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Package Insert

AUROTAZ-P Powder for Injection

Piperacillin and Tazobactam Powder for Injection 4.5 g

NAME OF DRUG PRODUCT : Piperacillin and Tazobactam Powder for Injection 4.5 g.
(TRADE) NAME OF PRODUCT : AUROTAZ-P Powder for Injection 4.5 g
STRENGTH : 4.5 g.

PHARMACEUTICAL DOSAGE FORM: Injection

QUALITATIVE AND QUANTITATIVE COMPOSITIONS:

Piperacillin and Tazobactam Powder for Injection 4.5 g
Each vial Contains:
Piperacillin Sodium equivalent to Piperacillin 4.0 g and Tazobactam Sodium equivalent to Tazobactam 0.50 g.

PHARMACEUTICAL FORM:

For dry powder: White to off white crystalline powder.
For reconstituted solution: Colourless to light yellow coloured clear solution.

CLINICAL PARTICULARS

Therapeutic Indications

Treatment of the following systemic and/or local bacterial infections in which susceptible organisms have been detected or are suspected: Lower respiratory tract infections; urinary tract infections (complicated and uncomplicated); intra-abdominal infections; skin and skin structure infections; bacterial septicaemia.

Polymicrobial infections including those where aerobic and anaerobic organisms are suspected (intra-abdominal, skin and skin structure, lower respiratory tract).

Piperacillin and Tazobactam, in combination with an aminoglycoside, is indicated for bacterial infections in neutropenic adults or children.

Posology and method of administration

Piperacillin and tazobactam may be given by slow intravenous injection (over at least 3-5 minutes) or by slow intravenous infusion (over 20-30 minutes).
Neutropenic patients with signs of infection (e.g. fever) should receive immediate empirical antibiotic therapy before laboratory results are available.

Adults and Children > 12 years

The usual dosage for adults and children over 12 years is 4.5 g piperacillin and tazobactam (4g piperacillin /500 mg tazobactam) given every 8 hours.

The total daily dose of piperacillin and tazobactam depends on the severity and localisation of the infection and can vary from 2.25 g (2 g piperacillin / 250 mg tazobactam) to 4.5 g (4 g piperacillin/ 500 mg tazobactam) administered every 6 or 8 hours.

In neutropenia the recommended dose is 4.5 g (4 g piperacillin / 500 mg tazobactam) given every 6 hours in combination with an aminoglycoside.

Paediatric Neutropenia: Children with Normal Renal Function and <50 kg: Dose should be adjusted to 80 mg piperacillin/10 mg tazobactam per kg administered every 6 hrs, in combination with the appropriate dose of an aminoglycoside. For children weighing >50 kg, follow the adult dosing, in combination with the appropriate dose of an aminoglycoside.

Children <12 years: Piperacillin and Tazobactam is only recommended for the treatment of children with neutropenia.

Children Weighing >50 kg: Follow adult dosing guidance, including the aminoglycoside.

Children with Normal Renal Function and Weighing <50 kg: Dose should be adjusted to 90 mg/kg (80 mg piperacillin/10 mg tazobactam) administered every 6 hrs in combination with an aminoglycoside.

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

Elderly: Piperacillin and tazobactam may be used at the same dose levels as adults except in cases of renal impairment.

Renal Insufficiency in Adults and Children Weighing >50 kg: In adult patients and children weighing >50 kg with renal insufficiency, the IV dose should be adjusted to the degree of actual renal impairment. The suggested daily doses are as follows:

IV Dosage Schedule for Adults and Children >50 kg with Impaired Renal Function	
Creatinine Clearance (mL/min)	Recommended Piperacillin/Tazobactam Dosage
20-80	12 g/1.5 g/day in divided doses of 4 g/500 mg every 8 hrs
<20	8 g/1 g/day in divided doses of 4 g/500 mg every 12 hrs

Patients on Haemodialysis: Maximum daily dose is 8 g/1 g piperacillin/tazobactam. In addition, because haemodialysis removes 30-50% of piperacillin in 4 hrs, 1 additional dose of 2 g/250 mg piperacillin/tazobactam should be administered following each dialysis period. For patients with renal failure and hepatic insufficiency, measurement of serum levels of piperacillin and tazobactam will provide additional guidance for adjusting dosage.

Renal Insufficiency in Adults and Children Weighing <50 kg: In adults and children weighing <50 kg with renal insufficiency, the IV dose should be adjusted to the degree of actual renal impairment. The IV dosage should be adjusted to the degree of actual renal impairment as follows:

IV Dosage Schedule for Children <50 kg with Impaired Renal Function	
Creatinine Clearance (mL/min)	Recommended Piperacillin/Tazobactam Dosage
40-80	90 mg (80 mg piperacillin/10 mg tazobactam)/kg every 6 hrs
20-40	90 mg (80 mg piperacillin/10 mg tazobactam)/kg every 8 hrs
<20	90 mg (80 mg piperacillin/10 mg tazobactam)/kg every 12 hrs

Children Weighing <50 kg on Haemodialysis: Recommended Dose: 45 mg/kg every 8 hrs.

The pharmacokinetics of piperacillin and tazobactam have not been studied in pediatric patients with renal impairment. Each patient must be monitored closely for signs of drug toxicity. Drug dose and interval dose should be adjusted accordingly. In patients with renal insufficiency or hemodialysis patients, IV dosages and administration intervals should be adjusted to the degree of renal function impairment.

Duration of Therapy

Therapy is recommended to be a minimum of 5 days and maximum of 14 days, considering that dose administration should continue at least 48 hrs after the resolution of clinical signs and symptoms or fever.

Contraindications

Patients with a history of allergic reactions to any of the penicillins and/or cephalosporins or beta-lactamase inhibitors.

Special warnings and precautions for use

Warnings

Serious and occasionally fatal hypersensitivity reactions (including anaphylactoid and severe cutaneous adverse reactions) have been reported in patients receiving therapy with beta-lactams. Before initiating therapy with Piperacillin and Tazobactam, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, carbapenems or other beta-lactam agents. If an allergic reaction occurs, Piperacillin and Tazobactam must be discontinued immediately and appropriate alternative therapy instituted.

Serious anaphylactic/ anaphylactoid reactions (including shock) require immediate emergency treatment with epinephrine. Oxygen, intravenous steroids and airway management eg, intubation, should also be administered as indicated.

Pseudomembranous colitis may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by Clostridium difficile is one primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against Clostridium difficile colitis.

Haemophagocytic lymphohistiocytosis (HLH)

Rare cases of haemophagocytic lymphohistiocytosis (HLH) have been observed following therapy (>10 days) with Piperacillin, often as a complication of DRESS. HLH is a pathologic immune activation which leads to excessive systemic inflammation and can be life-threatening and early diagnosis and rapid initiation of immunosuppressive therapy is essential. Characteristic signs and symptoms include fever,hepatosplenomegaly, cytopenias, hyperferitinaemia, hypertriglyceridaemia, hypofibrinogenaemia, and haemophagocytosis. If Piperacillin is suspected as possible trigger, treatment should be discontinued.

Precautions

Bleeding manifestations occurs in some patients receiving beta-lactam antibiotics, including piperacillin. These reactions sometimes may associate with abnormalities of coagulation tests eg, clotting time, platelet aggregation and prothrombin time and are more likely to occur in patients with renal failure. If bleeding manifestations occur, Piperacillin and Tazobactam Powder for Injection should be discontinued and appropriate therapy instituted.

Piperacillin and Tazobactam Powder for Injection contains 2.79 mEq (64 mg) of sodium/g of piperacillin which may increase a patient's overall sodium intake. Hypokalemia may occur in patients with low potassium reserves or who are receiving concomitant medications that may lower potassium levels; periodic electrolyte determinations may be advisable in such patients.

The possibility of the emergence of resistant organisms that might cause superinfections should be taken 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 IV (particularly in the presence of renal failure).

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 IV dose should be adjusted to the degree of renal function impairment.

Prescribing 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.

Leukopenia and neutropenia may occur, especially during prolonged therapy. Therefore, periodic assessment of hematopoietic function should be performed.

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

Use in the elderly: Patients >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.

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 and tazobactam contains 64 mg (2.79 mEq) of sodium per gram of piperacillin in the combination product. At the usual recommended doses, patients would receive between 768 and 1024 mg/day (33.5 and 44.6 mEq) of sodium. The geriatric population may respond with a blunted natriuresis to salt loading. This may be clinically important with regard to diseases eg, 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.

Interaction with other medicinal products and other forms of interaction

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 drug are unaffected.

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 and 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 and tazobactam prolongs the half-life of piperacillin by 21% and that of tazobactam by 71%.

Vancomycin: No pharmacokinetic interactions have been noted between piperacillin and tazobactam 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 and 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.

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.

A/s : 210 x 360 mm ■ Black

eugia Packaging Development		Product Name	Component	Item Code	Date & Time
		Aurotaz-P	Leaflet_SPC	P1540962	13.07.2026 & 12:10 PM
		Customer / Country	Version No.	Reason Of Issue	Reviewed / Approved by
Malaysia_SEZ (Tender)	02	Submission			
Team Leader	Sivakumar	Dimensions	No. of Colours : 01		
Initiator	Jitendra	210 x 360 mm			
Artist:	ision Graphic Designers	Pharmacode			
		40962			
Additional Information :					Sign / Date

Incompatibilities: Whenever piperacillin and tazobactam is used concurrently with another antibiotic, the drug must be administered separately. The mixing of piperacillin and tazobactam with an aminoglycoside in vitro can result in substantial inactivation of the aminoglycoside.

Due to the in vitro inactivation of the aminoglycoside by the beta-lactam antibiotics, piperacillin/ tazobactam and the aminoglycoside are recommended for separate administration. Piperacillin/tazobactam and the aminoglycoside should be reconstituted and diluted separately when concomitant therapy with aminoglycoside is indicated.

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

Because of chemical instability, piperacillin and tazobactam should not be used in solutions containing only sodium bicarbonate.

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

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

Pregnancy and lactation

Piperacillin and tazobactam cross the placenta in humans. Pregnant women should be treated only if the expected benefit outweighs the possible risks to the pregnant woman and fetus.

Piperacillin is excreted in low concentrations in human milk; Tazobactam concentrations in human milk have not been studied. Caution should be exercised when Piperacillin and Tazobactam Powder for Injection is administered to a nursing woman.

Effects on ability to drive and use machines

Piperacillin and Tazobactam is not known to affect ability to drive or operate machines.

Undesirable effects

Diarrhoea, skin rashes, occasionally platelet mediated bleeding, rigors, malaise, ulcerative stomatitis. Injection site reactions such as pain, erythema, induration and thrombophlebitis. **Potentially Fatal:** Serious, anaphylactic reactions.

Overdosage

Overdosage includes nausea, vomiting and diarrhea with the usual recommended dosages. Patients may experience neuromuscular excitability or convulsions if higher than recommended doses are given IV (particularly in the presence of renal failure).

Treatment: 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.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

Piperacillin and Tazobactam Powder for Injection is an injectable antibacterial combination product consisting of the semisynthetic antibiotic piperacillin sodium and the beta-lactamase inhibitor tazobactam sodium for IV administration.

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

Piperacillin/tazobactam has been shown to be active against most strains of the following microorganisms.

Aerobic and Facultative Gram-Positive Microorganisms: *Staphylococcus aureus* (excluding methicillin- and oxacillin-resistant isolates).

Aerobic and Facultative Gram-Negative Microorganisms: *Acinetobacter baumani*, *Escherichia coli*, *Haemophilus influenzae* (excluding beta-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).

At least 90% of the following microorganisms exhibit minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for piperacillin/tazobactam.

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**.

Note: *These are not beta-lactamase-producing bacteria and, therefore, are susceptible to piperacillin alone.

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*.

MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds.

Pathogen	Minimal InhibitoryConcentration (MIC in mcg/mL)		
	Susceptible	Intermediate	Resistant
<i>Enterobacteriaceae</i> and <i>Acinetobacter baumani</i>	≤ 16	32-64	≥ 128
	≤ 1	-	≥ 2
	≤ 64	-	≥ 128
	≤ 8	-	≥ 16
	≤ 32	64	≥ 128
<i>Haemophilus influenzae</i>			
<i>Pseudomonas aeruginosa</i>			
<i>Staphylococcus aureus</i>			
<i>Bacteroides fragilis</i> group			

Pharmacokinetics: Peak plasma concentrations of piperacillin and tazobactam are attained immediately after completion of an IV infusion of piperacillin and tazobactam. Piperacillin plasma concentrations, following a 30-min infusion of piperacillin and tazobactam, were similar to those attained when equivalent doses of piperacillin were administered alone.

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 50-100% 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 <20 mL/min, the increase in half-life is 2-fold for piperacillin and 4-fold for tazobactam compared to subjects with normal renal function. Dosage adjustments

for piperacillin and tazobactam are recommended when creatinine clearance is <40 mL/min in patients receiving the usual recommended daily dose of Piperacillin and Tazobactam Powder for Injection.

Hemodialysis removes 30-40% 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.

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 and tazobactam due to hepatic cirrhosis.

PHARMACEUTICAL PARTICULARS

List of excipients

None.

Incompatibilities

Whenever piperacillin and tazobactam is used concurrently with another antibiotic, the drug must be administered separately. The mixing of piperacillin and tazobactam with an aminoglycoside in vitro can result in substantial inactivation of the aminoglycoside.

Due to the *in vitro* inactivation of the aminoglycoside by the beta-lactam antibiotics, piperacillin/tazobactam and the aminoglycoside are recommended for separate administration. Piperacillin/tazobactam and the aminoglycoside should be reconstituted and diluted separately when concomitant therapy with aminoglycoside is indicated.

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

Because of chemical instability, piperacillin and tazobactam should not be used in solutions containing only sodium bicarbonate.

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

Piperacillin and Tazobactam should not be added to blood products or albumin hydrolysates.

Directions for Use:

Intravenous Injection

Each vial of Piperacillin and Tazobactam Powder for Injection 4.5 g should be reconstituted with 20 ml of one of the following diluents:

- Sterile Water for Injection
- 0.9% Sodium Chloride for Injection
- 5% Dextrose

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

Intravenous Infusion

Each vial of Piperacillin and Tazobactam Powder for Injection 4.5 g should be reconstituted with 20 ml of one of the above diluents.

The reconstituted solution should be further diluted to at least 50 ml with one of the reconstitution diluents.

Instruction for inserting the needle into the rubber stopper:

In order to avoid a coring phenomenon of the plug, when inserting the needle into the rubber stopper, it is recommended to use a needle of outside diameter less than or equal to 0.8 mm(21 gauge) for the reconstitution of the product

Needle should be inserted only at the centre of the rubber stopper, in vertical direction.

Shelf life

24 months.

Special precautions for storage

Store in a dry place below 30°C.

To reduce the risk of microbial contamination Piperacillin and Tazobactam should be used immediately.

After reconstitution with SWFI or 5% Dextrose under aseptic conditions, store at room temperature (15 - 30°C) and to be used within 24 hours or store in a refrigerator at 2-8°C and to be used within 48 hours.

After reconstitution with 0.9% NaCl under aseptic conditions, store at room temperature (15 - 30°C) and to be used immediately, store in a refrigerator at 2-8°C and to be used within 48 hours.

Nature and contents of container:

Piperacillin and Tazobactam Powder for Injection 4.5 g:

Mono vial and 10's vial without Sterile Water for Injection.

MAL No. MAL16045059AZ

Manufactured by:

Eugia SEZ Private Limited,
Plot No.: S-5/B, S-6 & S-7, Sy. No.: 408 to 412, 418 to 435,
437 to 445, 452 to 459, TSIIC, SEZ, Polepalle Village,
Jadcherla Mandal, Mahabubnagar District,
Telangana State, India.

Product registration holder:

Healol Pharmaceuticals Sdn. Bhd.,
74-3, Jalan Wangsa Delima 6,
KLSC Wangsa Maju,
53300 Kuala Lumpur,
Malaysia.

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