Tazocilin™

Piperacillin & Tazobactam

COMPOSITION

Tazocilin™ 2.25 IV infusion: Each vial contains sterile powder of Piperacillin & Tazobactam for Injection USP equivalent to Piperacillin 2.00 gm as Piperacillin Sodium & Tazobactam 0.25 gm as Tazobactam Sodium.

Tazocilin™ 4.5 IV infusion: Each vial contains sterile powder of Piperacillin & Tazobactam for Injection USP equivalent to Piperacillin 4.00 gm as Piperacillin Sodium & Tazobactam 0.50 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 **Tazocilin™** IV infusion enhances and extends the antibiotic spectrum of Piperacillin to include many beta-lactamase producing bacteria normally resistant to it. Thus, **Tazocilin™** 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 (mg/ml)						
Piperacillin/Tazobactam Dose	30*min	1 hr	1.5 hr	2 hr	3 hr	4 hr
4 g/500 mg	298	141	87	47	16	7
Tazobactam plasma levels (mg/ml)						
Piperacillin/Tazobactam Dose	30*min	1 hr	1.5 hr	2 hr	3 hr	4 hr
4 g/500 mg	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

Tazocilin™ 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 (moderate severity only)
3. Uncomplicated and complicated skin and skin structure infections, including cellulitis, cutaneous abscesses and ischemic/diabetic foot infections
4. Postpartum endometritis or pelvic inflammatory disease
5. Appendicitis (complicated by rupture or abscess) and peritonitis

Tazocilin™ 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.

DOSAGE AND ADMINISTRATION

Piperacillin & Tazobactam should be administered by intravenous infusion over 30 minutes.

Adult Patients

The usual total daily dose of Piperacillin & Tazobactam for adults is 3.375 gm every six hours totaling 13.5 gm (12.0 gm Piperacillin & 1.5 gm Tazobactam). The usual duration of treatment is from 7 to 10 days.

Nosocomial Pneumonia

Initial presumptive treatment of patients with nosocomial pneumonia should start with Piperacillin & Tazobactam at a dosage of 4.5 gm every six hours plus an aminoglycoside, totaling 18.0 gm (16.0 gm Piperacillin & 2.0 gm Tazobactam). The recommended duration of treatment for nosocomial pneumonia is 7 to 14 days. Treatment with the aminoglycoside should be continued in patients from whom P. aeruginosa is isolated.

Renal Impairment

In patients with renal impairment (creatinine clearance ≤ 40 mL/min) and dialysis patients (hemodialysis and CAPD), the intravenous dose of Piperacillin & Tazobactam should be reduced to the degree of actual renal function impairment. The recommended daily doses of Piperacillin & Tazobactam for patients with renal impairment are as follows:

Renal Function (creatinine clearance, mL/min)	All Indications (except nosocomial pneumonia)	Nosocomial Pneumonia
>40 mL/min	3.375 qm 6 h	4.5 qm 6 h
20-40 mL/min*	2.25 qm 6 h	3.375 qm 6 h
<20 mL/min*	2.25 qm 8 h	2.25 qm 6 h
Hemodialysis**	2.25 qm 12 h	2.25 qm 8 h
CAPD	2.25 qm 12 h	2.25 qm 8 h

* Creatinine clearance for patients not receiving hemodialysis

** 0.75 g (0.67 gm Piperacillin & 0.08 gm Tazobactam) should be administered following each hemodialysis session on hemodialysis days

For patients on hemodialysis, the maximum dose is 2.25 gm every twelve hours for all indications other than nosocomial pneumonia and 2.25 gm every eight hours for nosocomial pneumonia. Since hemodialysis removes 30% to 40% of the administered dose, an additional dose of 0.75 gm Piperacillin & Tazobactam (0.67 gm Piperacillin & 0.08 gm Tazobactam) should be administered following each dialysis period on hemodialysis days. No additional dosage of Piperacillin & Tazobactam is necessary for CAPD patients.

Pediatric Patients

For children with appendicitis and/or peritonitis 9 months of age or older, weighing up to 40 kg, and with normal renal function, the recommended dosage is 100 mg Piperacillin &12.5 mg Tazobactam per kg of body weight, every 8 hours. For pediatric patients between 2 months and 9 months of age, the recommended dosage based on pharmacokinetic modeling, is 80 mg Piperacillin & 10 mg Tazobactam per Kg of body weight, every 8 hours. Pediatric patients weighing over 40 kg and with normal renal function should receive the adult dose. It has not been determined how to adjust Piperacillin & Tazobactam dosage in pediatric patients with renal impairment.

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 hypoglycemia, 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 anticoagulants:

During simultaneous administration of heparin, oral anticoagulants and other drugs which may affect the blood coagulation system including thrombocyte 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

Store below 25^{0}C. Protected from light & moisture. Keep the medicine out of the reach of children.

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.

HOW SUPPLIED

Tazocilin™ 2.25 IV infusion: Each combipack contains one vial of **Tazocilin™ 2.25** IV infusion and 1 bottle of 50 ml normal saline, one disposable syring (10 ml), one infusion set, one baby needdle, one alcohol prep. pad, and one first aid band.

Tazocilin™ 4.5 IV infusion: Each combipack contains one vial of **Tazocilin™ 4.5** IV infusion and 1 bottle of 100 ml normal saline, one disposable syring (20 ml), one infusion set, one butterfly needdle, one alcohol prep. pad, and one first aid band.

Manufactured by

SQUARE PHARMACEUTICALS LTD.

Bangladesh