COMPOSITION
Tazocin™ 4.5 IV infusion: Each vial contains Sterile Lysophospholipid Piperacillin and Tazobactam for Injection USP equivalent to Piperacillin 4.0 gm as Piperacillin Sodium and Tazobactam 0.5 gm as Tazobactam Sodium.

PHARMACOLOGY
Pharmacodynamic properties: Piperacillin, a broad spectrum, semi-synthetic penicillin active against many gram-positive and gram-negative aerobic and anaerobic bacteria, exerts bactericidal activity by inhibition of both septum and cell wall synthesis. Tazobactam is a potent inhibitor of many beta-lactamases, including the plasmid and chromosomally mediated enzymes that commonly cause resistance to penicillins. The presence of Tazobactam in the Tazocin™ 4.5 IV infusion enhances and extends the antibiotic spectrum of Piperacillin to include many beta-lactamase producing bacteria normally resistant to it. Thus, Tazocin™ 4.5 IV infusion combines the properties of a broad-spectrum antibiotic and a beta-lactamase inhibitor.

Pharmacokinetic properties: Plasma levels in adults after a thirty-minute intravenous infusion of Piperacillin/Tazobactam (steady state)

- Piperacillin plasma levels (μg/ml)
  - Dose: 4 g/500 mg
    - 30 min: 1 hr 1.5 hr 2 hr 3 hr 4 hr
    - 208: 141 87 47 16 7
- Tazobactam plasma levels (μg/ml)
  - Dose: 4 g/500 mg
    - 30 min: 1 hr 1.5 hr 2 hr 3 hr 4 hr
    - 33.8: 17.3 11.7 6.8 2.8 1.3

*Completion of 30 minutes infusion
In healthy subjects Piperacillin/Tazobactam plasma elimination half lives range from 0.7 to 1.2 hours following single or multiple doses. These half-lives are unaffected by dose or duration of infusion. Plasma protein binding of Piperacillin and Tazobactam are 21% and 23% respectively. Piperacillin and Tazobactam are widely distributed in tissues and body fluids including intestinal mucosa, gall bladder, lung and bile. Piperacillin and Tazobactam are eliminated by the kidney via glomerular filtration and tubular secretion. Piperacillin is excreted rapidly as unchanged drug, with 69% of the dose appearing in the urine. Piperacillin is also secreted into bile. Tazobactam and its metabolite are eliminated primarily by renal excretion, with 80% of the dose appearing as unchanged drug and the remainder of the dose appearing as the metabolite.

INDICATION
Tazocin™ 4.5 IV infusion is indicated for the treatment of the following systemic and/or local bacterial infections:
1. Nosocomial pneumonia (moderate to severe)
2. Community-acquired pneumonia (mild to moderate)
3. Uncomplicated and complicated skin and skin structure infections, including cellulitis, cutaneous abscesses and septic/cystic/diabetic foot infections
4. Postpartum endometritis or pelvic inflammatory disease
5. Appendicitis (complicated by rupture or abscess) and peritonitis

Tazocin™ 4.5 IV Infusion may also be used in the management of neutropenic patients (adults, adolescents and children) with fever suspected to be due to bacterial infections.

DOSE AND ADMINISTRATION
Piperacillin/Tazobactam may be given by slow intravenous infusion (over 20-30 minutes).

- Adults, Elderly and Children Over 12 Years
  - The usual dosage for adults and children over 12 years of age is Piperacillin/Tazobactam 4,000/500 mg given every eight hours. The total daily dose of Piperacillin/Tazobactam depends on the severity and localisation of the infection and can vary from Piperacillin/Tazobactam 2,000/250 mg to 4,000/500 mg administered every six or eight hours. In neutropenia the recommended dose is Piperacillin/Tazobactam 4,000/500 mg given every six hours in combination with an aminoglycoside.

- Renal Insufficiency in Adults, Elderly and Children (over 40 kg)
  - In patients with renal insufficiency, the intravenous dose should be adjusted as following:

<table>
<thead>
<tr>
<th>Creatinine Clearance (ml/min)</th>
<th>Recommended Piperacillin/Tazobactam Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total Dosed Division Dosed</td>
</tr>
<tr>
<td>20 - 80</td>
<td>12/1.5 g/day</td>
</tr>
<tr>
<td>20 - 80</td>
<td>4,000/500 mg 8 hourly</td>
</tr>
<tr>
<td>&lt; 20</td>
<td>8/1 g/day</td>
</tr>
<tr>
<td>&lt; 20</td>
<td>4,000/500 mg 12 hourly</td>
</tr>
</tbody>
</table>

For patients on haemodialysis, the maximum daily dose is Piperacillin/Tazobactam 8,000/1,000 mg. In addition, because haemodialysis removes 30%-50% of Piperacillin in four hours, one additional dose of Piperacillin/Tazobactam 2,000/250 mg should be administered following each dialysis period.

- Children Aged 2 to 12 Years with Normal Renal Function
  - The usual recommended dosage is Piperacillin/Tazobactam 4,000/500 mg every six hours.

- Renal Insufficiency in Children Aged 2-12 Years (or body weight less than 40 kg)
  - In children with renal insufficiency, the intravenous dosage should be adjusted as following:

<table>
<thead>
<tr>
<th>Creatinine Clearance (ml/min)</th>
<th>Recommended Piperacillin / Tazobactam Dosage</th>
<th>Frequency</th>
<th>Maximum Daily Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>40</td>
<td>No adjustment necessary</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20-39</td>
<td>90 mg (Piperacillin / Tazobactam 80/10 mg) / kg</td>
<td>8 hourly</td>
<td>12/1.5 g daily</td>
</tr>
<tr>
<td>&lt; 20</td>
<td>90mg (Piperacillin / Tazobactam 80/20 mg) / kg</td>
<td>12 hourly</td>
<td>8/1 g daily</td>
</tr>
</tbody>
</table>

For children weighing <30 kg on haemodialysis the recommended dose is 45mg (Piperacillin / Tazobactam 40/5 mg/kg) every eight hours. The above dosage modifications are only an approximation. Each patient should be monitored closely for signs of drug toxicity. Drug dose and interval should be adjusted accordingly.

Tazocin™ 4.5 IV infusion is not recommended for use in children below 2 years old due to insufficient data on safety.

Hepatic Impairment: No dose adjustment is necessary.

Duration of Therapy: The duration of therapy should be guided by the severity of the infection and the patient's clinical and bacteriological progress. In acute infections, treatment with Piperacillin/Tazobactam should be continued for 48 hours beyond the resolution of clinical symptoms or the fever.

Preparation of the solution for IV infusion: Please see the inner carton.

CONTRAINDICATION
- Hypersensitivity to Piperacillin or any of the beta-lactam antibiotics and to Tazobactam or any other beta-lactamase inhibitor.

PREGNANCY AND LACTATION
- There are no adequate and well-controlled studies with Piperacillin/Tazobactam in combination or with Piperacillin or Tazobactam alone in pregnant women. Piperacillin/Tazobactam should only be used during pregnancy if clearly indicated.

Piperacillin is excreted in low concentrations in breast milk. Women who are breast-feeding should be treated only if clearly indicated. Diarrhoea and fungal infections of the mucous membranes as well as sensitization could occur in the breast-fed infant.

SIDE EFFECT
- Nausea, vomiting, diarrhoea; less commonly stomatitis, dyspepsia, constipation, jaundice, hypotension, headache, insomnia, and injection-site reactions; rarely abdominal pain, hepatitis, oedema, fatigue, and eosinophilia; very rarely hypoglycaemia, hypokalaemia, pancytopenia, Stevens-Johnson syndrome, and toxic epidermal necrolysis

DRUG INTERACTION
- Interaction with Probenecid: Concurrent administration of Probenecid and Piperacillin/Tazobactam produced a longer half-life and lower renal clearance for both Piperacillin and Tazobactam. However, peak plasma concentrations of either drug are unaffected.

- Interaction with anti-coagulants:
  - During simultaneous administration of heparin, oral anticoagulants and other drugs which may affect the blood coagulation system including thromboctye function, appropriate coagulation tests should be performed more frequently and monitored regularly.

- Interaction with vecuronium:
  - Piperacillin when used concomitantly with Vecuronium has been implicated in the prolongation of the neuromuscular blockade of vecuronium. Due to their similar mechanism of action, it is expected that the neuromuscular blockade produced by any of the non-polarizing muscle relaxants could be prolonged in the presence of Piperacillin. This should be taken into account when Piperacillin/Tazobactam is used peri-operatively.

- Interaction with methotrexate:
  - Piperacillin may reduce the excretion of methotrexate. Serum levels of methotrexate should be monitored in patients on methotrexate therapy.

OVERDOSE
- 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).

STORAGE
- When reconstituted with water for injections or saline, reconstituted solutions will remain stable for 24 hours at 25°C and for 48 hours at 4°C. From a microbiological point of view, once opened, the product should be used immediately. If not used immediately, in use-storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2-8°C, unless reconstitution has taken place in controlled and validated aseptic conditions.

HOW SUPPLIED
- Tazocin™ 4.5 IV infusion: Each vial contains one vial of Tazocin™ 4.5 IV infusion and 1 bag of 100 ml normal saline (Solo), one disposible syring (20 ml), one infusion set, one butterfly needle, one alcohol prep pad, and one first aid band.

Manufactured by:
SQUARE PHARMACEUTICALS LTD. BANGLADESH
TM-Trade Mark