PRESCRIBING INFORMATION

PIPERACILLINE / TAZOBACTAM PANPHARMA

1. NAME OF THE MEDICINAL PRODUCT

PIPERACILLINE/TAZOBACTAM PANPHARMA 4 g/500 mg, powder for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

PIPERACILLINE/TAZOBACTAM PANPHARMA 4 g/500 mg, powder for solution for infusion
Each vial contains 4 g of piperacillin (as piperacillin sodium) and 500 mg of tazobactam (as tazobactam sodium).

Each vial of PIPERACILLINE/TAZOBACTAM PANPHARMA 4 g/500 mg contains 9.38 mmol (216 mg) of sodium.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for infusion.
White to off-white powder.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Piperacillin/tazobactam is indicated for the treatment of infections caused by susceptible organisms.

Piperacillin/tazobactam in combination with an aminoglycoside is indicated for the treatment of suspected bacterial infections in neutropenic adults and children above 2 years.
Appendicitis complicated by rupture with peritonitis and/or abscess formation in children aged 2-12 years.

Appropriate culture and susceptibility tests should be performed before treatment in order to identify organisms causing infections and to determine their susceptibilities to piperacillin/ tazobactam. Because of its broad spectrum of activity against Gram-positive and Gram-negative aerobic and anaerobic organisms as listed below, piperacillin/tazobactam is particularly useful in the treatment of mixed infections and in presumptive therapy prior to the availability of the results of sensitivity tests.

Therapy with piperacillin/tazobactam may, however, be initiated before results of such test are known. Modification of the treatment may be required once these results become available or if there is no clinical response.

In serious infections presumptive therapy with piperacillin/tazobactam may be initiated before susceptibility test results are available.
Piperacillin/tazobactam acts synergistically with aminoglycosides against certain strains of Pseudomonas aeruginosa. Combined therapy has been successful, especially in patients with impaired host defenses. Both drugs should be used in full therapeutic doses. As soon as results of culture and susceptibility test become available, antimicrobial therapy should be adjusted.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Piperacillin/ Tazobactam Panpharma (piperacillin and tazobactam) injection and other antibacterial drugs, Piperacillin/Tazobactam Panpharma (piperacillin and tazobactam) should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

4.2. Posology and method of administration

Piperacillin/Tazobactam Panpharma should be administered by intravenous infusion over 30 minutes.

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

Adults and adolescents (over 12 years)

The usual dosage for adults and juveniles with normal renal function is 4.5 g piperacillin/tazobactam given every eight 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.

Nosocomial Pneumonia

Initial presumptive treatment of patients with nosocomial pneumonia should start with Piperacillin/ Tazobactam Panpharma at a dosage of 4.5 g every six hours plus an aminoglycoside, totaling 18.0 g (16.0 g piperacillin/2.0 g tazobactam). Treatment with the aminoglycoside should be continued in patients from whom Pseudomonas aeruginosa is isolated. If Pseudomonas aeruginosa is not isolated, the aminoglycoside may be discontinued at the discretion of the treating physician.

Due to the in vitro inactivation of the aminoglycoside by beta-lactam antibiotics, Piperacillin/Tazobactam Panpharma and the aminoglycoside are recommended for separate administration.

Renal Insufficiency: Adults

In patients with renal insufficiency (Creatinine Clearance ≤40 mL/min), the intravenous dose of Piperacillin/Tazobactam Panpharma (piperacillin and tazobactam for injection) should be adjusted to the degree of actual renal function impairment. In patients with nosocomial pneumonia receiving concomitant aminoglycoside therapy, the aminoglycoside dosage should be adjusted according to the recommendations of the manufacturer. The recommended daily doses of Piperacillin/ Tazobactam Panpharma for patients with renal insufficiency are as follows:

Recommended Dosing of Piperacillin/Tazobactam Panpharma in Patients with Normal Renal Function and Renal Insufficiency (As total grams piperacillin/tazobactam).

TABLE 1

Renal Function (Creatinine Clearance, mL/min)	All Indications (except nosocomial pneumonia)	Nosocomial Pneumonia
>40 mL/min	No dose adjustment necessary	4.5 q 6 h
20-40 mL/min*	Maximum dose suggested: 4.5 g q 8 h	3.375 q 6 h
<20 mL/min*	Maximum dose suggested: 4.5 g q 12 h	2.25 q 6 h
Hemodialysis**	2.25 q 12 h	2.25 q 8 h
CAPD	2.25 q 12 h	2.25 q 8 h

* Creatinine clearance for patients not receiving hemodialysis

** 0.75 g should be administered following each hemodialysis session on hemodialysis days

For patients on hemodialysis, the maximum dose is 2.25 g every twelve hours for all indications other than nosocomial pneumonia and 2.25 g every eight hours for nosocomial pneumonia. Since hemodialysis removes 30% to 40% of the administered dose, an additional dose of 0.75 g Piperacillin/Tazobactam Panpharma should be administered following each dialysis period on hemodialysis days. No additional dosage of Piperacillin/Tazobactam Panpharma is necessary for CAPD patients.

Duration of Therapy

The usual duration of Piperacillin/Tazobactam Panpharma treatment for most indications is in the range of 5-14 days. However, the recommended duration of Piperacillin/Tazobactam Panpharma treatment of nosocomial pneumonia is 7 to 14 days. In all conditions, the duration of therapy should be guided by the severity of the infection and the patient's clinical and bacteriological progress.

Pediatric Patients (2-12 years of age)

For children with appendicitis older than 2 years and/or peritonitis, weighing up to 40 kg, and with normal renal function, the recommended Piperacillin/Tazobactam Panpharma dosage is 100 mg piperacillin/12.5 mg tazobactam per kilogram of body weight, every 8 hours. Pediatric patients weighing over 40 kg and with normal renal function should receive the adult dose.

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

TABLE 2

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

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):

TABLE 3

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

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

Geriatric Use

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

In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Piperacillin/Tazobactam Panpharma contains 54 mg (2.35 mEq) of sodium per gram of piperacillin in the combination product. At the usual recommended doses, patients would receive between 648 and 864 mg/day (28.2 and 37.6 mEq) of sodium. The geriatric population may respond with a blunted natriuresis to salt loading. This may be clinically important with regard to such diseases as congestive heart failure.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

4.3. 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).

4.4. Special warnings and precautions for use

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

Before initiating therapy with PIPERACILLINE/TAZOBACTAM PANPHARMA, 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.

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

Haemophagocytic lymphohistiocytosis (HLH): cases of HLH have been reported in patients treated with piperacillin, 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 treatment should be discontinued.

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 PIPERACILLINE/TAZOBACTAM PANPHARMA, should be discontinued.

Therapy with PIPERACILLINE/TAZOBACTAM PANPHARMA 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 (seizures) may occur when high doses are administered, especially in patients with impaired renal function (see section 4.8).

Each vial of PIPERACILLINE/TAZOBACTAM PANPHARMA 4 g/ 500 mg contains 216 mg of sodium, equivalent to 10.8% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

This should be taken into account in patients on a strict low-sodium diet.

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 hemodialysis patients. Intravenous dosages 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 multicenter, 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).

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 PIPERACILLINE/TAZOBACTAM PANPHARMA 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 PIPERACILLINE/TAZOBACTAM PANPHARMA. 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 PIPERACILLINE/TAZOBACTAM PANPHARMA should be confirmed by other diagnostic methods.

4.6. Fertility, pregnancy and lactation

Pregnancy

There are no or a limited amount of data from the use of PIPERACILLINE/TAZOBACTAM PANPHARMA 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).

4.7. Effects on ability to drive and use machines

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

4.8. Undesirable effects

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)	**Frequency not known (cannot be estimated from available data)**
Infections and infestations		candida infection*		pseudo-membranous	
Blood and lymphatic system disorders		thrombocytopenia, anaemia*	leukopenia	agranulocytosis	pancytopenia*, neutropenia, haemolytic anaemia*, thrombocytosis*,

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)	Frequency not known (cannot be estimated from available data)
Immune system disorders					anaphylactoid shock*, anaphylactic shock*, anaphylactoid reaction*, anaphylactic
Metabolism and nutrition			hypokalaemia		
Psychiatric disorders		insomnia			delirium*
Nervous system disorders		headache	seizure*		
Vascular disorders			hypotension, phlebitis, thrombophlebitis, flushing		
Respiratory, thoracic and mediastinal disorders				epistaxis	eosinophilic pneumonia
Gastrointestinal disorders	diarrhoea	abdominal pain, vomiting, constipation, nausea, 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*

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)	Frequency not known (cannot be estimated from available data)
General disorders and administration site conditions		pyrexia, injection-site reaction	chills		
Investigations		alanine aminotransferase increased, aspartate aminotransferase increased, protein total decreased, blood albumin decreased, Coombs direct test positive, blood creatinine increased, blood alkaline phosphatase increased, blood urea increased, activated partial thromboplastin time prolonged	blood glucose decreased, blood bilirubin increased, prothrombin time prolonged		bleeding time prolonged, gamma-glutamyltransferase increased

*ADR identified post marketing

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

Beta-lactam antibiotic class effects

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization 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 as per local regulations.

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 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 tazobactam or piperacillin may be reduced by haemodialysis (see section 4.4).

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use, **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. Tazobactum extends the antibiotic spectrum of piperacillin to include many beta-lactamase-producing bacteria that have acquired resistance to piperacillin alone.

Phamacokinetic / 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 (EUCAST

Clinical Breakpoint Table Version 10.0, valid from 2020-01-01)). For Susceptibility Testing Purposes, the Concentration of Tazobactam is Fixed at 4 mg/L.

Pathogen	**Species-related breakpoints (S≤/R>), mg/L de pipéracilline**
Enterobacterales (anciennement *Enterobacteriacae*)	8/16
Pseudomonas aeruginosa	< 0,001/16[1]
Staphylococcus species	-[2]
Enterococcus species	-[3]
Streptococcus Groups A, B, C and G	-[4]
Streptococcus pneumoniae	-[5]
Viridans group *Streptococci*	-[6]

Haemophilus influenzae	0,25/0,25
Moraxella catarrhalis	-[7]
Gram-positive anaerobes (except *Clostridioides difficile*)	8/16
Gram-negative anaerobes	8/16
Non-species related (PK/PD) breakpoints	4/16

[1] For several agents, EUCAST has introduced breakpoints which categorise wild-type organisms (organisms without phenotypically detectable acquired resistance mechanisms to the agent) as "Susceptible, increased exposure (I)" instead of "Susceptible, standard dosing regimen (S)". Susceptible breakpoints for these organism-agent combinations are listed as arbitrary, "off scale" breakpoints of S ≤ 0,001 mg/L.

[2] Most *S. aureus* are penicillinase producers, and some are methicillin resistant. Either mechanism renders them resistant to benzylpenicillin, phenoxymethylpenicillin, ampicillin, amoxicillin, piperacillin and ticarcillin. Isolates that test susceptible to benzylpenicillin and cefoxitin can be reported susceptible to all penicillins. Isolates that test resistant to benzylpenicillin but susceptible to cefoxitin are susceptible to β-lactamase inhibitor combinations, the isoxazolylpenicillins (oxacillin, cloxacillin, dicloxacillin and flucloxacillin) and nafcillin. For agents given orally, care to achieve sufficient exposure at the site of the infection should be exercised. Isolates that test resistant to cefoxitin are resistant to all penicillins. Most coagulase-negative staphylococci are penicillinase producers and some are methicillin resistant. Either mechanism renders them resistant to benzylpenicillin, phenoxymethylpenicillin, ampicillin, amoxicillin, piperacillin and ticarcillin. No currently available method can reliably detect penicillinase production in coagulase-negative staphylococci but methicillin resistance can be detected with cefoxitin as described. Ampicillin susceptible *S. saprophyticus* are *mecA*-negative and susceptible to ampicillin, amoxicillin and piperacillin (without or with a beta-lactamase inhibitor).

[3] Susceptibility to ampicillin, amoxicillin and piperacillin (with and without beta-lactamase inhibitor) can be inferred from ampicillin. Ampicillin resistance is uncommon in *E. faecalis* (confirm with MIC) but common in *E. faecium*.

[4] 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. Streptococcus groups A, B, C and G do not produce beta-lactamase. The addition of a beta-lactamase inhibitor does not add clinical benefit.

[5] The oxacillin 1 µg disk screen test or a benzylpenicillin MIC test shall be used to exclude betalactam resistance mechanisms. When the screen is negative (oxacillin inhibition zone ≥20 mm, or benzylpenicillin MIC ≤0.06 mg/L) all beta-lactam agents for which clinical breakpoints are available, including those with “Note” can be reported susceptible without further testing, except for cefaclor, which if reported, should be reported as “susceptible, increased exposure” (I). *Streptococcus pneumoniae* do not produce beta-lactamase. The addition of a beta-lactamase inhibitor does not add clinical benefit. Susceptibility inferred from ampicillin (MIC or zone diameter).

[6] For benzylpenicillin-susceptible isolates, susceptibility can be inferred from that of benzylpenicillin or ampicillin. For isolates resistant to benzylpenicillin, susceptibility is inferred from that of ampicillin.

[7] Susceptibility can be inferred from amoxicillin-clavulanic acid.

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.

COMMONLY SUSCEPTIBLE SPECIES
Aerobic Gram-positive micro-organisms *Enterococcus faecalis* (ampicillin-or penicillin-susceptible isolates only) *Listeria monocytogenes* *Staphylococcus aureus* (methicillin-susceptible isolates only) *Staphylococcus* species*, coagulase negative* (methicillin-susceptible isolates only) *Streptococcus agalactiae* (Group B *streptococci*)† *Streptococcus pyogenes* (Group A *streptococci*)†
Aerobic Gram-negative micro-organisms *Citrobacter koseri* *Haemophilus influenza* *Moraxella catarrhalis* *Proteus mirabilis*
Anaerobic Gram-positive micro-organisms *Clostridium* species *Eubacterium* species Anaerobic gram-positive cocci††
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 du groupe viridans*†
Aerobic Gram-negative micro-organisms *Acinetobacter baumannii* *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 *Burkholderia cepacia* *Legionella* species *Ochrobactrum anthropi* *Stenotrophomonas maltophilia*
Other microorganisms
Chlamydophilia pneumonia *Mycoplasma pneumonia*
† *Streptococci* are not β-lactamase producing bacteria; resistance in these organisms is due to alterations in penicillin-binding proteins (PBPs) and, therefore, suceptible isolates are susceptible to piperacillin alone. Penicillin resistance has not been reported in *S. pyogenes.* †† Including *Anaerococcus, Finegoldia, Parvimonas, Peptoniphilus,* and *Peptostreptococcus* spp.

Merino Trial (blood stream infections due to ESBL producers)
In a prospective, non-inferiority, parallel-group, published randomized clinical trial, definitive (i.e. based on susceptibility confirmed in-vitro) treatment with piperacillin/tazobactam, compared with meropenem,

did not result in a noninferior 30-day mortality in adult patients with ceftriaxone-non-susceptible E. coli or K. pneumoniae blood stream infections.
A total of 23 of 187 patients (12.3%) randomized to piperacillin/tazobactam met the primary outcome of mortality at 30 days compared with 7 of 191 (3.7%) randomized to meropenem (risk difference, 8.6% [1-sided 97.5% CI − ∞ to 14.5%]; P = 0.90 for non-inferiority). The difference did not meet the noninferiority margin of 5%.
Effects were consistent in an analysis of the per-protocol population, with 18 of 170 patients (10.6%) meeting the primary outcome in a piperacillin/tazobactam group compared with 7 of 186 (3.8%) in the meropenem group (risk difference, 6.8% [one-sided 97.5% CI, - ∞ to 12.8%]; P = 0.76 for non-inferiority).
Clinical and microbiological resolution (secondary outcomes) by day 4 occurred in 121 of 177 patients (68.4%) in the piperacillin/tazobactam group compared with 138 of 185 (74.6%), randomized to meropenem (risk difference, 6.2% [95% CI − 15.5 to 3.1%]; P = 0.19). For secondary outcomes, statistical tests were 2-sided, with a P < 0.05 considered significant.
In this trial, a mortality imbalance between study groups was found. It was supposed that deaths occurred in piperacillin/tazobactam group were related to underlying diseases rather to the concomitant infection.

5.2. Pharmacokinetic properties

Absorption

The peak piperacillin and tazobactam concentrations after 4 g / 0.5 g administered over 30 minutes by intravenous infusion are 298 µg/mL and 34 µg/mL respectively.

Distribution

Both piperacillin and tazobactam are approximately 30 % bound to plasma proteins. The protein binding of either piperacillin or tazobactam is unaffected by the presence of the other compound. Protein binding of the tazobactam metabolite is negligible.

Piperacillin / tazobactam is widely distributed in tissues and body fluids including intestinal mucosa, gallbladder, lung, bile, and bone. Mean tissue concentrations are generally 50 to 100 % of those in plasma. Distribution into cerebrospinal fluid is low in subjects with non-inflamed meninges, as with other penicillins.

Biotransformation

Piperacillin is metabolised to a minor microbiologically active desethyl metabolite.

Tazobactam is metabolised to a single metabolite that has been found to be microbiologically inactive.

Elimination

Piperacillin and tazobactam are eliminated via the kidney by glomerular filtration and tubular secretion.

Piperacillin is excreted rapidly as unchanged substance, with 68% of the administered dose appearing in the urine. Tazobactam and its metabolite are eliminated primarily by 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.

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 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 fetuses 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 fetal 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

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

PIPERACILLINE/TAZOBACTAM PANPHARMA should not be mixed with other substances in a syringe or infusion bottle since compatibility has not been established.

Simultaneous administration of PIPERACILLINE/TAZOBACTAM PANPHARMA and aminoside by Y-line infusion can cause an inactivation of the aminoside by PIPERACILLINE/TAZOBACTAM PANPHARMA.

Due to chemical instability, PIPERACILLINE/TAZOBACTAM PANPHARMA should not be used in solutions containing only sodium bicarbonate.

In the absence of compatibility study, the Ringer-lactate solution must not be mixed with PIPERACILLINE/TAZOBACTAM PANPHARMA.

PIPERACILLINE/TAZOBACTAM PANPHARMA should not be added to blood products or albumin hydrolysates.

6.3. Shelf life

Unopened vial: 3 years.

Reconstituted solution in vial :

Chemical and physical stability of the diluted product has not been demonstrated. The solution after reconstitution should be diluted immediately (see section 6.6).

Diluted infusion solution :

Chemical and physical in-use stability of diluted infusion solutions has been demonstrated for 48 hours when stored in a refrigerator at 2-8°C, when reconstituted using one of the compatible solvents for further dilution of the reconstituted solution at the suggested dilution volumes (see section 6.6).

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions after reconstitution and prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2-8°C.

6.4. Special precautions for storage

Unopened vials: Store below 30°C.

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

6.5. Nature and contents of container

Powder for infusion in vial.

Box of 1, 10, 12, 25, 50 or 100 vials.

Not all pack sizes may be marketed.

6.6. 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 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 5 to 10 minutes (for details on handling, please see below).

Content of vial	**Volume of solvent* to be added to vial**
4 g / 500 mg (4 g piperacillin and 500 mg tazobactam)	20 mL

* Compatible solvents for reconsitution :
- 0.9% (9 mg/mL) sodium chloride solution for injection
- Water for injections
- Glucose 5 %

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

The reconstituted solutions may be further diluted in bag of 50 or 100 mL with one of the following compatible solvents:
- 0.9% (9 mg/mL) sodium chloride solution for injection
- Glucose 5 %

Then, the solution will be administered by infusion over 30 minutes.

Co-administration with aminoglycosides

Due to the *in vitro* inactivation of the aminoglycoside by beta-lactam antibiotics, PIPERACILLINE/TAZOBACTAM PANPHARMA and the aminoglycoside are recommended for separate administration.

PIPERACILLINE/TAZOBACTAM PANPHARMA and the aminoglycoside should be reconstituted and diluted separately when concomitant therapy with aminoglycosides is indicated.

See section 6.2 for incompatibilities.

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

For single use only. Discard any unused solution.

7. MANUFACTURER

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8. DATE OF REVISION OF THE TEXT

עלון לצרכן במתכונת עלון לרופא זה נערך במרץ 2024 .

This Patient Insert Leaflet in the format of Physician Leaflet was revised on March 2024.

Medicinal product subject to hospital prescription.