SUMMARY OF PRODUCT CHARACTERISTICS

Printed for Certificate of Pharmaceutical Product

1 NAME OF THE MEDICINAL PRODUCT

Piperacillin/Tazobactam 4g/0.5g Powder for Solution for Injection or Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 4 g piperacillin (as sodium salt) and 0. 5 g tazobactam (as sodium salt)
One vial of powder for solution for injection or infusion contains 9.44 mmol (217 mg) of sodium.

For a full list of excipients see section 6.1

3 PHARMACEUTICAL FORM

Powder for solution for injection or infusion.
White to off white powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Piperacillin/tazobactam is indicated for the treatment of moderate to severe systemic and/or local bacterial infections in which betalactamase producing bacteria are suspected or have been detected, such as:

Adults/Adolescents and the Elderly
Nosocomial pneumonia
Complicated urinary tract infections (including pyelonephritis)
Intra-abdominal infections
Skin and soft tissue infections
Bacterial infections in neutropenic adults

Children (2-12 years)
Bacterial infections in neutropenic children

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Piperacillin/tazobactam may be given by slow intravenous injection (over at least 3-5 minutes) or by slow intravenous infusion (over 20-30 minutes).

For reconstitution instructions, see section 6.6.

The treatment of mixed infections caused by piperacillin susceptible organisms and betalactamase producing organisms susceptible to piperacillin / tazobactam generally do not require the addition of another antibiotic.
In patients with nosocomial pneumonia and infections in neutropenic patients piperacillin/tazobactam can be used with an aminoglycoside. If the use of an aminoglycoside is needed with piperacillin/tazobactam, both piperacillin/tazobactam and the aminoglycoside must be used in completely therapeutic doses.

Neutropenic patients with signs of infection (e.g. fever) should receive immediate empirical antibiotic therapy before laboratory results are available.

SUMMARY OF PRODUCT CHARACTERISTICS

Printed for Certificate of Pharmaceutical Product

Adults and Children Over 12 Years, Each with Normal Renal Function

The usual dosage for adults and children over 12 years is piperacillin/tazobactam 4000/500 mg given every 8 hours.
The total daily dose of piperacillin/tazobactam depends on the severity and localisation of the infection and can vary from piperacillin/tazobactam 2000/250 mg to piperacillin/tazobactam 4000/500 mg administered every 6 or 8 hours.

In neutropenia the recommended dose is piperacillin/tazobactam 4000/500 mg given every 6 hours in combination with an aminoglycoside.

Elderly with Normal Renal Function

Piperacillin/tazobactam may be used at the same dose levels as adults except in cases of renal impairment (see below):

Renal Insufficiency in Adults, the Elderly and Children (over 40 kg) Receiving the Adult Dose
In patients with renal insufficiency, the intravenous dose should be adjusted to the degree of actual renal impairment. The suggested daily doses are as follows:

Creatinine clearance (ml/min)	Recommended Piperacillin/Tazobactam dosage	
	Total	Divided doses
20 - 80	12/1.5g /day	4000/500 mg q 8H
< 20	8/1g /day	4000/500 mg q 12H

For patients on haemodialysis, the maximum daily dose is piperacillin/tazobactam 8/1 g. In addition, because haemodialysis removes 30%-50% of piperacillin in 4 hours, one additional dose of piperacillin/tazobactam 2000/250 mg 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.

Children Aged 2-12 Years with Normal Renal Function

Piperacillin/tazobactam is only recommended for the treatment of children with neutropenia.

Neutropenia
For children weighing less than 40 kg the dose should be adjusted to 90 mg/kg (piperacillin/tazobactam 80/10 mg) administered every 6 hours, in combination with an aminoglycoside, not exceeding Piperacillin/Tazobactam 4000/500 mg every 6 hours.

Renal Insufficiency in Children Aged 2-12 Years (or bodyweight less than 40 kg)

In children with renal insufficiency the intravenous dosage should be adjusted to the degree of actual renal impairment as follows:

SUMMARY OF PRODUCT CHARACTERISTICS

Printed for Certificate of Pharmaceutical Product

Creatinine clearance (ml/min)	Recommended piperacillin/tazobactam dosage	Frequency	Maximum daily dosage
>40	No adjustment necessary		
20-39	90 mg (piperacillin/tazobactam 80/10 mg) /kg	q 8H	12/1.5g /day
< 20	90mg (piperacillin/tazobactam 80/10 mg) /kg	q 12H	8/1g /day

For children weighing < 50 kg on haemodialysis the recommended dose is 45 mg (piperacillin/tazobactam 40/5 mg) /kg every 8 hours.

The above dosage modifications are only an approximation. Each patient must be monitored closely for signs of drug toxicity. Drug dose and interval should be adjusted accordingly.

Children under 2 years

Piperacillin/tazobactam is not recommended for use in children below 2 years old due to insufficient data on safety.

Hepatic Impairment
No dose adjustment is necessary.

Duration of Therapy
The duration of therapy should be guided by the severity of the infection and the patient's clinical and bacteriological progress.
In acute infections, treatment with Piperacillin/Tazobactam should be continued for 48 hours beyond the resolution of clinical symptoms or the fever.

4.3 Contraindications

Hypersensitivity to piperacillin or any other beta-lactam antibiotics and to tazobactam or any other beta-lactamase inhibitor.

4.4 Special warnings and precautions for use

Warnings
Serious and occasionally fatal hypersensitivity (anaphylactic / anaphylactoid [including shock]) reactions have been reported in patients receiving therapy with penicillins including piperacillin/tazobactam. These reactions are more likely to occur in persons with a history of sensitivity to multiple allergens.
There have been reports of patients with a history of penicillin hypersensitivity who have experienced severe reactions when treated with a cephalosporin.
If an allergic reaction occurs during therapy with piperacillin/tazobactam, the antibiotic should be discontinued. Serious hypersensitivity reactions may require adrenaline and other emergency measures.
Before initiating therapy with piperacillin/tazobactam, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, and other allergens.
In case of severe, persistent diarrhoea, the possibility of antibiotic-induced, life threatening pseudomembranous colitis must be taken into consideration. The onset of pseudomembranous colitis symptoms may occur during or after antibacterial treatment. Therefore, piperacillin/tazobactam must be discontinued immediately in such cases, and suitable therapy should be initiated.

SUMMARY OF PRODUCT CHARACTERISTICS

Printed for Certificate of Pharmaceutical Product

Precautions
Leukopenia and neutropenia may occur, especially during prolonged therapy. Therefore, periodic assessment of a full blood count should be performed.
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 occur in patients with renal failure. If bleeding manifestations occur, the antibiotic should be discontinued and appropriate therapy instituted.

The possibility of the emergence of resistant organisms, which might cause superinfections, should be kept in mind, particularly during prolonged treatment. Microbiological follow-up may be required to detect any important superinfection. If this occurs, appropriate measures should be taken.
Patients may experience neuromuscular excitability or convulsions if higher than recommended doses are given intravenously.

This medicinal product contains 9.44 mmol (217 mg) of sodium per vial of powder for solution for injection or infusion. To be taken into account by patients on a controlled sodium diet.

Hypokalaemia may occur in patients with low potassium reserves or who are receiving concomitant medications that may lower potassium levels; periodic electrolyte determinations should be performed in such patients. Modest elevation of indices of liver function may be observed.

Piperacillin therapy has been associated with an increased incidence of fever and rash in cystic fibrosis patients (see also 4.8).

Until further experience is available, piperacillin / tazobactam should not be used in children who do not have neutropenia.

4.5 Interaction with other medicinal products and other forms of interaction
Interaction with 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 drug are unaffected.

Interaction with antibiotics:
No clinically relevant adverse pharmacokinetic interaction with tobramycin or vancomycin has been observed in healthy adults with a normal renal function. The clearance of tobramycin and gentamicin was enhanced in patients with severe renal dysfunction using piperacillin/tazobactam. In these patients mixing of piperacillin/tazobactam formulation with tobramycin and gentamicin was excluded.

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

Interaction with anticoagulants:
During simultaneous administration of heparin, oral anticoagulants and other drugs which may affect the blood coagulation system including thrombocyte function, appropriate coagulation tests should be performed more frequently and monitored regularly.

SUMMARY OF PRODUCT CHARACTERISTICS

Printed for Certificate of Pharmaceutical Product

Interaction with vecuronium:
Piperacillin when used concomitantly with vecuronium has been implicated in the prolongation of the neuromuscular blockade 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. This should be taken into account when piperacillin/tazobactam is used peri-operatively.

Interaction with methotrexate:
Piperacillin may reduce the excretion of methotrexate. Serum levels of methotrexate should be monitored in patients on methotrexate therapy.

Interaction with laboratory test results:
The administration of piperacillin/tazobactam may result in a false-positive reaction for glucose in the urine using a copper-reduction method. It is recommended that glucose tests based on enzymatic glucose oxidase reaction be used.

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 Piperacillin-Tazobactam should be interpreted cautiously and confirmed by other diagnostic methods.

4.6 Pregnancy and lactation

There are no adequate and well-controlled studies with piperacillin/tazobactam in combination or with piperacillin or tazobactam alone in pregnant women. Studies in animals have shown reproductive toxicity (see 5.3). Piperacillin and tazobactam cross the placenta. Piperacillin/tazobactam should only be used during pregnancy if clearly indicated.

Piperacillin is excreted in low concentrations in breast milk. Tazobactam concentrations in human milk have not been studied. The effect on the suckling infant is unknown. Women who are breast feeding should be treated only if clearly indicated. Diarrhoea and fungal infections of the mucous membranes as well as sensitisation could occur in the breast-fed infant.

4.7 Effects on ability to drive and use machines

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

However, side effects may occur (see also 4.8), which may influence the ability to drive and use machines.

4.8 Undesirable effects

Undesirable effects are listed by frequency as follows: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1 000 to ≤ 1/100); rare (≥1/10 000 to ≤1/1 000); very rare (≤1/10 000); not known (cannot be estimated from the available data).

The most commonly reported adverse reactions are diarrhoea, nausea, vomiting, and rash, each having a frequency of ≥ 1% but ≤ 10%.

SUMMARY OF PRODUCT CHARACTERISTICS

Printed for Certificate of Pharmaceutical Product

Body System	Frequency	Adverse Reaction
Infections and infestations	Uncommon	Candidal superinfection
Blood and lymphatic system disorders	Uncommon	Leucopenia, neutropenia, thrombocytopenia
	Rare	Anaemia, bleeding manifestations (including purpura, epistaxis, bleeding time prolonged), eosinophilia, haemolytic anaemia
	Very rare	Agranulocytosis, Coombs' direct test positive, pancytopenia, prolonged partial thromboplastin time, prothrombin time prolonged, thrombocytosis
Immune system disorders	Uncommon	Hypersensitivity reaction
	Rare	Anaphylactic/anaphylactoid reaction (including shock)
Metabolism and nutritional disorders	Very rare	Hypoalbuminaemia, hypoglycaemia, hypoproteinaemia, hypokalaemia.
Nervous system disorders	Uncommon	Headache, insomnia
	Rare	Muscular weakness, hallucination, convulsion
Vascular disorders	Uncommon	Hypotension, phlebitis, thrombophlebitis
	Rare	Flushing
Gastrointestinal disorders	Common	Diarrhoea, nausea, vomiting
	Uncommon	Constipation, dyspepsia, jaundice, stomatitis
	Rare	Abdominal pain, pseudomembranous colitis, dry mouth
Hepatobiliary disorders	Uncommon	Alanine aminotransferase increased, aspartate aminotransferase increased
	Rare	Bilirubin increased, blood alkaline phosphatase increased, gamma- glutamyltransferase increased, hepatitis
Skin and subcutaneous tissue disorders	Common	Rash including maculopapular rash
	Uncommon	Pruritus, urticaria, erythema
	Rare	Bullous dermatitis, erythema multiforme, increased sweating, eczema, exanthema
	Very rare	Stevens-Johnson Syndrome, toxic epidermal necrolysis
Musculoskeletal, connective tissue and bone disorders	Rare	Arthralgia, myalgia
Renal and urinary disorders	Uncommon	Blood creatinine increased
	Rare	Interstitial nephritis, renal failure
	Very rare	Blood urea nitrogen increased
General disorders and administration site conditions	Uncommon	Fever, injection site reaction
	Rare	Rigors, tiredness, oedema

The administration of high doses of beta-lactams, particularly in patients with renal insufficiency, can lead to encephalopathies (consciousness fluctuation, myoclonus and convulsions).

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

SUMMARY OF PRODUCT CHARACTERISTICS

Printed for Certificate of Pharmaceutical Product

4.9 Overdose

Symptoms

There have been post-marketing reports of overdose with piperacillin/tazobactam. The majority of those events experienced including nausea, vomiting, and diarrhoea have also been reported with the usual recommended dosages. Patients may experience neuromuscular excitability or convulsions if higher than recommended doses are given intravenously (particularly in the presence of renal failure).

Treatment of Intoxication:

In the event of an overdose, piperacillin/tazobactam treatment should be discontinued.

No specific antidote is known.

Treatment should be supportive and symptomatic according to the patient's clinical presentation. In the event of an emergency, all required intensive medical measures are indicated as in the case of piperacillin.

Excessive serum concentrations of either piperacillin or tazobactam will be reduced by haemodialysis (for more details see section 5.2).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Combinations of penicillins, including beta-lactamase inhibitors.

ATC Classification: 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 sulphone, is a potent inhibitor of many beta-lactamases, in particular the plasmid mediated enzymes which commonly cause resistance to penicillins and cephalosporins including third-generation cephalosporins. The presence of tazobactam in the piperacillin/tazobactam formulation enhances and extends the antibiotic spectrum of piperacillin to include many beta-lactamase producing bacteria normally resistant to it and other beta-lactam antibiotics. Thus, piperacillin/tazobactam combines the properties of a broad spectrum antibiotic and a beta-lactamase inhibitor.

Mechanism of resistance:

The presence of tazobactam expands the spectrum of activity of piperacillin to include microorganisms that would otherwise, due to the formation of beta-lactamase, be resistant to piperacillin and other beta-lactam antibiotics. *In vitro* investigation has demonstrated that the type I beta-lactamase inducing ability of tazobactam is insignificant with regard to Gram-negative bacteria. *In vitro* studies have demonstrated a synergetic effect of piperacillin/tazobactam and aminoglycosides against *Pseudomonas aeruginosa* and other bacteria, including beta-lactamase producing strains.

Breakpoints:

The minimum inhibitory concentration (MIC) breakpoints separating susceptible, intermediately susceptible and resistant organisms have been defined as follows:

Classification from the Clinical and Laboratory Standards Institute (CLSI) 2006:

SUMMARY OF PRODUCT CHARACTERISTICS

Printed for Certificate of Pharmaceutical Product

Pathogen	Equivalent MIC breakpoints (mg/L)		
	Susceptible	**Intermediate**	**Resistant**
Staphylococcus spp.	≤ 8/4	-	≥ 16/4
Enterobacteriaceae	≤ 16/4	32/4 to 64/4	≥ 128/4
Pseudomonas aeruginosa	≤ 64/4	-	≥ 128/4
Acinetobacter spp.	≤ 16/4	32/4 to 64/4	≥ 128/4
Haemophilus influenzae & *H .parainfluenzae*	≤ 1/4	-	≥ 2/4

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Commonly susceptible species

Gram positive aerobes
Brevibacterium spp
Enterococcus faecalis
Listeria monocytogenes
Staphylococcus spp. methicillin-sensitive
Streptococcus pneumoniae
Streptococcus pyogenes
Group B *streptococci*
Streptococcus spp*

Gram negative aerobes
Branhamella catarrhalis
Citrobacter koseri
*Haemophilus influenzae**
Haemophilus spp.
Proteus mirabilis
Salmonella spp.
Shigella spp.

Gram positive anaerobes
Clostridium spp.
Eubacterium spp.

SUMMARY OF PRODUCT CHARACTERISTICS

Printed for Certificate of Pharmaceutical Product

Peptococcus spp.
Peptostreptococcus spp.

Gram negative anaerobes
*Bacteroides fragilis**
Bacteroides fragilis group
Fusobacterium spp.
Porphyromonas spp.
Prevotella spp*

Species for which resistance may be a problem

Gram positive aerobes
Staphylococcus aureus, methicillin-sensitive
Staphylococcus epidermis, methicillin-sensitive
Enterococcus avium ($)
Enterococcus faecium (+ $)
Propionibacterium acnes ($)
Viridans streptococci

Gram negative aerobes
Actinobacter spp (+ $)
Burkholderia cepacia
Citrobacter freundii
Enterobacter spp.
*Escherichia coli **
Klebsiella spp.
Proteus, indole positive
*Pseudomonas aeruginosa**
*Pseudomonas spp. **
Pseudomonas stutzeri $
Serratia spp.

Gram negative anaerobes
Bacteroides spp. *

Inherently resistant organisms

Gram positive aerobes
Corynebacterium jeikeium
Staphylococcus spp. methicillin resistant

SUMMARY OF PRODUCT CHARACTERISTICS

Printed for Certificate of Pharmaceutical Product

Gram negative aerobes
Legionella spp
Stenotrophomonas maltophilia +$

* Clinical effectiveness against this has been demonstrated in the registered indications.
($) Species showing natural intermediate susceptibility
(+) Species for which high resistance rates (more than 50%) have been observed in one or more areas/countries/regions within the EU.

5.2 Pharmacokinetic properties

Distribution
Peak piperacillin and tazobactam plasma concentrations are attained immediately after completion of an intravenous infusion or injection. Piperacillin plasma levels produced when given with tazobactam are similar to those attained when equivalent doses of piperacillin are administered alone.

There is a greater proportional (approximately 28%) increase in plasma levels of piperacillin and tazobactam with increasing dose over the dosage range of piperacillin/tazobactam 2000/250 mg to piperacillin/tazobactam 4000/500 mg.

Both piperacillin and tazobactam are 20 to 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 tissue and body fluids including intestinal mucosa, gall bladder, lung, bile and bone.

Biotransformation
Piperacillin is metabolised to a minor microbiologically active desethyl metabolite. Tazobactam is metabolised to a single metabolite, which has been found to be micro-biologically inactive.

Elimination
Piperacillin and tazobactam are eliminated by the kidney via glomerular filtration and tubular secretion. Piperacillin is excreted rapidly as unchanged drug 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 drug 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 reduce the rate of elimination of tazobactam.

Impaired Renal Function

Piperacillin and tazobactam are haemodialysable: 31% (piperacillin) and 39% (tazobactam) of administered doses are filtrated. During peritoneal dialysis, 5% of administered piperacillin and 12% of

administered tazobactam are found in the dialysis liquid. Patients treated by chronic ambulatory peritoneal dialysis should receive the same dose as non dialysed patients with severe renal insufficiency.

Impaired Liver Function
Plasma concentrations of piperacillin and tazobactam are prolonged in hepatically impaired patients. The half-life of piperacillin and of tazobactam increases by approximately 25% and 18%, respectively, in patients with hepatic cirrhosis compared to healthy subjects. However, dosage adjustments in patients with hepatic impairment are not necessary.

Paediatric patients
The pharmacokinetics of piperacillin/tazobactam has been studied in paediatric patients with intra-abdominal infections and other kinds of infections. In every age group, renal fraction of elimination of piperacillin and tazobactam was approximately 70% and 80%, respectively, like in adults.

Mean pharmacokinetic parameters of piperacillin/tazobactam of paediatric patients of different age groups.

	Piperacillin		Tazobactam	
Age group	Half-life	Clearance (ml/min/kg)	Half-life	Clearance (ml/min/kg)
2-5 years	0.7	5.5	0.8	5.5
6-12 years	0.7	5.9	0.9	6.2

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity and genotoxicity. Carcinogenicity studies have not been conducted with piperacillin/tazobactam. A fertility study of piperacillin/ tazobactam reported a decrease in litter size and an increase in fetuses with ossification delays and variations of ribs following i.p. administration to rats. Fertility of the F1 generation and embryonic development of the F2 generation was not impaired. A teratogenicity study in rats, did not show teratogenic effects after i.v. administration. In the rat, effects on the embryonic development were observed at maternal toxic doses. Peri/postnatal development was impaired (reduced fetal weights, increase in pup mortality, increase in stillbirths) concurrently with maternal toxicity after i.p. administration in the rat.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

Whenever piperacillin/tazobactam is used concurrently with another antibiotic (e.g. aminoglycosides), the drugs must be administered separately. The mixing of piperacillin/tazobactam with an aminoglycoside *in vitro* can result in substantial inactivation of the aminoglycoside.

SUMMARY OF PRODUCT CHARACTERISTICS

Printed for Certificate of Pharmaceutical Product

Piperacillin/tazobactam should not be mixed with other drugs in a syringe or infusion bottle since compatibility has not been established.

Piperacillin/tazobactam should be administered through an infusion set separately from any other drugs unless compatibility is proven.

Due to chemical instability, piperacillin/tazobactam should not be used in solutions that contain sodium bicarbonate.

Lactated Ringer's solution is not compatible with piperacillin/tazobactam.

Piperacillin/tazobactam should not be added to blood products or albumin hydrolysates.

6.3 Shelf life

Unopened: 2 years

After reconstitution:

After reconstitution, chemical and in-use stability has been demonstrated for 24 hours when stored in a refrigerator at 2-8°C.

From a microbiological point of view, once opened, 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 2-8°C, unless reconstitution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions.
Keep vial(s) in the outer carton.
For storage conditions of the reconstituted/diluted product see section 6.3.

6.5 Nature and contents of container

Type I glass vials with a bromo butyl rubber stopper and flip off seal.
Pack sizes: 1 or 12 vials per carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Reconstitution Directions

Intravenous Injection
Each vial of Piperacillin/Tazobactam 4g/0.5g Powder for Solution for Injection or Infusion should be reconstituted with 20 ml of one of the following diluents:

- Sterile Water for Injection
- 9 mg/ml (0.9%) Sodium Chloride for Injection

Swirl until dissolved. Intravenous injection should be given over at least 3-5 minutes.

SUMMARY OF PRODUCT CHARACTERISTICS

Printed for Certificate of Pharmaceutical Product

Intravenous Infusion
Each vial of Piperacillin/Tazobactam 4g/0.5g should be reconstituted with 20 ml of one of the above diluents.

The reconstituted solution should be further diluted to at least 50 ml with one of the reconstitution diluents, or with Dextrose 5% in Water.

For single use only. Discard any unused solution.

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

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

7 MARKETING AUTHORISATION HOLDER
HOSPIRA UK LIMITED
QUEENSWAY
ROYAL LEAMINGTON SPA
WARWICKSHIRE
CV31 3RW
UNITED KINGDOM

8 MARKETING AUTHORISATION NUMBER(S)
PL 04515/0374

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
27/06/2008

10 DATE OF REVISION OF THE TEXT
10/02/2011