meninges.

Biotransformation

Piperacillin is metabolised in the liver to a 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 renal excretion, with 80 % of the administered dose appearing as unchanged substance and the remainder as the single metabolite.

Piperacillin, tazobactam and the desethyl piperacillin metabolite are also secreted into the bile.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glacial acetic acid (for pH-adjustment)

Sodium bicarbonate (for pH-adjustment)

Water for injection

All the excipients are removed during lyophilisation and therefore do not appear in the finished product.

6.2 Incompatibilities

PIPERACILLIN/TAZOBACTAM FRESENIUS 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.

Because of chemical instability, PIPERACILLIN/TAZOBACTAM FRESENIUS should not be used with solutions containing only sodium bicarbonate.

PIPERACILLIN/TAZOBACTAM FRESENIUS should not be added to blood products or albumin hydrolysates.

6.3 Shelf life

Unopened vial: 36 months.

Reconstituted and diluted solutions:

Chemical and physical in-use stability has been demonstrated for 2 hours at 25 °C and 24 hours at 2 – 8 °C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8 °C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

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

6.4 Special precautions for storage

Store at or below 25 °C.

Keep vial in original container until required for use.

Discard any unused portion.

For storage conditions after reconstitution and dilution, see section 6.3.

6.5 Nature and contents of container

PIPERACILLIN/TAZOBACTAM 2 g/0,25 g FRESENIUS: Packed in a clear 50 mL Type II glass vial with a grey 32 mm chlorobutyl rubber stopper sealed with an aluminium cap with a blue polypropylene flip-off lid or a clear 15 mL Type II glass vial with a grey 20 mm chlorobutyl rubber stopper sealed with an aluminium cap with a blue polypropylene flip-off lid.

PIPERACILLIN/TAZOBACTAM 4 g/0,5 g FRESENIUS: A clear 50 mL Type II glass vial with a grey 32 mm chlorobutyl rubber stopper sealed with an aluminium cap with a red polypropylene flip-off lid.

Pack sizes: 1, 5, 10 or 12 vials in an outer carton.

Not all packs or pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Reconstitution directions

Diluents for reconstitution:

Sterile water for injection

0,9 % *m/v* Sodium chloride

Each vial of 2 g/0,25 g PIPERACILLIN/TAZOBACTAM FRESENIUS should be reconstituted with at least 10 mL of one of the above diluents. Shake until dissolved.

Each vial of 4 g/0,5 g PIPERACILLIN/TAZOBACTAM FRESENIUS should be reconstituted with at least 20 mL of one of the above diluents. Shake until dissolved.

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 % *m/v* in water

0,9 % *m/v* Sodium chloride

Co-administration of PIPERACILLIN/TAZOBACTAM FRESENIUS with aminoglycosides:

Due to *in vitro* inactivation of the aminoglycoside by the beta-lactam antibiotics, PIPERACILLIN/TAZOBACTAM FRESENIUS and the aminoglycoside should be reconstituted and diluted separately when concomitant therapy with aminoglycosides is indicated (see section 4.2).

7. HOLDER OF CERTIFICATE OF REGISTRATION

Fresenius Kabi South Africa (Pty) Ltd

Stand 7, Growthpoint Business Park

162 Tonetti Street

Halfway House extension 7

Midrand

Gauteng

1685

SOUTH AFRICA

Telephone number: (011) 545 0000

8. REGISTRATION NUMBER

PIPERACILLIN/TAZOBACTAM 2 g/0,25 g FRESENIUS: 45/20.1.1/1172

PIPERACILLIN/TAZOBACTAM 4 g/0,5 g FRESENIUS: 45/20.1.1/1173

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25 November 2016

10. DATE OF REVISION OF THE TEXT

27 May 2025