1.3 Product Information

1.3.1 Summary of Product Characteristics (SmPC) - Enclosed

SHALBACTAM TZ

(Ceftriaxone and Tazobactam for Injection)

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

SHALBACTAM TZ (Ceftriaxone and Tazobactam for Injection)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Ingredients	Qty/vial in mg
Ceftriaxone Sodium USP Equivalent to Ceftriaxone	1194 ≡ 1000
Tazobactam Sodium Equivalent to Tazobactam	130 ≡ 125

Note: USP = United States Pharmacopoeia

3. PHARMACEUTICAL FORM

Powder for Injection

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Following Infections caused by the susceptible organisms in Bacterial meningitis, Bone & joint infections, Community-acquired pneumonia, Intra-abdominal infections, Lower respiratory tract infections, Pelvic inflammatory disease, Uncomplicated gonorrhoea, Skin and skin structure infections, Bacterial septicaemia, Urinary tract infections.

4.2 Posology and method of administration

Route of Administration: IM/IV

Dosage:

Shalbactam TZ should be administered intravenously and intramuscularly. ADULTS: The usual adult daily dose of Shalbactam TZ is 1.125 to 2.250 grams given once a day (or in equally divided doses twice a day) depending on the type and severity of infection. The total daily dose should not exceed 4.5 grams.

For preoperative use (surgical prophylaxis), a single dose of 1.125 gm administered intravenously ½ to 2 hours before surgery is recommended.

Pediatric patients:

1. For the treatment of skin and skin structure infections, the recommended total daily dose of ceftriaxone is 50 to 75 mg/kg given once a day (or in equally divided doses twice a day). The total daily doses of Shalbactam TZ should not exceed 2.250 grams.

2. For the treatment of acute bacterial otitis media, a single intramuscular Ceftriaxone dose of 50 mg/kg (total combination dose not to exceed 1.125 gram) is recommended.

3. For the treatment of serious miscellaneous infections other than meningitis, the recommended total daily dose is 50 to 75 mg/kg, given in divided doses every 12 hours. The total daily dose of combination should not exceed 2.250 grams.

4. In the treatment of meningitis, it is recommended that the initial therapeutic dose of ceftriaxone be 100 mg/kg (total combination dose not to exceed 4.5 gram). The daily dose may be administered once a day (or in equally divided doses every 12 hours). The usual duration of therapy is 7 to 14 days. Generally, Shalbactam TZ therapy should be continued for at least 2 days after the signs and symptoms of infection have disappeared.

The usual duration of therapy is 4 to 14 days; in complicated infections, longer therapy may be required.

When treating infections caused by Streptococcus pyogenes, therapy should be continued for at least 10 days. Blood levels should be monitored in patients with severe renal impairment (eg, dialysis patients) and in patients with both renal and hepatic dysfunctions.

Incompatibility: Vancomycin and fluconazole are incompatible with ceftriaxone in admixture.

The reconstituted solution should be used immediately. Discard if reconstituted solution contains visible particulate matter. For I.V. use - Dissolve the contents in 9.6 ml of Sterile water for Injetion BP provided.

For I.M. use - Dissolve the contents in 3.6 ml of sterile water for injection BP provided.

4.3 Contraindications

Hypersensitivity to cephalosporins and b-lactamase inhibitors.

4.4 Special warnings and precautions for use

Warnings: Before therapy with ceftriaxone/tazobactam is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to cephalosporins, penicillins or other drugs. This product should be given cautiously to penicillin-sensitive patients. Antibiotics should be administered with caution to any patient who has demonstrated some form of allergy, particularly to drugs. Serious acute hypersensitivity reactions may require the use of subcutaneous epinephrine and other emergency measures.

Precautions: General: Prescribing Ceftriaxone / 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 the development of drug-resistant bacteria. Patients with renal failure normally require no adjustment in dosage when usual doses of Ceftriaxone/Tazobactam are administered but concentrations of drug in the serum should be

monitored periodically. Dosage adjustments should not be necessary in patients with hepatic dysfunction; however, in patients with both hepatic dysfunction and significant renal disease, Shalbactam TZ dosage should not exceed 2.250 gm daily without close monitoring of serum concentrations. Ceftriaxone should be prescribed with caution in individuals with a history of gastrointestinal disease, especially colitis. There have been reports of sonographic abnormalities in the gallbladder of patients treated with Ceftriaxone; some of these patients also had symptoms of gallbladder disease. Therefore, Shalbactam TZ should be discontinued in patients who develop signs and symptoms suggestive of gallbladder disease. Carcinogenesis, Mutagenesis, Impairment of Fertility. Carcinogenesis: Considering the maximum duration of treatment and the class of the compound, carcinogenicity studies with ceftriaxone in animals have not been performed. The maximum duration of animal toxicity studies was 6 months. Mutagenesis: Genetic toxicology tests included the Ames test, a micronucleus test and a test for chromosomal aberrations in human lymphocytes cultured in vitro with ceftriaxone. Ceftriaxone showed no potential for mutagenic activity in these studies. Impairment of Fertility: Ceftriaxone produced no impairment of fertility when given intravenously to rats at daily doses up to 586 mg/kg/day, approximately 20 times the recommended clinical dose of 2 gm/day. Pregnancy Teratogenic Effects: Pregnancy Category B. Reproductive studies have been performed in mice and rats at doses up to 20 times the usual human dose and have no evidence of embryotoxicity, fetotoxicity or teratogenicity. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. Tazobactam: Reproduction studies have been performed in rats and have revealed no evidence of imp aired fertility due to Tazobactam administered up to a dose 3 times the human dose based on body-surface area. Nursing Mothers: Low concentrations of ceftriaxone are excreted in human milk. Caution should be exercised when Ceftriaxone is administered to a nursing woman. Tazobactam concentrations in milk have not been studied. Pediatric Use: Safety and effectiveness of Ceftriaxone in neonates, infants and children have been established for the dosages described above. In vitro studies have shown that ceftriaxone like some other cephalosporins, can displace bilirubin from serum albumin. Ceftriaxone should not be administered to hyperbilirubinemic neonates, especially prematures.

4.5 Interaction with other medicinal products and other forms of interaction

Ceftriaxone: Interaction is seen with Chloramphenicol, Solutions and Solvents with Calcium, Vancomicin, fluconazole, aminoglycosides, hormonal contraceptives & Coomb's test.

Tazobactam: Interaction is seen with Probenecid, heparin, warfarin, anti-coagulants, methotrexate.

4.6 Pregnancy and lactation

This drug should be used during pregnancy only if clearly needed.

Nursing Mothers: Low concentrations of ceftriaxone are excreted in human milk.

Caution should be exercised when Ceftriaxone is administered to a nursing woman.

4.7 Effects on ability to drive and use machines

Since ceftriaxone sometimes induces dizziness, the ability to drive and use machines can be impaired.

4.8 Adverse Reactions

Ceftriaxone/Tazobactam is generally well tolerated. In clinical trials, the following adverse reactions, which were considered to be related to Ceftriaxone therapy or of uncertain etiology, were observed: Local Reactions: Pain, induration and tenderness was 1% overall. Phlebitis was reported in <11% after IV administration. Hypersensitivity: Rash (1.7%). Less frequently reported (<1%) were pruritus, fever or chills. Hematologic: Eosinophilia (6%), thrombocytosis (5.1%) and leukopenia (2.1%). Less frequently reported (<1%) were anemia, hemolytic anemia, neutropenia, lymphopenia, thrombocytopenia and prolongation of the prothrombin time. Gastrointestinal: Diarrhea (2.7%). Less frequently reported (<1%) were nausea or vomiting, and dysgeusia. The onset of pseudomembranous colitis symptoms may occur during or after antibacterial treatment. Hepatc: Elevations of SGOT/AST (3.1%) or SGPT/ALT (3.3%). Renal: Elevations of the BUN (1.2%). Less frequently reported (<1%) were elevations of creatinine and the presence of casts in the urine. Central Nervous System: Headache or dizziness were reported occasionally (<1%). Genitourinary: Moniliasis or vaginitis were reported occasionally (<1%). Miscellaneous: Diaphoresis, flushing were reported occasionally (<1%). Other rarely observed adverse reactions (<0.1%) include abdominal pain, agr anulocytosis, allergic pneumonitis, anaphylaxis, basophilia, biliary lithiasis, bronchospasm, colitis, dyspepsia, epistaxis, flatulence, gallbladder sludge, glycosuria, hematuria, jaundice, leukocytosis, lymphocytosis, monocytosis, nephrolithiasis, palpitations, a decrease in the prothrombin time, renal precipitations, seizures, and serum sickness.

4.9 Symptoms of Overdosage & Treatment

Symptomatic and supportive treatment should be initiated

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological category: Broad spectrum cephalosporin antibiotic.

Pharmacological action: Ceftriaxone interferes with the biosynthesis of the peptidoglycan component of the bacterial cell way by binding to and inactivating penicllin-binding proteins (PBPs). Tazobactam is a penicillanic acid sulfone derivative with β-lactamase inhibitory properties. It enhances the activity of β-lactam antibacterials against β-lactamase-producing bacteria. The bactericidal activity of ceftriaxone results from inhibition of cell wall synthesis. Ceftriaxone has a high degree of stability in the presence of beta-lactamases, both penicillinases and cephalosporinases, of gram-negative and gram-positive bacteria. In an in vitro study antagonistic effects have been observed with the combination of chloramphenicol and ceftriaxone. Ceftriaxone has been shown to be active against most strains of the following microorganisms, both in vitro & in clinical infections - Aerobic gram-negative microorganisms: Acinetobacter calcoaceticus. Enterobacter aerogenes. Enterobacter cloacae. Escherichia coli. Haemophilus influenzae (including ampicillin-resistant and beta-lactamase producing strains). Haemophilus parainfluenzae. Klebsiella oxytoca. Klebsiella pneumoniae. Moraxella catarrhalis (including beta-lactamase producing strains). Morganella morganii. Neisseria gonorrhoeae (including penicillinase- and nonpenicillinase-producing strains). Neisseria meningitidis. Proteus mirabilis. Proteus vulgaris. Serratia marcescens. Ceftriaxone is also active against many strains of Pseudomonas aeruginosa. NOTE: Many strains of the above organisms that are resistant to multiple antibiotics, e.g., penicillins, cephalosporins, and aminoglycosides, are susceptible to ceftriaxone. Aerobic gram-positive microorganisms: Staphylococcus aureus (including penicillinase-producing strains). Staphylococcus epidermidis. Streptococcus pneumoniae. Streptococcus pyogenes. Viridans group streptococci. NOTE: Methicillin-resistant staphylococci are resistant to cephalosporins, including ceftriaxone. Most strains of Group D streptococci and enterococci, e.g., Enterococcus (Streptococcus) faecalis, are resistant. Anaerobic microorganisms: Bacteroides fragilis. Clostridium species. Peptostreptococcus species.

NOTE: Most strains of Clostridium difficile are resistant. The following in vitro data are available, but their clinical significance is unknown. Ceftriaxone exhibits in vitro minimal inhibitory concentrations (MICs) of £8 mcg/mL or less against most strains of the following microorganisms, however, the safety and effectiveness of ceftriaxone in treating clinical infections due to these microorganisms have not been established in adequate and well controlled clinical trials. Aerobic gram-negative microorganisms: Citrobacter diversus.

Citrobacter freundii. Providencia species (including Providencia rettgeri). Salmonella species (including Salmonella typhi). Shigella species. Aerobic gram-positive microorganisms: Streptococcus agalactiae. Anaerobic microorganisms: Prevotella (Bacteroides) bivius. Porphyromonas (Bacteroides) melaninogenicus. Tazobactam lacks significant antibacterial activity of its own.

It combines irreversibly with the common plasmid-encoded beta lactamases belonging to Richmond and Sykes class III and has been shown to inhibit many other enzymes of different classes, including those that are resistant to penicillins and third generation cephalosporins.

5.2 Pharmacokinetic properties

Average Pharmacokinetic Parameters of Ceftriaxone

Absorption: Ceftriaxone was completely absorbed following IM administration with mean maximum plasma concentrations occurring between 2 and 3 hours post-dose.

Distribution: Ceftriaxone: 98% bound to plasma proteins; crosses the blood brain barrier.

Excretion: Ceftriaxone 33-67% removed as unchanged drug.

Pharmacokinetic Parameters of Tazobactam: Plasma half-life: Mean (dose dependent): 0.35-0.67 h,

Volume of distribution: 141 L, Plasma protein binding: 23%, Excretion: Renal route.

Tazobactam is metabolized to a single metabolite which lacks pharmacological and antibacterial activities.

Tazobactam and its metabolite are eliminated primarily by renal excretion with 80% of the dose as unchanged drug and the remainder as the single metabolite.

Tazobactam is 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 is generally 50 to 100% of those in plasma.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None

6.2 Incompatibilities

None.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Do not store above 30°C. Protect from sunlight and moisture. Keep out of reach of children. Do not freeze. The reconstituted solution should be used immediately.

6.5 Nature and contents of container

Shalbactam TZ is available in a 20ml glass vial with 10ml water for injection in plastic ampoule in a carton along with a leaflet.

7. MARKETING AUTHORISATION HOLDER

SHALINA HEALTHCARE DMCC
30th Floor, Almas Towers,
Jumeirah Lakes Towers Dubai-UAE.
Telephone: +971 4 4309111
Telefax: +971 4 4309112
Website: www.shalina.com

8. MANUFACTURER

M/s Innova Captab Pvt. Ltd
1281/1, Hilltop Industrial Estate,
Near EPIP Phase – I, Jharmajri,
Baddi (HP), India.