1.3 Product Information

1.3.1 Summary of Product Characteristics (SmPC)

1. NAME OF THE MEDICINAL PRODUCT:

1.1 (INVENTED) NAME OF THE MEDICINAL PRODUCT

International Non-Proprietary Name: UKACEF TZ (CEFTRIAXONE AND TAZOBACTAM FOR INJECTION 1.125 GM)

1.2 STRENGTH

1.125 gm/ml

1.3 PHARMACEUTICAL FORM

Powder for Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 QUALITATIVE DECLARATION

Ceftriaxone

Tazobactam

2.2 QUANTITATIVE DECLARATION

Each vial contains:

Ceftriaxone Sodium USP equivalent to

Ceftriaxone …… 1 gm

Tazobactam Sodium equivalent to

Tazobactam ..... 125 mg

3. PHARMACEUTICAL FORM

Powder for Injection

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Ceftriaxone and Tazobactam for Injection, it should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria.

CEFTRIAXONE AND TAZOBACTAM FOR INJECTION is mainly indicated in the following conditions:

- Lower respiratory tract infections and community-acquired pneumonia
- Acute bacterial otitis media
- Skin and skin structure infections
- Urinary tract infections
- Uncomplicated gonorrhea
- Pelvic inflammatory disease
- Bacterial septicemia
- Bone and joint infections
- Intra-abdominal infections
- Bacterial meningitis
- Peri-operative prophylaxis of infections associated with surgery

Surgical Prophylaxis: The pre-operative administration of a single 1 gm dose of Ceftriaxone and Tazobactam for Injectionmay reduce the incidence of post-operative infections in patients undergoing surgical procedures classified as contaminated or potentially contaminated (eg, vaginal or abdominal hysterectomy; or cholecystectomy for chronic calculous cholecystitis in high-risk patients, such as those over 70 years of age, with acute cholecystitis not requiring therapeutic antimicrobials; obstructive jaundice or common duct bile stones) and in surgical patients for whom infection at the operative site would present a serious risk (eg, during coronary artery bypass surgery).

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Pediatric Patients: For the treatment of serious infections, the recommended dose is 50–75 mg/kg (in terms of ceftriaxone) given in divided doses every 12 hours. The total daily dose should not exceed 2 gm (in terms of ceftriaxone). For the treatment of acute bacterial otitis media, a single intramuscular dose of 50 mg/kg (not to exceed 1 gram) is recommended.
Adults: The usual adult dose is 1000/125 mg of ceftriaxone/tazobactam given once a day (or in equally divided doses twice a day) depending upon the severity of the infection. The total daily dose should not exceed 4 gm (in terms of ceftriaxone).
For pre-operative use (surgical prophylaxis), a single I.V. dose of 1 gm administered ½ hour to 2 hours before surgery is recommended.
Generally, ceftriaxone/tazobactam should be continued for at least 2 days after the signs and symptoms of infection have disappeared. The usual duration of therapy is 4–14 days; in

complicated infections, longer therapy may be required. When treating Streptococci pyogenes, the therapy should be continued for at least 10 days.

Ceftriaxone may be administered by deep intramuscular injection, or as a slow intravenous injection/ infusion, after reconstitution of the solution according to the directions given below.

Directions for Use

I.V. injection should be administered over at least 2–4 minutes.

I.V. infusion should be over a period of 30 minutes.

After reconstitution the solution should be administered by deep *I.M. injection*. Doses greater than 1gm should be divided and injected at more than one site.

Reconstitute ceftriaxone/tazobactam with the appropriate diluent, e.g., Water for Injection IP, Normal Saline Water, or Dextrose Solutions.

Strength	250 mg	500 mg	1000 mg
Amount of diluent (ml) I.V. administration	2.4	4.8	9.6
Amount of Diluent (ml) I.M. administration	0.5-0.9	1.0-1.8	3.6

Use reconstituted solution in the vial immediately.

4.3 CONTRAINDICATIONS

Hypersensitivity to cephalosporins and beta-lactamase inhibitors.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Before therapy with Ceftriaxone and Tazobactam for Injectionis instituted, a detailed 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.

Serious acute hypersensitivity reactions may require the use of subcutaneous epinephrine and other emergency measures.

Clostridium difficile associated diarrhea has been reported with nearly all antibacterial agents, including ceftriaxone/tazobactam, and 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.

An immune mediated hemolytic anemia has been observed in patients receiving cephalosporin class antibacterials including CEFTRIAXONE AND TAZOBACTAM FOR INJECTION. Severe cases of hemolytic anemia, including fatalities, have been reported during treatment in both adults and children. If a patient develops anemia while on ceftriaxone, the diagnosis of a cephalosporin associated anemia should be considered and ceftriaxone stopped until the etiology is determined.

Although transient elevations of BUN and serum creatinine have been observed, at the recommended dosages, the nephrotoxic potential of ceftriaxone/tazobactam is similar to that of other cephalosporins. Alterations in prothrombin times have occurred infrequently in patients treated with ceftriaxone/tazobactam. Patients with impaired vitamin K synthesis or low vitamin K stores (eg, chronic hepatic disease and malnutrition) may require monitoring of prothrombin time during Ceftriaxone and Tazobactam for Injectiontreatment. Vitamin K administration (10 mg weekly) may be necessary if the prothrombin time is prolonged before or during therapy. Prolonged use of ceftriaxone/tazobactam may result in the overgrowth of non-susceptible organisms. Hence, careful observation of the patient is essential. If super infection occurs during therapy, ,appropriate measures should be taken.

Ceftriaxone and Tazobactam for Injectionshould be prescribed with caution in individuals with a history of gastrointestinal disease, especially colitis. There have been reports of sonographic abnormalities in the gall bladder of patients treated with ceftriaxone/tazobactam; some of these patients also had symptoms of gall bladder disease. On a sonography, these abnormalities appear as an echo without acoustical shadowing, suggesting sludge, or as an echo with acoustical shadowing, which may be misinterpreted as gallstones. The chemical nature of the sonographically-detected material has been determined to be, predominantly, a ceftriaxonecalcium salt. The condition appears to be transient and reversible upon the discontinuation of ceftriaxone/tazobactam and the institution of conservative management. Therefore, ceftriaxone/tazobactam should be discontinued in patients who develop signs and symptoms suggestive of gall bladder disease and/or the sonographic findings described above.

Cases of pancreatitis, possibly secondary to biliary obstruction, have been reported rarely in patients treated with CEFTRIAXONE AND TAZOBACTAM FOR INJECTION.

Most patients presented with risk factors for biliary stasis and biliary sludge (preceding major therapy, severe illness, total parenteral nutrition). A cofactor role of CEFTRIAXONE AND TAZOBACTAM FOR INJECTION -related biliary precipitation cannot be ruled out.

As with other cephalosporins, anaphylactic shock cannot be ruled out even if a thorough patient history is taken.

Renal Impairment

Ceftriaxone is excreted via both biliary and renal excretion. Therefore, patients with renal failure normally require no dosage adjustment when the usual doses of Ceftriaxone and Tazobactam for Injection are administered, but concentrations of the drug in the serum should be monitored periodically. If evidence of accumulation exists, the dosage should be decreased accordingly.

No data are available in the case of pediatric patients with impaired renal function. Hepatic Impairment Dosage adjustments should not be necessary in patients with hepatic dysfunction; however, in patients with both hepatic dysfunction and significant renal disease, the dosage of Ceftriaxone and Tazobactam for Injectionshould not exceed 2 gm daily without close monitoring of serum concentrations. No data are available in the case of pediatric patients with impaired hepatic function.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS & OTHER FORMS OF INTERACTION

None.

4.6 PREGNANCY AND LACTATION

Pregnancy

Ceftriaxone and Tazobactam for Injection should be used during pregnancy only if clearly needed.

Lactation

Low concentrations of ceftriaxone/tazobactam are excreted in human milk. Hence, caution should be exercised when ceftriaxone/tazobactam is administered to a nursing mother.

Pediatric Use

Ceftriaxone/tazobactam should not be administered to hyperbilirubinemic neonates, especially prematures.

Geriatric Use

The pharmacokinetics of Ceftriaxone and Tazobactam for Injection were only minimally altered in geriatric patients compared to healthy adult subjects and dosage adjustments are not necessary for geriatric patients with Ceftriaxone and Tazobactam for Injection dosages up to 2 grams per day.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

None stated

4.8 UNDESIRABLE EFFECTS

Local reactions—pain, induration and tenderness was 1% overall. Phlebitis was reported in <1% 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.

Hepatic—elevations of SGOT (3.1%) or SGPT (3.3%). Less frequently reported (<1%) were elevations of alkaline phosphatase and bilirubin.

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 and flushing were reported occasionally (<1%).

Other rarely observed adverse reactions (<0.1%) include abdominal pain, agranulocytosis, 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.

Gastrointestinal—stomatitis and glossitis.

Genitourinary—oliguria.

Dermatologic—exanthema, allergic dermatitis, urticaria, edema. As with many medications, isolated cases of severe cutaneous adverse reactions (erythema multiforme,

Stevens-Johnson syndrome or Lyell's syndrome/toxic epidermal necrolysis) have been reported.

Cephalosporin Class Adverse Reactions

In addition to the adverse reactions listed above which have been observed in patients treated with ceftriaxone, the following adverse reactions and altered laboratory test results have been reported for cephalosporin class antibiotics:

Adverse Reactions: Allergic reactions, drug fever, serum sickness-like reaction, renal dysfunction, toxic nephropathy, reversible hyperactivity, hypertonia, hepatic dysfunction including cholestasis, aplastic anemia, hemorrhage, and superinfection.

Altered Laboratory Tests: Positive direct Coombs' test, false-positive test for urinary glucose, and elevated LDH. Several cephalosporins have been implicated in triggering seizures, particularly in patients with renal impairment when the dosage was not reduced. If seizures associated with drug therapy occur, the drug should be discontinued.

Anticonvulsant therapy can be given if clinically indicated.

4.9 OVERDOSE

In the case of overdosage, drug concentration would not be reduced by hemodialysis or peritoneal dialysis. There is no specific antidote. Treatment of overdosage should be symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Ceftriaxone is a 2-aminothiazolyl methoxylmino third-generation cephalosporin derivative. Ceftriaxone, a bactericidal antimicrobial, inhibits bacterial cell wall synthesis of actively dividing cells by binding to one or more penicillin-binding proteins (PBPs). These proteins are associated with the bacterial cell membrane and probably serve in synthesis. The result is the formation of a defective cell wall that is osmotically unstable. Bacterial species have a unique set of PBPs. The affinity pattern of ceftriaxone for the PBPs for different bacterial species affects the drug’s antimicrobial spectrum of activity. It is also felt that cephalosporins, as well as penicillins, may increase the breakdown of the cell wall of the bacteria by decreasing the availability of an inhibitor of murein hydrolase, an enzyme involved in cell division. If unimposed, this enzyme can destroy the integrity of the cell wall.

Tazobactam is a penicillinate sulfone, structurally related to sulbactam. Being a betalactamase inhibitor, it is synergistic with many beta-lactamase labile drugs such as penicillins and cephalosporins.

Tazobactam inhibits all beta-lactamases inhibited by clavulanic acid, but, in addition, it also has some activity against chromosomally-mediated induced (or derepressed) enzymes of Morganella morganii, Citrobacter freundii, Enterobacter cloacae, Serratia marcescens and Pseudomonas aeruginosa. Tazobactam also appears to be a weaker enzyme inducer than other beta-lactamase inhibitors.

Combination of Tazobactam and Ceftriaxone

The combination of tazobactam and ceftriaxone is active against all the organisms sensitive to ceftriaxone. In addition, it demonstrates synergistic activity (reduction in minimal inhibitory concentrations [MICs] for the combination versus those of each component) in a variety of organisms.

Gram-negative Aerobes

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 non – penicillinase 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 multiply resistant to other antibiotics, eg, penicillins, cephalosporins and aminoglycosides, are susceptible to ceftriaxone.

Gram-positive Aerobes

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

Anaerobes

Bacteroides fragilis

Clostridium species

Peptostreptococcus species

NOTE: Most strains of Clostridium difficile are resistant

Ceftriaxone

The in vitro data are available, but their clinical significance is unknown. Ceftriaxone exhibits in vitro MICs of </=8 µg/mL or lesser 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

5.2 PHARMACOKINETIC PROPERTIES

Average plasma concentrations of ceftriaxone after administration of a single dose are given in the table below:

Does/Ratio	**½ Hour**	**1 hour**	**2 Hour**	**4 Hour**	**6 Hour**	**8 Hour**	**12 Hour**	**16 Hour**	**24 Hour**

0.5 gm I.V.	82	59	48	37	29	23	15	10	5
1 gm I.V.	151	111	88	67	53	43	28	18	9

Ceftriaxone achieves high concentrations in the urine. Altogether, 33–67% of ceftriaxone is excreted as unchanged drug and the remainder is excreted in the bile and the feces. After a 1 gm I.V. dose, average concentrations of ceftriaxone achieved in the gall bladder bile is 581 mcg/ml, 788 mcg/ml in the common bile duct, 898 mcg/ml in the cystic bile duct, 78.2 mcg/ml in the gall bladder wall and 62.1 mcg/ml in concurrent plasma. The elimination half-life is 8.7 hours. Ceftriaxone is 98% bound to plasma proteins. Ceftriaxone crosses the blood brain barrier.

Tazobactam is metabolized to a single metabolite that lacks pharmacological and antibacterial activities. Tazobactam is eliminated via the kidneys by glomerular filtration and tubular secretion. Tazobactam and its metabolite are eliminated primarily by renal excretion, with 80% of the administered dose excreted as unchanged drug and the remainder as a single metabolite. Tazobactam is also secreted into the bile. Tazobactam is approximately 30% bound to plasma proteins. Protein binding of the tazobactam metabolite is negligible.

Tazobactam is widely distributed to tissues and body fluids including the intestinal mucosa, gall bladder, lungs, female reproductive tissues (uterus, ovary and fallopian tube), interstitial fluid, and bile.

5.3 PRECLINICAL SAFETY DATA

None.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENT(S)

None.

6.2 INCOMPATIBILITIES

Vancomycin, amsacrine, aminoglycosides, and fluconazole are physically incompatible with Ceftriaxone and Tazobactam for Injection in admixtures. When any of these drugs are to be administered concomitantly with Ceftriaxone and Tazobactam for Injection by intermittent intravenous infusion, it is recommended that they be given sequentially, with

thorough flushing of the intravenous lines (with one of the compatible fluids) between the administrations.

6.3 SHELF-LIFE

36 months

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store in a cool and dry place, not above 30˚C.Protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

20 ml plain glass packed Glass Vial

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

Not Applicable

7 APPLICANT

UKANWA PHARMACEUTICAL COMPANY NIGERIA LIMITED
No. 2 Onyekwere Street Fegge, Onitsha, Anambra State.

8 MANUFACTURER

SWISS PARENTERALS LIMITED
Plot no 402,412-414, Kerala Industrial Estate, G.I.D.C., Near, Bavla, Dist.: Ahmedabad-382220, Gujarat (INDIA).