

SUMMARY OF PRODUCT CHARACTERISTICS

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1. NAME OF THE MEDICINAL PRODUCT

Piperacillin Tazobactam Sandoz 2 g / 0.25 g powder for solution for infusion.
Piperacillin Tazobactam Sandoz 4 g / 0.5 g powder for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 2 g piperacillin (as piperacillin sodium) and 0.25 g tazobactam (as tazobactam sodium).

Excipients with known effect

Each vial contains 4.72 mmol (109 mg) sodium.

Each vial or bottle contains 4 g piperacillin (as piperacillin sodium) and 0.5 g tazobactam (as tazobactam sodium).

Excipients with known effect:

Each vial or bottle contains 9.44 mmol (217 mg) sodium. For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for infusion.

A white to off-white powder.

4. CLINICAL PARTICULARS

Therapeutic indications

Piperacillin Tazobactam Sandoz is indicated for the treatment of the following infections in adults and children over 2 years of age (see sections 4.2 and 5.1):

Adults and adolescents

- Severe pneumonia including hospital-acquired and ventilator-associated pneumonia
- Complicated urinary tract infections (including pyelonephritis)
- Complicated intra-abdominal infections
- Complicated skin and soft tissue infections (including diabetic foot infections)

Treatment of patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above.

Piperacillin Tazobactam Sandoz may be used in the management of neutropenic patients with fever suspected to be due to a bacterial infection.

Children 2 to 12 years of age

- Complicated intra-abdominal infections

Piperacillin Tazobactam Sandoz may be used in the management of neutropenic children with fever suspected to be due to a bacterial infection.

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

Posology and method of administration

Posology

The dose and frequency of Piperacillin Tazobactam Sandoz depends on the severity and localisation of the infection and expected pathogens.

Adult and adolescent patients

Infections

The usual dose is 4 g piperacillin / 0.5 g tazobactam given every 8 hours.

For nosocomial pneumonia and bacterial infections in neutropenic patients, the recommended dose is 4 g piperacillin / 0.5 g tazobactam administered every 6 hours. This regimen may also be applicable to treat patients with other indicated infections when particularly severe.

The following table summarises the treatment frequency and the recommended dose for adult and adolescent patients by indication or condition:

Treatment frequency	Piperacillin Tazobactam Sandoz 4 g / 0.5 g
Every 6 hours	Severe pneumonia
	Neutropenic adults with fever suspected to be due to a bacterial infection.
Every 8 hours	Complicated urinary tract infections (including pyelonephritis)
	Complicated intra-abdominal infections
	Skin and soft tissue infections (including diabetic foot infections)

Patients with renal impairment

The intravenous dose should be adjusted to the degree of actual renal impairment as follows (each patient must be monitored closely for signs of substance toxicity; medicinal product dose and interval should be adjusted accordingly):

Creatinine clearance (ml/min)	Piperacillin Tazobactam Sandoz (recommended dose)
>40	No dose adjustment necessary
20-40	Maximum dose suggested: 4 g / 0.5 g every 8 hours
<20	Maximum dose suggested: 4 g / 0.5 g every 12 hours

For patients on haemodialysis, one additional dose of piperacillin / tazobactam 2 g / 0.25 g should be administered following each dialysis period, because haemodialysis removes 30%-50% of piperacillin in 4 hours.

Patients with hepatic impairment

No dose adjustment is necessary (see section 5.2).

Elderly patients

No dose adjustment is required for the elderly with normal renal function or creatinine clearance values above 40 ml/min.

Paediatric population (2-12 years of age)

Infections

The following table summarises the treatment frequency and the dose per body weight for paediatric patients 2-12 years of age by indication or condition:

Dose per weight and treatment frequency	Indication / condition
80 mg Piperacillin / 10 mg Tazobactam per kg body weight / every 6 hours	Neutropenic children with fever suspected to be due to bacterial infections*
100 mg Piperacillin / 12.5 mg Tazobactam per kg body weight / every 8 hours	Complicated intra-abdominal infections*

* Not to exceed the maximum 4 g / 0.5 g per dose over 30 minutes.

Patients with renal impairment

The intravenous dose should be adjusted to the degree of actual renal impairment as follows (each patient must be monitored closely for signs of substance toxicity; medicinal product dose and interval should be adjusted accordingly):

Creatinine clearance (ml/min)	Piperacillin Tazobactam Sandoz (recommended dose)
>50	No dose adjustment needed.
≤50	70 mg piperacillin / 8.75 mg tazobactam / kg every 8 hours.

For children on haemodialysis, one additional dose of 40 mg piperacillin / 5 mg tazobactam / kg should be administered following each dialysis period.

Use in children aged below 2 years

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

No data from controlled clinical studies are available.

Treatment duration

The usual duration of treatment for most indications is in the range of 5-14 days. However, the duration of treatment should be guided by the severity of the infection, the pathogen(s) and the patient's clinical and bacteriological progress.

Method of administration

[nationally completed name 2 g / 0.25 g] is administered by intravenous infusion (over 30 minutes).
[nationally completed name 4 g / 0.5 g] is administered by intravenous infusion (over 30 minutes).

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

Contraindications

Hypersensitivity to the active substances, any other penicillin-antibacterial agent or to any of the excipients listed in section 6.1.

History of acute severe allergic reaction to any other beta-lactam active substances (e.g. cephalosporin, monobactam or carbapenem).

Special warnings and precautions for use

The selection of piperacillin / tazobactam to treat an individual patient should take into account the appropriateness of using a broad-spectrum semi-synthetic penicillin based on factors such as the severity of the infection and the prevalence of resistance to other suitable antibacterial agents.

Before initiating therapy with Piperacillin Tazobactam Sandoz, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, other beta-lactam agents (e.g.

cephalosporin, monobactam or carbapenem) and other allergens. Serious and occasionally fatal hypersensitivity (anaphylactic/anaphylactoid [including shock]) reactions have been reported in patients receiving therapy with penicillins, including piperacillin / tazobactam. These reactions are more likely to occur in persons with a history of sensitivity to multiple allergens. Serious hypersensitivity reactions require the discontinuation of the antibiotic, and may require administration of epinephrine and other emergency measures.

Piperacillin/tazobactam 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 piperacillin/tazobactam discontinued if lesions progress.

Antibiotic-induced pseudomembranous colitis may be manifested by severe, persistent diarrhoea which may be life-threatening. The onset of pseudomembranous colitis symptoms may occur during or after antibacterial treatment. In these cases Piperacillin Tazobactam Sandoz should be discontinued.

Therapy with Piperacillin Tazobactam Sandoz may result in the emergence of resistant organisms, which might cause super-infections.

Bleeding manifestations have occurred in some patients receiving beta-lactam antibiotics. These reactions sometimes have 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.

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

As with treatment with other penicillins, neurological complications in the form of convulsions may occur when high doses are administered, especially in patients with impaired renal function.

[nationally completed name 2 g / 0.25 g]

This medicinal product contains 109 mg of sodium per vial, equivalent to 6% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

[nationally completed name 4 g / 0.5 g]

This medicinal product contains 217 mg of sodium per each vial or bottle, equivalent to 11% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Hypokalaemia may occur in patients with low potassium reserves or those receiving concomitant medicinal products that may lower potassium levels; periodic electrolyte determinations may be advisable in such patients.

Renal impairment

Due to its potential nephrotoxicity (see section 4.8), piperacillin/tazobactam should be used with care in patients with renal impairment or in haemodialysis patients. Intravenous doses and administration intervals should be adjusted to the degree of renal function impairment (see section 4.2).

In a secondary analysis using data from a large multicentre, randomized-controlled trial when 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 compared with the other antibiotics. This secondary analysis concluded that piperacillin/tazobactam was a cause of delayed renal recovery in these patients.

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

Interaction with other medicinal products and other forms of interaction Non-

depolarising muscle relaxants

Piperacillin when used concomitantly with vecuronium has been implicated in the prolongation of the neuromuscular blockade of vecuronium. Due to their similar mechanisms 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.

Oral anticoagulants

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

Methotrexate

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

Probenecid

As with other penicillins, concurrent administration of probenecid and piperacillin / tazobactam produces a longer half-life and lower renal clearance for both piperacillin and tazobactam; however, peak plasma concentrations of either substances are unaffected.

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.

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.

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, as with other penicillins. Therefore, enzymatic urinary glucose measurement is required under Piperacillin Tazobactam Sandoz 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.

Bio-Rad Laboratories Platelia Aspergillus EIA tests may lead to false-positive results for patients receiving Piperacillin Tazobactam Sandoz. Cross-reactions with non-Aspergillus polysaccharides and polyfuranoses with Bio-Rad Laboratories Platelia Aspergillus EIA test have been reported.

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

Fertility, pregnancy and lactation

Pregnancy

There are no or a limited amount of data from the use of Piperacillin Tazobactam Sandoz in pregnant women.

Studies in animals have shown developmental toxicity, but no evidence of teratogenicity, at doses that are maternally toxic (see section 5.3).

Piperacillin and tazobactam cross the placenta. Piperacillin / tazobactam should only be used during pregnancy if clearly indicated, i.e. only if the expected benefit outweighs the possible risks to the pregnant woman and foetus.

Breast-feeding

Piperacillin is excreted in low concentrations in human milk; tazobactam concentrations in human milk have not been studied. Women who are breast-feeding should be treated only if the expected benefit outweighs the possible risks to the woman and child.

Fertility

A fertility study in rats showed no effect on fertility and mating after intraperitoneal administration of tazobactam or the combination piperacillin / tazobactam (see section 5.3).

Effects on ability to drive and use machines

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

Undesirable effects

The most commonly reported adverse reaction is diarrhoea (occurring in 1 patient out of 10). Among the most serious adverse reactions pseudo-membranous colitis and toxic epidermal necrolysis occur in 1 to 10 patients in 10,000. The frequencies for pancytopenia, anaphylactic shock and Stevens-Johnson syndrome cannot be estimated from the currently available data.

In the following table, adverse reactions are listed by system organ class and MedDRA-preferred term. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System Organ Class	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	Not known (cannot be estimated from available data)
Infections and infestations		Candidal superinfection*		Pseudo-membranous colitis	
Blood and lymphatic system disorders		thrombocytopenia, anaemia*	leukopenia	agranulocytosis	pancytopenia*, neutropenia, haemolytic anaemia*, eosinophilia*, thrombocytosis*,
Immune system disorders					anaphylactoid shock*, anaphylactic shock*, anaphylactoid reaction*, anaphylactic reaction*, hypersensitivity*
Metabolism and nutrition disorders			hypokalaemia,		
Psychiatric disorders		insomnia			
Nervous system disorders		headache			
Vascular			hypotension,		

System Organ Class	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	Not known (cannot be estimated from available data)
disorders			phlebitis, thrombophlebitis, flushing		

Respiratory, thoracic and mediastinal disorders				epistaxis	eosinophilic pneumonia
Gastrointestinal disorders	diarrhoea	abdominal pain, vomiting, nausea, constipation, dyspepsia		stomatitis	
Hepatobiliary disorders					hepatitis*, jaundice,
Skin and subcutaneous tissue disorders		rash, pruritus	erythema multiforme*, urticaria, rash maculopapular*	toxic epidermal necrolysis*	Stevens-Johnson syndrome*, dermatitis exfoliative, drug reaction with eosinophilia and systemic symptoms (DRESS)*, acute generalised exanthematous pustulosis (AGEP)*, dermatitis bullous, purpura
Musculoskeletal and connective tissue disorders			arthralgia, myalgia		
Renal and urinary disorders					renal failure, tubulointerstitial nephritis*
General disorders and administration site conditions		pyrexia, injection site reaction	chills		
Investigations		alanine aminotransferase, increased, aspartate aminotransferase increased, protein	blood glucose decreased, blood bilirubin increased, prothrombin time prolonged		bleeding time prolonged, gammaglutamyltransferase increased

System Organ Class	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	Not known (cannot be estimated from available data)
		total decreased, blood albumin decreased, Coombs direct test positive, blood creatinine increased, blood alkaline phosphatase increased, blood urea increased, activated partial thromboplastin time prolonged			

*ADR identified post-marketing

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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 dose. Patients may experience neuromuscular excitability or convulsions if higher than recommended doses are given intravenously (particularly in the presence of renal failure).

Treatment

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.

Excessive serum concentrations of either piperacillin or tazobactam may be reduced by haemodialysis (see section 4.4)

5. PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use, Beta-lactam antibacterials, Penicillins, Combinations of penicillins incl. beta-lactamase inhibitors; ATC code: J01C R05.

Mechanism of action

Piperacillin, a broad-spectrum, semisynthetic penicillin exerts bactericidal activity by inhibition of both septum and cell-wall synthesis.

Tazobactam, a beta-lactam structurally related to penicillins, is an inhibitor of many beta-lactamases, which commonly cause resistance to penicillins and cephalosporins, but it does not inhibit AmpC enzymes or metallo beta-lactamases. Tazobactam extends the antibiotic spectrum of piperacillin to include many beta-lactamase-producing bacteria that have acquired resistance to piperacillin alone.

Pharmacokinetic / Pharmacodynamic relationship

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

Mechanism of resistance

The two main mechanisms of resistance to piperacillin / tazobactam 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 piperacillin / tazobactam, especially in Gram-negative bacteria.

Breakpoints

EUCAST Clinical MIC Breakpoints for piperacillin/tazobactam (Version 7.1, 2017-03-10)

Pathogen	MIC breakpoint (mg/l)	
	S ≤	R >
Enterobacteriaceae (Enterobacterales)	81	161
Pseudomonas spp.2	161	161
Acinetobacter spp.	IE	IE
Staphylococcus spp.	Note3,4	Note3,4
Enterococcus spp.5	Note5	Note5
Streptococcus groups A, B, C and G6	Note7	Note7
Streptococcus pneumoniae	Note8,9	Note8,9
Viridans group streptococci	Note10	Note10
Haemophilus influenzae11	Note12	Note12
Moraxella catarrhalis	Note12	Note12
Gram-positive anaerobes except Clostridium difficile	81	161
Gram-negative anaerobes	81	161
PK/PD (Non-species related) breakpoints	41	161

- 1 For susceptibility testing purposes, the concentration of tazobactam is fixed at 4 mg/l.
- 2 Breakpoints are based on high dose therapy (4 g x 4, with or without tazobactam).
- 3 Most staphylococci are penicillinase producers, which make them resistant to benzylpenicillin, phenoxymethylpenicillin, ampicillin, amoxicillin, piperacillin and ticarcillin. When staphylococci test as susceptible to benzylpenicillin and ceftiofur they can be reported as susceptible to the above agents. However, the efficacy of oral formulations, particularly phenoxymethylpenicillin, is uncertain. Isolates that test as resistant to benzylpenicillin but susceptible to ceftiofur are susceptible to β -lactamase inhibitor combinations, the isoxazolylpenicillins (oxacillin, cloxacillin, dicloxacillin and flucloxacillin), nafcillin and many cephalosporins. With the exception of ceftaroline and ceftolozane, ceftiofur-resistant isolates are resistant to all beta-lactam agents.
- 4 Ampicillin susceptible *S. saprophyticus* are mecA -negative and susceptible to ampicillin, amoxicillin and piperacillin (without or with a beta-lactamase inhibitor).
- 5 Susceptibility to ampicillin, amoxicillin and piperacillin with and without beta-lactamase inhibitor can be inferred from ampicillin.
- 6 Streptococcus groups A, B, C and G do not produce beta-lactamase. The addition of a beta-lactamase inhibitor does not add clinical benefit.
- 7 The susceptibility of streptococcus groups A, B, C and G to penicillins is inferred from the benzylpenicillin susceptibility with the exception of phenoxymethylpenicillin and isoxazolylpenicillins for streptococcus group B.
- 8 Breakpoints for penicillins other than benzylpenicillin relate only to non-meningitis isolates. Isolates fully susceptible to benzylpenicillin (MIC ≤ 0.06 mg/l and/or susceptible by oxacillin disk screen) can be reported susceptible to beta-lactam agents for which clinical breakpoints are listed (including those with "Note").
- 9 Susceptibility inferred from the MIC of ampicillin.
- 10 For isolates susceptible to benzylpenicillin, susceptibility can be inferred from benzylpenicillin or ampicillin. For isolates resistant to benzylpenicillin, susceptibility is inferred from ampicillin.
- 11 Breakpoints are based on intravenous administration.
- 12 Susceptibility can be inferred from amoxicillin-clavulanic acid.

"IE" indicates that there is insufficient evidence that the organism or group is a good target for therapy with the agent. An MIC with a comment but without an accompanying S, I or R categorisation may be reported.

Susceptibility

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.

Groupings of relevant species according to piperacillin / tazobactam susceptibility
COMMONLY SUSCEPTIBLE SPECIES
Aerobic Gram-positive micro-organisms
Enterococcus faecalis
Listeria monocytogenes
Staphylococcus aureus, methicillin-susceptible†
Staphylococcus species, coagulase negative, methicillin-susceptible
Streptococcus pyogenes
Group B streptococci
Aerobic Gram-negative micro-organisms
Citrobacter koseri
Haemophilus influenza

Moraxella catarrhalis
Proteus mirabilis
Anaerobic Gram-positive micro-organisms
Clostridium species
Eubacterium species
Peptostreptococcus species
Anaerobic Gram-negative micro-organisms
Bacteroides fragilis group
Fusobacterium species
Porphyromonas species
Prevotella species

SPECIES FOR WHICH ACQUIRED RESISTANCE MAY BE A PROBLEM
Aerobic Gram-positive micro-organisms
Enterococcus faecium\$,+
Streptococcus pneumonia
Streptococcus viridans group
Aerobic Gram-negative micro-organisms
Acinetobacter baumannii\$
Burkholderia cepacia
Citrobacter freundii
Enterobacter species
Escherichia coli
Klebsiella pneumonia
Morganella morganii
Proteus vulgaris
Providencia ssp.
Pseudomonas aeruginosa
Serratia species
INHERENTLY RESISTANT ORGANISMS
Aerobic Gram-positive micro-organisms
Corynebacterium jeikeium
Aerobic Gram-negative micro-organisms
Legionella species
Stenotrophomonas maltophilia+,\$
Other microorganisms
Chlamydia pneumonia
Mycoplasma pneumonia
\$ 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. £ All methicillin-resistant staphylococci are resistant to piperacillin / tazobactam.

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 renal 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

The half-life of piperacillin and of tazobactam increases by approximately 25% and 18%, respectively, in patients with hepatic cirrhosis compared to healthy subjects.

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 a 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.

Race

No difference in piperacillin or tazobactam pharmacokinetics was observed between Asian (n=9) and Caucasian (n=9) healthy volunteers who received single 4 g / 0.5 g doses.

Preclinical safety data

Non-clinical 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 and general reproduction study in rats using intraperitoneal administration of tazobactam or the combination piperacillin / tazobactam reported a decrease in litter size and an increase in foetuses with ossification delays and variations of ribs, concurrent with maternal toxicity. Fertility of the F1 generation and embryonic development of F2 generation were not impaired.

Teratogenicity studies using intravenous administration of tazobactam or the combination piperacillin / tazobactam in mice and rats resulted in slight reductions in rat foetal weights at maternally toxic doses but did not show teratogenic effects.

Peri-/postnatal development was impaired (reduced pup weights, increase in stillbirths, increase in pup mortality) concurrent with maternal toxicity after intraperitoneal administration of tazobactam or the combination piperacillin / tazobactam in the rat.

6. PHARMACEUTICAL PARTICULARS

List of excipients

None.

Incompatibilities

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

This product must not be mixed or co-administrated with any aminoglycoside. The mixing of beta-lactam antibiotics with an aminoglycoside in vitro can result in substantial inactivation of the aminoglycoside.

Piperacillin / tazobactam should not be mixed with other substances 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 containing only sodium bicarbonate.

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

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

Shelf life

Unopened:

2 years

After reconstitution (and dilution):

Chemical and physical in-use stability has been demonstrated for 24 hours at 20-25°C and for 48 hours 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/dilution has taken place in controlled and validated aseptic conditions.

Special precautions for storage

Unopened vials:

This medicinal product does not require any special storage conditions.

For storage conditions after reconstitution and dilution of the medicinal product, see section 6.3.

Nature and contents of container

2 g / 0.25 g:

30 ml vial glass type III, with halogenated butyl rubber stopper and aluminium overseal with flip-off cap.

Pack sizes of 1, 5, 10, 12 and 50 vials.

4 g /0.5 g:

100 ml bottle glass type II, with halogenated butyl rubber stopper and aluminium overseal with flip-off cap.

50 ml bottle glass type II, with halogenated butyl rubber stopper and aluminium overseal with flip-off cap.

Pack sizes of 1, 5, 10, 12 and 50 bottles.

50 ml injection vial glass type III, with halogenated butyl rubber stopper and aluminium overseal with flip-off cap.

Pack sizes of 1, 5, 10, 12 and 50 vials.

Not all pack sizes may be marketed.

Special precautions for disposal and other handling

The reconstitution and dilution is 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.

Intravenous use

Reconstitute each vial/bottle with the volume of solvent shown in the table below, using one of the compatible solvents for reconstitution. Swirl until dissolved. When swirled constantly, reconstitution generally occurs within 3 minutes (for details on handling, please see below).

Content of vial/bottle	Volume of solvent* to be added to vial/bottle
2 g/0.25 g (2 g piperacillin and 0.25 g tazobactam)	10 ml
4 g/0.5 g (4 g piperacillin and 0.5 g tazobactam)	20 ml

* Compatible solvents for reconstitution:

- water for injection;
- sodium chloride 9 mg/ml (0.9 %) solution in water for injection;
- glucose 50 mg/ml (5 %) solution in water for injection;
- glucose 50 mg/ml (5 %) solution in sodium chloride 9 mg/ml (0.9%) solution.

The reconstituted solutions should be withdrawn from the vial/bottle by syringe. When reconstituted as directed, the vial/bottle contents withdrawn by syringe will provide the labelled amount of piperacillin and tazobactam.

The reconstituted solutions may be further diluted to the desired volume (e.g. 50 ml to 150 ml) with one of the following compatible solvents:

- sodium chloride 9 mg/ml (0.9 %) solution in water for injection;
- glucose 50 mg/ml (5 %) solution in water for injection;
- dextran (grade 40) 60 mg/ml (6%) solution in sodium chloride 9 mg/ml (0.9%) solution.

See section 6.2 for incompatibilities.

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

For single use only. Discard any unused solution.

7. MARKETING AUTHORISATION HOLDER

[To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: {DD month YYYY}

Date of latest renewal: {DD month YYYY} [To be completed nationally]

10. DATE OF REVISION OF THE TEXT

[MM/YYYY]

[To be completed nationally]