AKUMS DRUGS & PHARMACEUTICALS LTD. AND ITS SUBSIDIARIES
HARIDWAR
CORPORATE PACKAGING DEVELOPMENT
FORMAT FOR APPROVAL OF ARTWORK

Direction of Grain

Commercial Order
Insert Specification : 60 ± 15% GSM Maplitho paper with 2 horizontal and 2 vertical fold as equal distance.
Reason of artwork : Shelf life change 24 to 36 months (EXPORT) R2
Insert Size: L (120) x H (330) mm
Insert folded size: L (30) x H (82.5) mm
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License F. No.: 17P/1/176/2006/6876 on dated: 10/09/2014
Country : Unosource Pharma Ltd. (Tanzania)
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FRONT SIDE

330 mm

For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only.

Piperacillin and Tazobactam for Injection USP

(Combipack with Sterile Water for Injection USP)

TAZOGARD

COMPOSITION
Each combipack contains:
(a) 1 vial of Piperacillin and Tazobactam for Injection USP
Each vial contains :

Piperacillin Sodium USP (Sterile) eq. to Piperacillin	4000 mg
Tazobactam Sodium (Sterile) eq. to Tazobactam	500 mg

(b) 2 Ampoules of Sterile Water for Injection USP
Each ampoule contains:
Sterile Water for Injection USP 10ml

PHARMACOLOGY
Pharmacodynamics
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 beta-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 chromo-somally-mediated beta-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.

Aerobic and facultative Gram-positive microorganisms:
Staphylococcus aureus (excluding methicillin and oxacillin-resistant isolates)

Aerobic and facultative Gram-negative microorganisms:
Acinetobacter baumannii

Escherichia coli
Haemophilus influenzae (excluding beta-lactamase negative, ampicillin resis-tant 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)*

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

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.

INDICATIONS
TAZOGARD injection is indicated for the treatment of patients with moderate to severe infections caused by Piperacillin-resistant, Piperacillin/ Tazobactam susceptible, beta-lactamase producing strains of the designated microorganisms in the specified conditions listed below:

Appendicitis (complicated by rupture or abscess) and peritonitis caused by Piperacillin-resistant, beta-lactamase producing strains of *Escherichia coli* or the following members of the *Bacteroides fragilis* group: *B. fragilis, B. ovatus, B. thetaiotaomicron,* or *B. vulgatus*.

Uncomplicated and complicated skin and skin structure infections, including cellulitis, cutaneous abscesses and ischemic/diabetic foot infections caused by Piperacillin-resistant, beta-lactamase producing strains of *Staphylococcus aureus*.

Postpartum endometritis or pelvic inflammatory disease caused by Piperacillin resistant, beta-lactamase producing strains of *Escherichia coli*.

Community-acquired pneumonia (moderate severity only) caused by Piperacillin resistant, beta-lactamase producing strains of *Haemophilus influenzae*.

Nosocomial pneumonia (moderate to severe) caused by Piperacillin-resistant, beta lactamase producing strains of *Staphylococcus aureus* and by Piperacillin/ Tazobactam susceptible.

DOSAGE AND ADMINISTRATION
TAZOGARD injection should be administered by intravenous infusion over 30 minutes.

Adults: The usual total daily dose of **TAZOGARD** Injection is every six hours or as directed by physician.

Pediatrics
TAZOGARD injection can be administered in pediatric patients from 2 months of age. The dosage and the indications in pediatric patients with normal renal function are as follows:

Age of pediatric patients	Infection/indication	Recommended Dosage
2 months and 9 months of age	Community-acquired pneumonia Intra-abdominal infections (appendicitis and/ or peritonitis), Uncomplicated and complicated skin and skin structure infections, Pelvic inflammatory disease. 8hr	80 mg Piperacillin/10 mg Tazobactam per kg q 8hr
9 months or older weighing upto 40 kg		100mg Piperacillin/12.5 mg Tazobactam per kg q
Weighing over 40 kg	Nosocomial pneumonia	3.375 gm Injection4.5 q 6hr (12.0gm Piperacillin/1.5gm Tazobactam per day)
		4.5 gm Injection 4.5 q 6hr (16.0gm Piperacillin /2.0gm Tazobactam per day) + aminoglycoside

120 mm

BACK SIDE

Duration of Therapy
The usual duration of **TAZOGARD** injection treatment is from seven to ten days. However, the recommended duration of **TAZOGARD** injection 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.

Pediatrics
There are no dosage recommendations for Piperacillin/Tazobactam in pediatric patients with impaired renal function.

CONTRAINDICATIONS
TAZOGARD injection is contraindicated in patients with a history of allergic reactions to any of the penicillins, cephalosporins, or beta-lactamase inhibitors.

WARNINGS AND PRECAUTIONS
Before initiating therapy with **TAZOGARD** injection, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, or other allergens since serious and occasionally fatal hypersensitivity (anaphy-lactic) reactions have been reported in patients on penicillin therapy. If an allergic reaction occurs, **TAZOGARD** injection should be discontinued and appropriate therapy instituted.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including Piperacillin/Tazobactam, and may range in severity from mild to life threatening.

Therefore, it is important to consider this diagnosis in patients who present with diarrhoea subsequent to the administration of antibacterial agents.

Mild cases of pseudomembranous colitis usually respond to drug dis-continuation 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.

Bleeding manifestations have occurred in some patients receiving beta-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, **TAZOGARD** injection should be discontinued and appropriate therapy instituted.

Drug Interactions
Aminoglycosides : The mixing of Piperacillin/Tazobactam with an amino-glycoside *in vitro* can result in substantial inactivation of the aminoglycoside. The Aminoglycoside should be reconstituted and administered separately.

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

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

Vecuronium : Piperacillin when used concomitantly with vecuronium has been implicated in the prolongation of the neuromuscular blockade of vecuronium.

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.

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.

Pregnancy
Reproduction studies performed in animals 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).

Lactation
Piperacillin is excreted in low concentrations in human milk; Tazobactam concentrations in human milk have not been studied. Caution should be exercised when **TAZOGARD** injection is administered to a nursing woman.

Pediatric Use
Safety and efficacy in pediatric patients less than 2 months of age have not been established.

Geriatric Use
Patients over 65 years are not an increased risk of developing adverse effects solely because of age. However, dosage should be adjusted in the presence of renal insufficiency.

UNDESIRABLE EFFECTS
90% of the adverse events reported in clinical trials were mild-moderate in severity and transient in nature.

The common adverse events were:
- Skin rashes (1.3%) including rash and pruritis
- Gastrointestinal (0.9%) including diarrhea, nausea and vomiting
- Allergic reactions (0.5%)

OVERDOSAGE
There have been post marketing reports of overdose with Piperacillin/ Tazobactam. The majority of those events experienced, including nausea, vomiting, and diarrhoea, have also been reported with the usual recommended 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 the patient's clinical presentation. Excessive serum concentrations of either Piperacillin or Tazobactam may be reduced by haemodialysis. Following a single 3.375 g dose of Piperacillin/Tazobactam, the percentage of the Piperacillin and Tazobactam dose removed by haemodialysis was approximately 31% and 39%, respectively.

SHELF LIFE
36 Months

STORAGE AND HANDLING INSTRUCTIONS
Do not store above 30°C. Protect from light & moisture. Do not freeze.

Prior to constitution:
Dissolve the contents of vial in 20 ml of Sterile Water for Injection USP.
The constituted solution should be used immediately after preparation.

Keep out of reach of children.

PRESENTATION
TAZOGARD INJECTION IN A 4.5G VIAL.

Product From
Unosource Pharma Ltd.

Manufactured by:
Akums Drugs & Pharmaceuticals Ltd.
2,3,4 & 5, Sector-6B, I.I.E., SIDCUL,
Ranipur, Haridwar-249 403, INDIA.

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