PRESCRIBING INFORMATION

1. NAME OF THE MEDICINAL PRODUCT

PIPERACILLIN/TAZOBACTAM PANPHARMA 2 g/250 mg
PIPERACILLIN/TAZOBACTAM PANPHARMA 4 g/500 mg
Powder for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains: Piperacillin (as sodium) 2 g
Tazobactam (as sodium) 250 mg
(108 mg of sodium i.e., 4.69 mmol sodium/vial)

Each vial contains: Piperacillin (as sodium) 4 g
Tazobactam (as sodium) 500 mg
(216 mg of sodium i.e., 9.36 mmol sodium/vial)

3. PHARMACEUTICAL FORM

Powder for solution for infusion

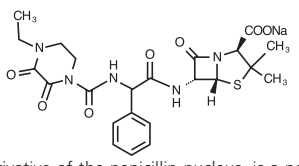
To reduce the development of drug-resistant bacteria and maintain the effectiveness of Piperacillin/Tazobactam Panpharma (piperacillin and tazobactam) injection and other antibacterial drugs, Piperacillin/Tazobactam Panpharma (piperacillin and tazobactam) should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

Description

Piperacillin/Tazobactam Panpharma (Piperacillin/Tazobactam for Injection) is an injectable antibacterial combination product consisting of the semisynthetic antibiotic piperacillin sodium and the beta-lactamase inhibitor tazobactam sodium for intravenous administration.

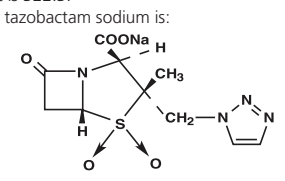
Piperacillin sodium is derived from D(-)-α-aminobenzyl-penicillin. The chemical name of piperacillin sodium is sodium (2S,5R,6R)-6-[(R)-2-(4-ethyl-2,3-dioxo-1-piperazinecarboxamido)-2-phenylacetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate. The chemical formula is $C_{23}H_{26}N_5NaO_7S$ and the molecular weight is 539.5.

The chemical structure of piperacillin sodium is:



Tazobactam sodium, a derivative of the penicillin nucleus, is a penicillanic acid sulfone. Its chemical name is sodium (2S,3S,5R)-3-methyl-7-oxo-3-(1H-1,2,3-triazol-1-methyl)-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid 4,4-dioxide. The chemical formula is $C_{10}H_{11}N_4NaO_5S$ and the molecular weight is 322.3.

The chemical structure of tazobactam sodium is:



4. CLINICAL PARTICULARS

4.1 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 Dosage and 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

Piperacillin/Tazobactam Panpharma is contraindicated in patients with a history of allergic reactions to any of the penicillins and/or cephalosporins or β-lactamase inhibitors.

4.4 Special Warnings and Precautions for Use

Warnings

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC/ANAPHYLACTOID) REACTIONS (INCLUDING SHOCK) HAVE BEEN REPORTED IN PATIENTS RECEIVING THERAPY WITH PENICILLINS INCLUDING PIPERACILLIN/TAZOBACTAM PANPHARMA. THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY OR A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS.

THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE HYPERSENSITIVITY REACTIONS WHEN TREATED WITH A CEPHALOSPORIN. BEFORE INITIATING THERAPY WITH PIPERACILLIN/TAZOBACTAM, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, AND OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS DURING THERAPY WITH PIPERACILLIN/TAZOBACTAM, PIPERACILLIN/TAZOBACTAM PANPHARMA SHOULD BE DISCONTINUED AND APPROPRIATE THERAPY INSTITUTED. **SERIOUS ANAPHYLACTIC/ANAPHYLACTOID REACTIONS (INCLUDING SHOCK) REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS, STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTRATED AS INDICATED.**

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including Piperacillin/Tazobactam Panpharma, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

Serious skin reactions, such as Stevens-Johnson syndrome and toxic epidermal necrolysis, have been reported in patients receiving ZOSYN (see ADVERSE REACTIONS). If patients develop a skin rash they should be monitored closely and ZOSYN discontinued if lesions progress.

Precautions

General

Bleeding manifestations have occurred in some patients receiving β-lactam antibiotics, including piperacillin. 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 Piperacillin/Tazobactam Panpharma should be discontinued and appropriate therapy instituted.

The possibility of the emergence of resistant organisms that might cause superinfections should be kept in mind. If this occurs, appropriate measures should be taken.

As with other penicillins, patients may experience neuromuscular excitability or convulsions if higher than recommended doses are given intravenously (particularly in the presence of renal failure).

Piperacillin/Tazobactam Panpharma contains a total of 2.35 mEq (54 mg) of Na^+ per gram of piperacillin in the combination product.

This should be considered when treating patients requiring restricted salt intake. Periodic electrolyte determinations should be made in patients with low potassium reserves, and the possibility of hypokalemia should be kept in mind with patients who have potentially low potassium reserves and who are receiving cytotoxic therapy or diuretics.

As with other semisynthetic penicillins, piperacillin therapy has been associated with an increased incidence of fever and rash in cystic fibrosis patients.

In patients with creatinine clearance ≤40 mL/min and dialysis patients (hemodialysis and CAPD), the intravenous dose should be adjusted to the degree of renal function impairment. (See DOSAGE AND ADMINISTRATION.)

Prescribing Piperacillin/Tazobactam Panpharma (piperacillin and tazobactam) in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of development of drug-resistant bacteria.

Information for Patients

Patients should be counseled that antibacterial drugs including Piperacillin/Tazobactam Panpharma should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When Piperacillin/Tazobactam Panpharma is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by Piperacillin/Tazobactam Panpharma or other antibacterial drugs in the future.

Diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.

Laboratory Tests

Periodic assessment of hematopoietic function should be performed, especially with prolonged therapy, i.e., ≥21 days. (See ADVERSE REACTIONS - Adverse laboratory events.)

4.5 Interactions with Other Medicinal Products and Other Forms of Interaction

Aminoglycosides

The mixing of beta-lactam antibiotics with aminoglycosides *in vitro* can result in substantial inactivation of the aminoglycoside.

The inactivation of aminoglycosides in the presence of penicillin-class drugs has been recognized. It has been postulated that penicillin-aminoglycoside complexes form; these complexes are microbiologically inactive and of unknown toxicity. Sequential administration of Piperacillin/Tazobactam with tobramycin to patients with normal renal function and mild to moderate renal impairment has been shown to modestly decrease serum concentrations of tobramycin but does not significantly affect tobramycin pharmacokinetics. When aminoglycosides are administered in combination with piperacillin to patients with end-stage renal disease requiring hemodialysis, the concentrations of the aminoglycosides (especially tobramycin) may be significantly altered and should be monitored. Since aminoglycosides are not equally susceptible to inactivation by piperacillin, consideration should be given to the choice of the aminoglycoside when administered in combination with piperacillin to these patients.

Probenecid

Probenecid administered concomitantly with Piperacillin/Tazobactam Panpharma prolongs the half-life of piperacillin by 21% and that of tazobactam by 71%.

Vancomycin

No pharmacokinetic interactions have been noted between Piperacillin/Tazobactam Panpharma and vancomycin.

Heparin

Coagulation parameters should be tested more frequently and monitored regularly during simultaneous administration of high doses of heparin, oral anticoagulants, or other drugs that may affect the blood coagulation system or the thrombocyte function.

Vecuronium

Piperacillin when used concomitantly with vecuronium has been implicated in the prolongation of the neuromuscular blockade of vecuronium. Piperacillin/Tazobactam Panpharma (piperacillin/tazobactam) could produce the same phenomenon if given along with vecuronium. Due to their similar mechanism of action, it is expected that the neuromuscular blockade produced by any of the non-depolarizing muscle relaxants could be prolonged in the presence of piperacillin. (See package insert for vecuronium bromide.)

Methotrexate

Limited data suggests that co-administration of methotrexate and piperacillin may reduce the clearance of methotrexate due to competition for renal secretion. The impact of tazobactam on the elimination of methotrexate has not been evaluated. If concurrent therapy is necessary, serum concentrations of methotrexate as well as the signs and symptoms of methotrexate toxicity should be frequently monitored.

Drug/Laboratory Test Interactions

As with other penicillins, 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 reactions 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 the 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 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term carcinogenicity studies in animals have not been conducted with piperacillin/tazobactam, piperacillin, or tazobactam.

Piperacillin/Tazobactam

Piperacillin/tazobactam was negative in microbial mutagenicity assays at concentrations up to 14.84/1.86 μg/plate. Piperacillin/tazobactam was negative in the unscheduled DNA synthesis (UDS) test at concentrations up to 5689/711 μg/mL. Piperacillin/tazobactam was negative in a mammalian point mutation (Chinese hamster ovary cell HPRT) assay at concentrations up to 8000/1000 μg/mL. Piperacillin/tazobactam was negative in a mammalian cell (BALB/c-3T3) transformation assay at concentrations up to 8/1 μg/mL. *In vivo*, piperacillin/ tazobactam did not induce chromosomal aberrations in rats dosed I.V. with 1500/187.5 mg/kg; this dose is similar to the maximum recommended human daily dose on a body-surface-area basis (mg/m^2).

Piperacillin

Piperacillin was negative in microbial mutagenicity assays at concentrations up to 50 μg/plate. There was no DNA damage in bacteria (Rec assay) exposed to piperacillin at concentrations up to 200 μg/disk. Piperacillin was negative in the UDS test at concentrations up to 10,000 μg/mL. In a mammalian point mutation (mouse lymphoma cells) assay, piperacillin was positive at concentrations ≥2500 μg/mL. Piperacillin was negative in a cell (BALB/c-3T3) transformation assay at concentrations up to 3000 μg/mL. *In vivo*, piperacillin did not induce chromosomal aberrations in mice at I.V. doses up to 2000 mg/kg/day or rats at I.V. doses up to 1500 mg/kg/day. These doses are half (mice) or similar (rats) to the maximum recommended human daily dose based on body-surface area (mg/m^2). In another *in vivo* test, there was no dominant lethal effect when piperacillin was administered to rats at I.V. doses up to 2000 mg/kg/day, which is similar to the maximum recommended human daily dose based on body-surface area (mg/m^2). When mice were administered piperacillin at I.V. doses up to 2000 mg/kg/day, which is half the maximum recommended human daily dose based on body-surface area (mg/m^2), urine from these animals was not mutagenic when tested in a microbial mutagenicity assay. Bacteria injected into the peritoneal cavity of mice administered piperacillin at I.V. doses up to 2000 mg/kg/day did not show increased mutation frequencies.

Tazobactam

Tazobactam was negative in microbial mutagenicity assays at concentrations up to 333 μg/plate. Tazobactam was negative in the UDS test at concentrations up to 2000 μg/mL. Tazobactam was negative in a mammalian point mutation (Chinese hamster ovary cell HPRT) assay at concentrations up to 5000 μg/mL. In another mammalian point mutation (mouse lymphoma cells) assay, tazobactam was positive at concentrations ≥3000 μg/mL. Tazobactam was negative in a cell (BALB/c-3T3) transformation assay at concentrations up to 900 μg/mL. In an *in vitro* cytogenetics (Chinese hamster lung cells) assay, tazobactam was negative at concentrations up to 3000 μg/mL. *In vivo*, tazobactam did not induce chromosomal aberrations in rats at I.V. doses up to 5000 mg/kg, which is 23 times the maximum recommended human daily dose based on body-surface area (mg/m^2).

Pregnancy

Teratogenic effects - Pregnancy Category B

Piperacillin/tazobactam

Reproduction studies have been performed in rats and have revealed no evidence of impaired fertility due to piperacillin/tazobactam administered up to a dose which is similar to the maximum recommended human daily dose based on body-surface area (mg/m^2).

Teratology studies have been performed in mice and rats and have revealed no evidence of harm to the fetus due to piperacillin/tazobactam administered up to a dose which is 1 to 2 times and 2 to 3 times the human dose of piperacillin and tazobactam, respectively, based on body-surface area (mg/m^2).

Piperacillin and tazobactam cross the placenta in humans.

Piperacillin

Reproduction and teratology studies have been performed in mice and rats and have revealed no evidence of impaired fertility or harm to the fetus due to piperacillin administered up to a dose which is half (mice) or similar (rats) to the maximum recommended human daily dose based on body-surface area (mg/m^2).

Tazobactam

Reproduction studies have been performed in rats and have revealed no evidence of impaired fertility due to tazobactam administered at doses up to 3 times the maximum recommended human daily dose based on body-surface area (mg/m^2).

Teratology studies have been performed in mice and rats and have revealed no evidence of harm to the fetus due to tazobactam administered at doses up to 6 and 14 times, respectively, the human dose based on body-surface area (mg/m^2). In rats, tazobactam crosses the placenta. Concentrations in the fetus are less than or equal to 10% of those found in maternal plasma.

There are, however, no adequate and well-controlled studies with the piperacillin/tazobactam combination or with piperacillin or tazobactam alone in pregnant women. Because animal reproduction studies are not always predictive of the human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

Piperacillin is excreted in low concentrations in human milk; tazobactam concentrations in human milk have not been studied. Caution should be exercised when Piperacillin/Tazobactam Panpharma (piperacillin and tazobactam for injection) is administered to a nursing woman.

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.

4.7 Effects on Ability to Drive and Use Machines

The studies on the affects on the ability to drive and use machines have not been performed. However such effects may occur, which may influence the ability to drive and use machines.

4.8 Adverse Reactions

Adverse Events from Clinical Trials

During the initial clinical investigations, 2621 patients worldwide were treated with Piperacillin/Tazobactam Panpharma (piperacillin and tazobactam for injection) phase 3 trials. In the key North American clinical trials (n=830 patients), 90% of the adverse events reported were mild to moderate in severity and transient in nature. However, in 3.2% of the patients treated worldwide, Piperacillin/Tazobactam Panpharma was discontinued because of adverse events primarily involving the skin (1.3%), including rash and pruritus; the gastrointestinal system (0.9%), including diarrhea, nausea, and vomiting; and allergic reactions (0.5%).

Adverse local reactions that were reported, irrespective of relationship to therapy with Piperacillin/Tazobactam Panpharma were phlebitis (1.3%), injection site reaction (0.5%), pain (0.2%), inflammation (0.2%), thrombophlebitis (0.2%), and edema (0.1%).

Based on patients from clinical trials (n=1063), the events with the highest incidence in patients, irrespective of relationship to Piperacillin/Tazobactam Panpharma therapy, were diarrhea (11.3%); headache (7.7%); constipation (7.7%); nausea (6.9%); insomnia (6.6%); rash (4.2%), including maculopapular, bullous, urticarial, and eczematoid; vomiting (3.3%); dyspepsia (3.3%); pruritus (3.1%); stool changes (2.4%); fever (2.4%); agitation (2.1%); pain (1.7%); moniliasis (1.6%); hypertension (1.6%); dizziness (1.4%); abdominal pain (1.3%); chest pain (1.3%); edema (1.2%); anxiety (1.2%); rhinitis (1.2%); and dyspnea (1.1%).

Additional adverse systemic clinical events reported in 1.0% or less of the patients in the initial North American trials are listed below within each body system.

Autonomic Nervous System - hypotension, ileus, syncope

Body as a whole - rigors, back pain, malaise

Cardiovascular - tachycardia, including supraventricular and ventricular; bradycardia; arrhythmia, including atrial fibrillation, ventricular fibrillation, cardiac arrest, cardiac failure, circulatory failure, myocardial infarction

Central Nervous System - tremor, convulsions, vertigo

Gastrointestinal - melena, flatulence, hemorrhage, gastritis, hiccough, ulcerative stomatitis

Pseudomembranous colitis was reported in one patient during the clinical trials. The onset of pseudomembranous colitis symptoms may occur during or after antibacterial treatment. (See WARNINGS.)

Hearing and Vestibular System - tinnitus

Hypersensitivity - anaphylaxis

Metabolic and Nutritional - symptomatic hypoglycemia, thirst

Musculoskeletal - myalgia, arthralgia

Platelets, Bleeding, Clotting - mesenteric embolism, purpura, epistaxis, pulmonary embolism (see PRECAUTIONS, General).

Psychiatric - confusion, hallucination, depression

Reproductive, Female - leukorrhea, vaginitis

Respiratory - pharyngitis, pulmonary edema, bronchospasm, coughing

Skin and Appendages - genital pruritus, diaphoresis

Special senses - taste perversion

Urinary - retention, dysuria, oliguria, hematuria, incontinence

Vision - photophobia

Vascular (extracardiac) - flushing

Nosocomial Pneumonia Trials

In a completed study of nosocomial lower respiratory tract infections, 222 patients were treated with Piperacillin/Tazobactam Panpharma in a dosing regimen of 4.5 g every 6 hours in combination with an aminoglycoside and 215 patients were treated with imipenem/cilastatin (500 mg/500 mg q6h) in combination with an aminoglycoside. In this trial, treatment-emergent adverse events were reported by 402 patients, 204 (91.9%) in the piperacillin/tazobactam group and 198 (92.1%) in the imipenem/cilastatin group. Twenty-five (11.0%) patients in the piperacillin/tazobactam group and 14 (6.5%) in the imipenem/cilastatin group (p >0.05) discontinued treatment due to an adverse event.

In this study of Piperacillin/Tazobactam Panpharma in combination with an aminoglycoside, adverse events that occurred in more than 1% of patients and were considered by the investigator to be drug-related were: diarrhea (17.6%), fever (2.7%), vomiting (2.7%), urinary tract infection (2.7%), rash (2.3%), abdominal pain (1.8%), generalized edema (1.8%), moniliasis (1.8%), nausea (1.8%), oral moniliasis (1.8%), BUN increased (1.8%), creatinine increased (1.8%), peripheral edema (1.8%), abdomen enlarged (1.4%), headache (1.4%), constipation (1.4%), liver function tests abnormal (1.4%), thrombocythemia (1.4%), excoriations (1.4%), and sweating (1.4%).

Drug-related adverse events reported in 1% or less of patients in the nosocomial pneumonia study of Piperacillin/Tazobactam Panpharma with an aminoglycoside were: acidosis, acute kidney failure, agitation, alkaline phosphatase increased, anemia, asthenia, atrial fibrillation, chest pain, CNS depression, colitis, confusion, convulsion, cough increased, thrombocytopenia, dehydration, depression, diplopia, drug level decreased, dry mouth, dyspepsia, dysphagia, dyspnea, dysuria, eosinophilia, fungal dermatitis, gastritis, glossitis, grand mal convulsion, hematuria, hyperglycemia, hypernatremia, hypertension, hypertonia, hyperventilation, hypochromic anemia, hypoglycemia, hypokalemia, hyponatremia, hypophosphatemia, hypoxia, ileus, injection site edema, injection site pain, injection site reaction, kidney function abnormal, leukocytosis, leukopenia, local reaction to procedure, melena, pain, prothrombin decreased, pruritus, respiratory disorder, SGOT increased, SGPT increased, sinus bradycardia, somnolence, stomatitis, stupor, tremor, tachycardia, ventricular extrasystoles, and ventricular tachycardia.

In a previous nosocomial pneumonia study conducted with a dosing regimen of 3.375 g given every 4 hours with an aminoglycoside, the following adverse events, irrespective of drug relationship, were observed: diarrhea (20%); constipation (8.4%); agitation (7.1%); nausea (5.8%); headache (4.5%); insomnia (4.5%); oral thrush (3.9%); erythematous rash (3.9%); anxiety (3.2%); fever (3.2%); pain (3.2%); pruritus (3.2%); hiccough (2.6%); vomiting (2.6%); dyspepsia (1.9%); edema (1.9%); fluid overload (1.9%); stool changes (1.9%); anorexia (1.3%); cardiac arrest (1.3%); confusion (1.3%); diaphoresis (1.3%); duodenal ulcer (1.3%); flatulence (1.3%); hypertension (1.3%); hypotension (1.3%); inflammation at injection site (1.3%); pleural effusion (1.3%); pneumothorax (1.3%); rash, not otherwise specified (1.3%); supraventricular tachycardia (1.3%); thrombophlebitis (1.3%); and urinary incontinence (1.3%).

Adverse events irrespective of drug relationship observed in 1% or less of patients in the above study with Piperacillin/Tazobactam Panpharma and an aminoglycoside included: aggressive reaction (combative), angina, asthenia, atelectasis, balanoposthitis, cerebrovascular accident, chest pain, conjunctivitis, deafness, dyspnea, earache, ecchymosis, fecal incontinence, gastric ulcer, gout, hemoptysis, hypoxia, pancreatitis, perineal irritation/pain, urinary tract infection with trichomonas, vitamin B_{12} deficiency anemia, xerosis, and yeast in urine.

Pediatrics

Studies of Piperacillin/Tazobactam Panpharma in pediatric patients suggest a similar safety profile to that seen in adults. In a prospective, randomized, comparative, open-label clinical trial of pediatric patients with severe intra-abdominal infections (including appendicitis and/or peritonitis), 273 patients were treated with Piperacillin/Tazobactam Panpharma (112.5 mg/kg every 8 hours) and 269 patients were treated with cefotaxime (50 mg/kg) plus metronidazole (7.5 mg/kg) every 8 hours. In this trial, treatment-emergent adverse events were reported by 146 patients, 73 (26.7%) in the Piperacillin/Tazobactam Panpharma group and 73 (27.1%) in the cefotaxime/metronidazole group. Six patients (2.2%) in the Piperacillin/Tazobactam Panpharma group and 5 patients (1.9%) in the cefotaxime/metronidazole group discontinued due to an adverse event.

In this study, adverse events that were reported in more than 1% of patients, irrespective of relationship to therapy with Piperacillin/Tazobactam Panpharma, were: diarrhea (7.0%), fever (4.8%), vomiting (3.7%), local reaction (3.3%), abscess (2.2%), sepsis (2.2%), abdominal pain (1.8%), infection (1.8%), bloody diarrhea (1.1%), pharyngitis (1.5%), constipation (1.1%), and SGOT increase (1.1%).

Adverse events reported in 1% or less of pediatric patients receiving Piperacillin/Tazobactam Panpharma are consistent with adverse events reported in adults.

Additional controlled studies in pediatric patients showed a similar safety profile as that described above.

Post-Marketing Experience

Additional adverse events reported from worldwide marketing experience with Piperacillin/Tazobactam Panpharma, occurring under circumstances where causal relationship to Piperacillin/Tazobactam Panpharma is uncertain:

Gastrointestinal - hepatitis, cholestatic jaundice

Hematologic - hemolytic anemia, anemia, thrombocytosis, agranulocytosis, pancytopenia

Immune - hypersensitivity reactions, anaphylactic/anaphylactoid reactions (including shock)

Infections - candidal superinfections

Renal - interstitial nephritis, renal failure

Skin and Appendages - erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis

Post-marketing experience with Piperacillin/Tazobactam Panpharma in pediatric patients suggests a similar safety profile to that seen in adults.

Adverse Laboratory Events: (seen during Clinical Trials)

Of the studies reported, including that of nosocomial lower respiratory tract infections in which a higher dose of Piperacillin/Tazobactam Panpharma (piperacillin and tazobactam for injection) was used in combination with an aminoglycoside, changes in laboratory parameters, without regard to drug relationship, include:

Hematologic - Decreases in hemoglobin and hematocrit thrombocytopenia, increases in platelet count, eosinophilia, leukopenia, neutropenia. The leukopenia/neutropenia associated with Piperacillin/Tazobactam Panpharma administration appears to be reversible and most frequently associated with prolonged administration, i.e., ≥21 days of therapy. These patients were withdrawn from therapy; some had accompanying systemic symptoms (e.g., fever, rigors, chills).

Coagulation - Positive direct Coombs' test, prolonged prothrombin time, prolonged partial thromboplastin time

Hepatic - Transient elevations of AST (SGOT), ALT (SGPT), alkaline phosphatase, bilirubin

Renal - Increases in serum creatinine, blood urea nitrogen

Urinalysis - Proteinuria, hematuria, pyuria

Additional laboratory events include abnormalities in electrolytes (i.e., increases and decreases in sodium, potassium and calcium), hyperglycemia, decreases in total protein or albumin, blood glucose decreased, gamma-glutamyltransferase increased, hypokalemia, and bleeding time prolonged.

The following adverse reaction has also been reported for piperacillin (piperacillin for injection):

Skeletal - prolonged muscle relaxation (See PRECAUTIONS, INTERACTIONS WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION.)

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

4.9 Overdosage

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

Treatment should be supportive and symptomatic according to the patient's clinical presentation. Excessive serum concentrations of either piperacillin or tazobactam may be reduced by hemodialysis. Following a single 3.375 g dose of piperacillin/tazobactam, the percentage of the piperacillin and tazobactam dose removed by hemodialysis was approximately 31% and 39%, respectively. (See CLINICAL PHARMACOLOGY.)

5. CLINICAL PHARMACOLOGY

ADULTS

Peak plasma concentrations of piperacillin and tazobactam are attained immediately after completion of an intravenous infusion of Piperacillin/Tazobactam Panpharma. Piperacillin plasma concentrations, following a 30-minute infusion of Piperacillin/Tazobactam Panpharma, were similar to those attained when equivalent doses of piperacillin were administered alone, with mean peak plasma concentrations of approximately 134, 242 and 298 μg/mL for the 2.25 g, 3.375 g and 4.5 g Piperacillin/Tazobactam Panpharma (piperacillin/tazobactam) doses, respectively. The corresponding mean peak plasma concentrations of tazobactam were 15, 24 and 34 μg/mL, respectively.

Following a 30-minute I.V. infusion of 3.375 g Piperacillin/Tazobactam Panpharma every 6 hours, steady-state plasma concentrations of piperacillin and tazobactam were similar to those attained after the first dose. In like manner, steady-state plasma concentrations were not different from those attained after the first dose when 2.25 g or 4.5 g doses of Piperacillin/Tazobactam Panpharma were administered via 30-minute infusions every 6 hours. Steady-state plasma concentrations after 30-minute infusions every 6 hours are provided in Table 4.

Following single or multiple Piperacillin/Tazobactam Panpharma doses to healthy subjects, the plasma half-life of piperacillin and of tazobactam ranged from 0.7 to 1.2 hours and was unaffected by dose or duration of infusion.

Piperacillin is metabolized to a minor microbiologically active desethyl metabolite. Tazobactam is metabolized to a single metabolite that lacks pharmacological and antibacterial activities. Both piperacillin and tazobactam are eliminated via the kidney by glomerular filtration and tubular secretion. Piperacillin is excreted rapidly as unchanged drug with 68% of the administered dose excreted in the urine. Tazobactam and its metabolite are eliminated primarily by renal excretion with 80% of the administered dose excreted as unchanged drug and the remainder as the single metabolite. Piperacillin, tazobactam and desethyl piperacillin are also secreted into the bile.

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 and tazobactam are widely distributed into tissues and body fluids including intestinal mucosa, gallbladder, lung, female reproductive tissues (uterus, ovary, and fallopian tube), interstitial fluid, and bile. Mean tissue concentrations are generally 50% to 100% of those in plasma. Distribution of piperacillin and tazobactam into cerebrospinal fluid is low in subjects with non-inflamed meninges, as with other penicillins.

After the administration of single doses of piperacillin/tazobactam to subjects with renal impairment, the half-life of piperacillin and of tazobactam increases with decreasing creatinine clearance. At creatinine clearance below 20 mL/min, the increase in half-life is twofold for piperacillin and fourfold for tazobactam compared to subjects with normal renal function. Dosage adjustments for Piperacillin/Tazobactam Panpharma are recommended when creatinine clearance is below 40 mL/min in patients receiving the usual recommended daily dose of Piperacillin/Tazobactam Panpharma (piperacillin and tazobactam for injection). (See DOSAGE AND ADMINISTRATION section for specific recommendations for the treatment of patients with renal insufficiency.)

Hemodialysis removes 30% to 40% of a piperacillin/tazobactam dose 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 16% of the tazobactam dose removed as the tazobactam metabolite. For dosage recommendations for patients undergoing hemodialysis, see DOSAGE AND ADMINISTRATION section.

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, this difference does not warrant dosage adjustment of Piperacillin/Tazobactam Panpharma due to hepatic cirrhosis.

TABLE 4
STEADY STATE MEAN PLASMA CONCENTRATIONS IN ADULTS AFTER 30-MINUTE INTRAVENOUS INFUSION OF PIPERACILLIN/TAZOBACTAM EVERY 6 HOURS

PIPERACILLIN

		Plasma Concentrations** (μg/mL)						AUC** (μg•hr/mL)
Piperacillin/ Tazobactam Dose[a]	No. of Evaluable Subjects	30 min	1 hr	2 hr	3 hr	4 hr	6 hr	AUC_{0-6}
2.25 g	8	134 (14)	57 (14)	17.1 (23)	5.2 (32)	2.5 (35)	0.9 (14)[b]	131 (14)
3.375 g	6	242 (12)	106 (8)	34.6 (20)	11.5 (19)	5.1 (22)	1.0 (10)	242 (10)
4.5 g	8	298 (14)	141 (19)	46.6 (28)	16.4 (29)	6.9 (29)	1.4 (30)	322 (16)

TAZOBACTAM

		Plasma Concentrations** (μg/mL)						AUC** (μg•hr/mL)
Piperacillin/ Tazobactam Dose[a]	No. of Evaluable Subjects	30 min	1 hr	2 hr	3 hr	4 hr	6 hr	AUC_{0-6}
2.25 g	8	14.8 (14)	7.2 (22)	2.6 (30)	1.1 (35)	0.7 (6)[c]	<0.5	16.0 (21)
3.375 g	6	24.2 (14)	10.7 (7)	4.0 (18)	1.4 (21)	0.7 (16)[b]	<0.5	25.0 (8)
4.5 g	8	33.8 (15)	17.3 (16)	6.8 (24)	2.8 (25)	1.3 (30)	<0.5	39.8 (15)

** Numbers in parentheses are coefficients of variation (CV%)

[a] Piperacillin and tazobactam were given in combination

[b] N = 4

[c] N = 3

Pediatrics

Piperacillin and tazobactam pharmacokinetics were studied in pediatric patients 2 months of age and older. The clearance of both compounds is slower in the younger patients compared to older children and adults.

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 pediatric patients 2-9 months old. In patients younger than 2 months of age, clearance of piperacillin is slower compared to older children; however, it is not adequately characterized for dosing recommendations. The population mean (SE) for piperacillin distribution volume is 0.243 (0.011) L/kg and is independent of age.

Microbiology

Piperacillin sodium exerts bactericidal activity by inhibiting septum formation and cell wall synthesis of susceptible bacteria. *In vitro*, piperacillin is active against a variety of gram-positive and gram-negative aerobic and anaerobic bacteria. Tazobactam sodium has little clinically relevant *in vitro* activity against bacteria due to its reduced affinity to penicillin-binding proteins. It is, however, a β-lactamase inhibitor of the Richmond-Sykes class III (Bush class 2b & 2b') penicillinases and cephalosporinases. It varies in its ability to inhibit class II and IV (2a & 4) penicillinases. Tazobactam does not induce chromosomally-mediated β-lactamases at tazobactam concentrations achieved with the recommended dosage regimen.

Piperacillin/tazobactam has been shown to be active against most strains of the following microorganisms both *in vitro* and in clinical infections as described in the INDICATIONS section.

Aerobic and facultative gram-positive microorganisms:

Staphylococcus aureus (excluding methicillin and oxacillin-resistant isolates)

Aerobic and facultative gram-negative microorganisms:

Acinetobacter baumanii

Escherichia coli

Haemophilus influenzae (excluding β-lactamase negative, ampicillin-resistant isolates)

Klebsiella pneumoniae

Pseudomonas aeruginosa (given in combination with an aminoglycoside to which the isolate is susceptible)

Gram-negative anaerobes:

Bacteroides fragilis group (B. fragilis, B. ovatus, B. thetaiotaomicron, and B. vulgatus)

The following *in vitro* data are available, but their clinical significance is unknown.

At least 90% of the following microorganisms exhibit an *in vitro* minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for piperacillin/tazobactam. However, the safety and effectiveness of piperacillin/tazobactam in treating clinical infections due to these bacteria have not been established in adequate and well-controlled clinical trials.

Aerobic and facultative gram-positive microorganisms:

Enterococcus faecalis (ampicillin or penicillin-susceptible isolates only)

Staphylococcus epidermidis (excluding methicillin and oxacillin resistant isolates)

Streptococcus agalactiae[†]

Streptococcus pneumoniae[†] (penicillin-susceptible isolates only)

Streptococcus pyogenes[†]

Viridans group streptococci[†]

Aerobic and facultative gram-negative microorganisms:

Citrobacter koseri

Moraxella catarrhalis

Morganella morganii

Neisseria gonorrhoeae

Proteus mirabilis

Proteus vulgaris

Serratia marcescens

Providencia stuartii

Providencia rettgeri

Salmonella enterica

Gram-positive anaerobes:

Clostridium perfringens

Gram-negative anaerobes:

Bacteroides distasonis

Prevotella melaninogenica

[†]These are not β-lactamase producing bacteria and, therefore, are susceptible to piperacillin alone.

Susceptibility Testing Methods

As is recommended with all antimicrobials, the results of *in vitro* susceptibility tests, when available, should be provided to the physician as periodic reports, which describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting the most effective antimicrobial.

Dilution Techniques:

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of piperacillin and tazobactam powders. MIC values should be determined using serial dilutions of piperacillin combined with a fixed concentration of 4 μg/mL tazobactam. The MIC values obtained should be interpreted according to criteria provided in Table 5.

Diffusion Technique:

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 100 μg of piperacillin and 10 μg of tazobactam to test the susceptibility of microorganisms to piperacillin/tazobactam. The disk diffusion interpreted criteria are provided in Table 5.

Anaerobic Techniques:

For anaerobic bacteria, the susceptibility to piperacillin/tazobactam can be determined by the reference agar dilution method.

TABLE 5
SUSCEPTIBILITY INTERPRETIVE CRITERIA FOR PIPERACILLIN/TAZOBACTAM

	Susceptibility Test Result Interpretive Criteria					
	Minimal Inhibitory Concentration (MIC in μg/mL)			Disk Diffusion (Zone Diameter in mm)		
Pathogen	S	I	R	S	I	R
Enterobacteriaceae and *Acinetobacter baumanii*	≤16	32-64	≥128	≥ 21	18-20	≤17
Haemophilus influenzae[a]	≤1	-	≥2	≥ 21	-	-
Pseudomonas aeruginosa	≤64	-	≥128	≥ 18	-	≤17
Staphylococcus aureus	≤8	-	≥16	≥ 18	-	≤17
Bacteroides fragilis group	≤32	64	≥128	-	-	-

[a] These interpretive criteria for *Haemophilus influenzae* are applicable only to tests performed using Haemophilus Test Medium inoculated with a direct colony suspension and incubated at 35°C in ambient air for 20 to 24 hours

A report of S ("Susceptible") indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentration usually achievable. A report of I ("Intermediate") indicates that the results should be considered equivocal, and if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone, which prevents small, uncontrolled technical factors from causing major discrepancies in interpretation. A report of R ("Resistant") indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentration usually achievable; other therapy should be considered.

Quality Control

Standardized susceptibility test procedures require the use of quality control microorganisms to control the technical aspects of the test procedures. Standard piperacillin/tazobactam powder should provide the following ranges of values noted in Table 6. Quality control microorganisms are specific strains of microorganisms with intrinsic biological properties relating to resistance mechanisms and their genetic expression within the microorganism; the specific strains used for microbiological quality control are not clinically significant.

TABLE 6
ACCEPTABLE QUALITY CONTROL RANGES FOR PIPERACILLIN/ TAZOBACTAM TO BE USED IN VALIDATION OF SUSCEPTIBILITY TEST RESULTS

	Acceptable Quality Control Ranges	
	Minimum Inhibitory Concentration	Disk Diffusion
QC Strain	Range (MIC in μg/mL)	Zone Diameter Ranges in mm
Escherichia coli ATCC 25922	1-4	24-30
Escherichia coli ATCC 35218	0.5-2	24-30
Pseudomonas aeruginosa ATCC 27853	1-8	25-33
Haemophilus influenzae[a] ATCC 49247	0.06-0.5	33-38
Staphylococcus aureus ATCC 29213	0.25-2	-
Staphylococcus aureus ATCC 25923	-	27–36
Bacteroides fragilis[b] ATCC 25285	0.12-0.5	-
Bacteroides thetaiotaomicron[b] ATCC 29741	4-16	-

[a] This quality control range for *Haemophilus influenzae* is applicable only to tests performed using Haemophilus Test Medium inoculated with a direct colony suspension and incubated at 35°C in ambient air for 20 to 24 hours

[b] The quality control ranges for *Bacteroides fragilis* and *Bacteroides thetaiotaomicron* are applicable only to tests performed using the agar dilution method

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

N/A

6.2 Incompatibilities

Since compatibility studies are not available, this medicinal product should not be mixed with other medicinal products except those indicated in the section 6.6 ("Special precautions for handling and removal").

The mixing of Piperacillin/Tazobactam with an aminoglycoside *in vitro* can result in substantial inactivation of the aminoglycoside. Consequently, the piperacillin/tazobactam combination should not be mixed in the same syringe or in the same infusion bottle with an aminoglycoside or any other compound for which the compatibility with piperacillin/tazobactam has not been established.

Because of chemical instability, the piperacillin/tazobactam combination should not be used with sodium bicarbonate solutions. Lactated Ringer's solution (an isotonic solution) is not compatible with the piperacillin/tazobactam combination.

Since no compatibilities studies are available, Lactated Ringer's solution should not be mixed with the piperacillin/tazobactam combination.

The piperacillin/tazobactam combination should not be added to blood products or albumin hydrolysates.

6.3 Shelf life

Before reconstitution: 3 years.

After reconstitution: the physical and chemical stability of the reconstituted solution has been demonstrated for 48 hours at temperatures ranging from 2°C and 8°C.

However, from a microbiological standpoint, 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 should not be longer than 24 hours including the duration of the treatment and should not normally exceed 24 hours at temperatures between 2°C and 8°C.

6.4 Special precautions for storage

Before reconstitution: Store at temperatures not exceeding 30°C.

After reconstitution: see section 6.3.

6.5 Nature and content of container

2.25 g and 4.5 g of powder for infusion in a vial type I, colourless glass

Box of 10

6.6 Special precautions for handling and removal

Each vial of Piperaciline/Tazobactam Panpharma 2 g/250 mg & 4 g/500 mg should be reconstituted with 10 mL or 20 mL respectively physiological saline solution or sterile water for injections. Reconstitution should be performed with continuous shaking, not exceeding 10 minutes.

The reconstituted solution should then be further diluted in 50 mL or 100 mL of 5% glucose or 0.9% NaCl solution.

However, direct reconstitution/dilution with a transfer set into a 50 or 100 mL bag of 5% glucose solution or 0.9% NaCl solution is possible.

The solution thus obtained should be administered during a 30-minute infusion.

REGISTRATION NUMBER:

Piperacillin/Tazobactam Panpharma 2 g/250 mg: 148 39 33137 00

Piperacillin/Tazobactam Panpharma 4 g/500 mg: 148 38 33136 00

7. MANUFACTURER

PANPHARMA
ZI du Clairay – LUITRE
35133 Fougères
FRANCE

8. IMPORTER & LICENSE HOLDER

PHARMALOGIC LTD
14, AMBER ST
P.O.B. 3838
PETAH-TIKVA

The format of this leaflet was determined by the Ministry of Health and its content was checked and approved in July 2012

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