PRIZMA®

(Piperacillin/Tazobactam)

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Microbiology - Prizma is a new injectable antibacterial medication for intravenous and intramuscular use. Its active ingredients are piperacillin sodium and tazobactam, an irreversible bacterial betalactamase inhibitor.

Piperacillin is a semi-synthetic penicilin belonging to the group of acylureidopenicillins, featuring wide spectrum antibacterial action extending both to gram-positive and to gram-negative bacteria, anaerobes included.

Tazobactam, a penicilin derivative, is a powerful irreversible inhibitor of many bacterial, plasmid and chromosomal beta-lactamases, generally capable of causing resistance to penicillins, and cephalosporins, including third generation cephalosporins. The presence of tazobactam in the combination with piperacillin enhances the drug's wide antibacterial spectrum while extending its antimicrobial activity against a large number of beta-lactamase producing strains of bacteria, including *staphylococci.*

The following pathogens have proved susceptible *in vitro* to the piperacillin/ tazobactam combination:

- Gram-positive beta-lactamase producing and non producing aerobes, such as strains of *streptococci (S. pneumoniae, S. pyogenes, S. bevis, S. agalactiae, S. viridans, C group, G group), enterococci (E. faecalis, E. faecium), Staphylococcus aureus (not methicilin-resistant S. aureus), S. saprophyticus, S epidermidis (coagulase-negative staphylococci), Corynebacterium, Listeria monoocytogenes, Nocardia spp.*
- Gram-negative beta-lactamase producing and non producing aerobes, such as *Escherichia coli, Citrobacter spp. (including C. freundii, C. diversus), Klebsiella spp. (including K. oxytoca, K. pneumoniae), Enterobacter spp. (including E. cloacae, E. aerogenes), Proteus vulgaris, Proteus mirabilis, Providencia rettgeri, Providencia stuarti, Plesiomonas shigelloides.*
- *Shigelladex, Morganella morganii, Serratia spp. (including S. marcescens, S. liquifaciens), Salmonella spp., Shigella spp., Pseudomonas aeruginosa and other Pseudomonas spp. (including P. cepacia, P. fluorescens), Xanthomonas maltophilia, Neisseria gonorrhoeae, Neisseria meningitidis, Moraxella spp. (including Branhamella catarrhalis), Acinetobacter spp., Haemophilus influenzae, H. parainfluenzae, Pasteurella multocida, Yersinia spp., Campylobacter spp., Gardnerella vaginalis.*
- Anaerobes beta-lactamase producing and non producing, such as *Bacteroides spp. (including B. bivius, B. disiens, B. capillosus, B. melaninogenicus, B. oralis), Bacteroides fragilis (including B. fragilis, B. vulgatus, B. distasonis, B. ovatus, B. thetaiotaomicron, B. uniformis, B. asaccharolyticus), as well as Peptostreptococcus spp., Fusobacterium spp., Eubacterium group, Clostridium spp. (including C. difficile, C. perfringens), Veillonella spp. and Actinomyces spp.*

Pharmacokinetic properties

Bioavailability and absorption:

Prizma is completely absorbed immediately following both intravenous and intramuscular administration, becoming 71% (piperacillin) and 84% (tazobactam) bioavailable. Peak plasma concentrations of Prizma are attained immediately after completion of intravenous infusion and 40-50 minutes after intramuscular administration.

Plasma protein binding reaches approx. 30%.

This means a large share of the drug becomes immediately available for distribution into the blood and body tissues, ready to perform its antibacterial activity. In fact, Prizma is widely distributed into all body tissues and fluids, and especially into the intestinal mucosa, the gallbladder, the lungs, bile and bone. Mean tissue concentrations range from 50% to 100% of plasma concentrations.

Excretion:

Prizma is excreted rapidly by the kidneys via glomerular filtration and tubular secretion. A high percentage of the administered dose (69%) is excreted unchanged in the urine.

Patients with renal impairment:

Individuals aged over 12 years

Dosage adjustment is recommended when creatinine clearance is lower than 40 ml/min. Both piperacilin and tazobactam are removed from the body during hemodialysis.

The dosages for dialysis patients are indicated in paragraph Dosage and administration.

Children aged between 2 and 12 years

See paragraph Dosage and administration.

Patients with liver function disorders:

No dosage adjustment is required for patients with liver function disorders.

The half-life of piperacillin and of tazobactam increase by about 25% and 18%, respectively, in patients with cirrhosis of the liver when compared to healthy subjects.

Preclinical safety data

LD_{50} in mice (Intravenously) is 4.5 g for piperacillin and 0.5625 g for tazobactam; the combination drug has not shown any teratogenic effects and has not affected the fertility rates of the animals tested.

No carcinogenic testing was conducted on piperacillin, on tazobactam or on the combination drug.

Prizma was negative in microbial mutagenicity assays. Prizma was negative in the unscheduled DNA synthesis (UDS) test.

Prizma was negative in a mammalian point mutation (Chinese hamster ovary cell HPRIT) assay. Prizma was negative in a mammalian cell (BALB/c-3T3) transformation assay. In vivo, Prizma did not induce chromosomal aberrations in rats dosed intravenously.

INDICATIONS

Prizma is indicated for the treatment of the following infection with proven or suspected presence of susceptible microorganisms: infections of the lower respiratory tract, infections of the urinary tract (complicated and not), Intra-abdominal infections, skin infections, bacterial septicemia, polymicrobial infections. Prizma is indicated for the treatment of mixed bacterial infections including those assumed to be caused by aerobic and anaerobic microorganisms (intra-abdominal, skin, lower respiratory tract).

Although Prizma is indicated only for the specific conditions indicated above, it may also be used for any infections caused by piperacillin-susceptible bacteria without requiring the addition of other antibiotics in presence of ß-lactamase producing organisms.

Prizma is especially useful in the treatment of mixed infections and, because of its wide spectrum of activity, can adequately cover the patient during presumptive therapy while wanting for susceptibility results.

In particular it is indicated for the presumptive monotherapy of infections in adult patients with febrile neutropenia; anyhow, the treatment must be adjusted in function of culture and bacteriological results.

Prizma acts synergistically with aminoglycosides against several strains of Pseudomonas aeruginosa. This combination, that involves the administration of the drugs at full dosage, is effective, especially in immunodepressed patients; anyhow, the treatment must be adjusted in function of culture and bacteriological results.

Children aged under 12 years

In hospitalized children aged between 2 and 12, Prizma is indicated for the treatment of intra-abdominal infections, including appendicitis complicated by rupture or abscess, peritonitis and biliary tract infections. The use of the drug for this indication in children aged under 2 has not been established.

DOSAGE AND ADMINISTRATION

Prizma 2 g/0.250 g may be administered either by intramuscular injection or by intravenous injection or slow Intravenous infusion over 20-30 minutes. Prizma 4 g/0.5 g may be administered only by slow intravenous infusion or phleboclysis.

DOSAGE IN PATIENTS OVER 12 YEARS OF AGE

The usual dosage for adults and for juveniles aged 12 and up with normal renal function is 2 g/0.250 g of piperacillin/tazobactam every 12 hours by intramuscular injection; viaintravenous administration dosage ranges from a minimum of 2 g/0.250 g up to a maximum of 4 g/0.50 g of piperacillin/tazobactam administered every 6, 8 or 12 hours.

When Prizma is used in the presumptive monotherapy of infections in adult patients with febrile neutropenia, the suggested dosage is 4 g/0.50 g of Prizma every 6-8 hours administered intravenously.

HOSPITALIZED CHILDREN WITH INTRA-ABDOMINAL INFECTIONS

In the case of children aged between 2 and 12 years, weighing up to 40 kg and with normal kidney function, the suggested dosage per kilogram of body weight is 100 mg of piperacillin/12.5 mg of tazobactam every 8 hours, administered by slow intravenous infusion.

In the case of children aged between 2 and 12 years, weighing more than 40 kg and with normal kidney function, the suggested daily dosage is 4 g of piperacillin/0.5 g of tazobactam every 8 hours, administered by slow intravenous infusion.

Therapy duration should be adjusted according to infection severity and to the patient's clinical and bacteriological response. It is recommended that the therapy be protracted for at least 5 days, up to a maximum of 14 days, considering that administration should continue for another 48 hours after resolution of all clinical signs and symptoms.

Children aged under 2 years

Since no data are available for children aged under 2 years, Prizma is not recommended for this age group.

Renal insufficiency in subjects aged over 12 years

In patients with renal insufficiency, intravenous administration, and the interval between administrations, must be adjusted based on the degree of residual kidney function. Suggested daily doses are the following:

In patients with renal insufficiency or in hemodialysis, the intravenous dose must be adapted to the degree of insufficiency of renal function.

Creatinine Clearance (ml/min)	Recommended Prizma Dosage
> 40	No dosage adjustment is necessary
20-40	Maximum dosage suggested: 4 g/0.5 g every 8 hours
< 20	Maximum dosage suggested: 4 g/0.5 g every 12 hours

For patients on hemodialysis, the maximum daily dosage is 8 g/1 g of Prizma. Because hemodialysis removes from 30% to 50% of piperacillin in 4 hours, patients on hemodialysis should receive a 2 g/0.250 g vial following each dialysis period.

For patients with renal impairment and renal insufficiency, measurement of serum levels of piperaciin and tazobactam will provide additional guidance for adjusting dosage.

Renal insufficiency in children aged between 2 and 12 years.

Since the pharmacokinetics of piperacillin/tazobactam have not been studied in pediatric patients with renal insufficiency, changes of the dosage indicated in the following table should be considered as purely indicative.

Each patient should be closely monitored for the onset of any signs of drug toxicity. Drug dosage and intervals then should be consequently adjusted.

In general, the following dosage adjustments are recommended for pediatric patients with renal insufficiency aged between 2 and 12 years:

Creatinine Clearance (ml/min)	Recommended dosage of Prizma
> 50 ml/min	100 mg piperacillin/12.5 mg tazobactam)/kg every 8 hours, by slow intravenous infusion
<= 50 ml/min	70 mg piperacillin/8.75 mg tazobactam)/kg every 8 hours, by slow intravenous infusion

Patients with renal impairment

In patients with altered kidney function no dosage adjustment is required.

Duration of therapy

For acute infections, treatment using Prizma should last at least 5 days and should be continued for another 48 hours after resolution of clinical symptoms or fever.

INSTRUCTIONS FOR RECONSTITUTION AND DILUTION

Intravenous administration

Reconstitute the product with the quantity of solvent indicated in the following table, using one of the compatible solutions listed below. Shake until completely dissolved.

Vial content (Piperacillin/tazobactam)	Quantity of solvent
Prizma 2 g/0.250 g	10 ml
Prizma 4 g/0.5 g	20 ml

Compatible solutions

Sterile water for injections, Saline solution, Water/Benzyl alcohol solution for injections, Bacteriostatic saline/Benzyl alcohol solution, Water/Parabens solution for injections, Bacteriostatic saline/Parabens solution, Dextrose 5%.

Pull up into a syringe the diluted solution from the vial. If reconstitution has been carried out as described, the solution in the syringe shall contain the quantity of piperacilin and tazobactam declared on the label.

The reconstituted solution can be further diluted to the required volume (50-150 ml) using a compatible intravenous diluent solution listed below:

Sterile water for injections*, saline solution, Glucose solution 5%, Dextran 6% in saline solution

* Maximum recommended volume of sterile water for injections per dose is 50 ml.

Intramuscular administration

Prizma 2.250 must be reconstituted using 4 ml of a compatible solution.

Incompatibility

Whenever Prizma is to be administered together with other antibiotics (such as aminoglycosides, for example), the drugs should be administered separately.

The *in vitro* admixture of Prizma with an aminoglycoside may cause substantial deactivation of the action of the aminoglycoside. Prizma should not be mixed with other drugs in the same syringe or infusion bottle, since compatibility has not been established. Prizma should not be used with solutions containing sodium bicarbonate alone because of its chemical instability. Prizma and the Ringer lactate solution are not compatible. Prizma should not be added to haematic products or to albumine hydrolysates.

CONTRAINDICATIONS

Hypersensitivity to penicillins, and or cephalosporins and other beta-lactamase inhibitors.

WARNINGS

As with other antibiotics, the prolonged use of penicillins may favor the development of penicillin-resistant microorganisms, including fungi, requiring the adoption of adequate therapy measures. Bleeding manifestations have been occasionally reported in several patients treated with beta-lactam antibiotics. These reactions have sometimes been associated with abnormalities of coagulation tests such as clotting time, platelet aggregation and prothrombin time, and are more likely to occur in patients with renal insufficiency. If bleeding manifestations occur, Prizma should be discontinued and appropriate therapy instituted. Rare cases of pseudomembranous colitis has been observed correlatable to the use of the antibiotic. The symptoms of antibiotic-induced pseudomembranous colitis may be severe and persistent diarrhea that may become life-threatening. The onset of pseudomembranous colitis symptoms may occur during or following antibacterial therapy. It is important to consider this diagnosis in the case of significant diarrhea or colitis during therapy with Prizma. Mild cases usually respond to drug discontinuation. In more severe cases; however, the use of fluids, electrolytes, protein supplements and, if required, treatment with oral vancomycin or oral teicoplanin are recommended. Peristalsis-inhibiting preparations are contraindicated.

Children aged under 2 years

Due to the lack of data concerning children aged under 2 years, the use of Prizma for such patients is not recommended.

PRECAUTIONS

During prolonged high dose therapy, periodic assessments of hematopoietic, kidney and liver function should be performed. This product contains 2.35 mEq (54 mg) of sodium per gram of piperacillin which may contribute in increasing the patient's total sodium intake. Since hypokalemia may occur in patients with low potassium reserves or in patients concomitantly taking potassium-reducing drugs, periodical testing for the electrolyte is recommended. Serious and sometimes fatal hypersensitivity and anaphylactic reactions have been reported in patients treated with penicillins, including piperacillin/tazobactam compounds. These reactions are more likely to occur in individuals with a history of hypersensitivity to multiple allergens, of asthma, hay fever and urticaria. Cross-allergy is possible with penicillin G., semi-synthetic penicillins and cephalosporins. Careful history-taking regarding prior hypersensitivity to penicillins, cephalosporins and other allergens is therefore recommended before starting therapy with piperacillin/ tazobactam. If an allergic reaction occurs, the treatment should be discontinued and appropriate therapy instituted (with vasopressor amines, antihistamines, corticosteroids) or, in the case of anaphylaxis, immediate therapy with adrenaline, epinechrine or other suitable emergency measures. As with other penicillins, in the case of intravenous administration of higher than recommended doses, patients may experience neuromuscular excitability or convulsions. Leukopenia and neutropenia may occur, especially after prolonged therapy.

Therefore, the hemopoietic should be checked frequently.

Use in patients with kidney impairment

In patients with kidney impairment or undergoing dialysis, the intravenous dosage should be adjusted to the degree of kidney insufficiency.

Use during pregnancy and nursing

Studies conducted in rats and mice have not disclosed any evidence for an embryotoxic or teratogenic potential of the piperacillin/tazobactam association. There are, however, no adequate and well-controlled studies with the piperacilin/ tazobactam combination or with piperacillin or tazobactam alone in pregnant women. Piperacillin and tazobactam cross the placenta.

This drug should be used during pregnancy only if the potential benefit justifies the potential risk to the pregnant woman and to the fetus. Piperacillin is excreted in low concentrations into human milk; tazobactam levels in human milk have not been studied. This drug should be used during nursing only if the potential benefit justifies the potential risk to the woman and to the infant.

Effects on ability to drive and use of machinery

The product does not interfere with driving and machine handling capabilities.

Interaction with other drugs

The contemporary administration of Probenecid with piperacillin/tazobactam causes a longer half-life and a lowering of renal clearance both of piperacillin and of tazobactam; however, the plasma concentrations of both drugs remain unaltered. No interactions have been observed between Prizma and Vancomycin or Tobramycin.

During the simultaneous administration of high doses of heparin, oral anti-coagulants and other drugs capable of affecting the blood coagulation system and/or the thrombocyte function, coagulation parameters should be tested more frequently and monitored regularly. When used contemporarily with vecuronium, piperacillin may prolong the neuromuscular blocking action of 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. Piperacillin may reduce the clearance of methotrexate. Serum methotrexate levels should therefore be monitored frequently to prevent methotrexate-induced toxicity.

Interference with laboratory tests and other diagnostic tests

As per other penicillins, the administration of Prizma may cause a false-positive reaction regarding glucose in the urine; this happens when the «reduction of copper test» is used. It is recommended the use of a test for the glucose, based on enzymatic reaction.

SIDE EFFECTS

Side effects are listed by target organs and systems and are subdivided by decreasing order of frequency as follows:

Very common: reactions occurring with a frequency >= 10%

Common: reactions occurring with a frequency >= 1 %

Uncommon: reactions occurring with a frequency >= 0.1 % to < 1 %

Rare: reactions occurring with a frequency >= 0.01 % to < 0.1 %

Very rare: reactions occurring with a frequency < 0.01 %

Infections and infestations

- Uncommon: superinfection by Candida.

Blood and lymphatic system

- Uncommon: leukopenia, neutropenia, thrombocytopenia.
- Rare: anemia, bleeding events (including purpura, epistaxis, prolongation of bleeding time), eosinophilia, hemolytic anemia.
- Very rare: agranulocytosis, positive direct Coombs test, protracted partial thromboplastin time, protracted prothrombin time, thrombocytosis.

Immune system disorders

- Uncommon: hypersensitivity reactions.
- Rare: anaphylactic/anaphylactoid (including shock) reactions.

Metabolic and nutritional disorders

- Very rare: decrease in blood albumin, decreased glycemia, decreased total blood protein, hypokalemia.

Nervous system disorders

- Uncommon: headache, insomnia.

Vascular affections

- Uncommon: hypotension, phlebitis, thrombophlebitis.
- Rare: flushing.

Gastro-intestinal affections

- Common: diarrhea, nausea, vomiting.
- Uncommon: constipation, dyspepsia, jaundice, stomatitis.
- Rare: stomach pain, pseudomembranous colitis.

Hepato-biliary disorders

- Uncommon: increased alanine aminotransferase, increased aspartate aminotransferase.
- Rare: increased bilirubin, increased blood alkaline phosphatase, increased gammaglutamyltransferase.

Cutaneous and subcutaneous disorders

- Common: rash.
- Uncommon: itching, urticaria.
- Rare: pemphigus, multiform erythema.
- Very rare; Stevens-Johnson syndrome, toxic epidermal necrolysis.

Musculoskeletal connective tissue and bone disorders

- Rare: arthralgia.

Kidney and urinary disorders

- Uncommon: increased blood creatinine.
- Rare: interstitial nephritis, kidney failure.
- Very rare: increased uremia.

General and injection site disorders

- Uncommon: fever, reaction at injection site.
- Rare: rigidity.

Therapy with piperacillin has been associated with increased occurrence of fever and rash in patients suffering from cystic fibrosis.

OVERDOSAGE

There have been post marketing reports of overdose with Prizma. 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 conditions. Excessive serum concentrations of either piperacillin or tazobactam may be reduced by hemodialysis.

STORAGE

Store below 25°C. After reconstitution using the appropriate solvent, the solutions for intravenous and intramuscular use are stable for 24 hours if stored at room temperature and for up to 48 hours if refrigerated (2-8°C). Unused solutions must be discarded.

PRESETATIONS

Vials

PRIZMA 4 g/0.5 g: Piperacillin sodium (equiv. to piperacillin 4 g) 4170 mg and Tazobactam sodium (equiv. to tazobactam 500 mg) 536.6 mg

PRIZMA 2 g/0.25 g: Piperacillin sodium (equiv. to piperacillin 2 g) 2085 mg and Tazobactam sodium (equiv. to tazobactam 250 mg) 268.3 mg

THIS IS A MEDICAMENT

- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous.
- Follow the doctor's prescription strictly, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are experts in medicine, its benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.

Keep medicament out of the reach of children

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