1.3 Product Information

1.3.1 Summary of Product Characteristics (SmPC)

Enclosed overleaf.

SUMMARY OF PRODUCT CHARACTERISTICS

1. Product Name

FERENS (Ceftriaxone and Tazobactam For Injection 1.125 gm and Sterile Water For Injection USP 10 ml)

2. Qualitative and Quantitative Composition
Each vial containing:
Sterile Ceftriaxone Sodium USP
equivalent to Ceftriaxone ……..….. 1000 mg.
Tazobactam Sodium
equivalent to Tazobactam ……..…… 125 mg.

Sterile Water for Injection USP ……..….. 10 ml.

3. Dosage Form and Strength

Dosage Form: Injection.
Dosage Strength: Ceftriaxone 1000 mg and Tazobactam 125 mg per vial.

4. Clinical Particulars

4.1 Therapeutic Indication
FERENS Injection is indicated for the treatment of following bacterial infections when caused by susceptible organisms.

- Bacterial meningitis
- Community acquired pneumonia
- Hospital acquired pneumonia
- Acute otitis media
- Intra-abdominal infections
- Complicated urinary tract infections (including pyelonephritis)
- Infections of bones and joints
- Complicated skin and soft tissue infections
- Gonorrhoea
- Syphilis
- Bacterial endocarditis
- Surgical prophylaxis

4.2 Posology and Method of Administration

FERENS Injection to be administered by deep intramuscular (I.M.) injection, slow intravenous (I.V.) injection, or as a slow I.V. infusion, after reconstitution with sterile water for injection (SWFI).

Dosage Recommendations in Adults

Usual Recommended Dose: 1.125 g to 2.25 g of FERENS Injection (1 g / 2 g ceftriaxone + 125 mg / 250 mg tazobactam) per day given once a day or in two equally divided doses every 12 hours. The total daily dose of ceftriaxone should not exceed 4 grams. Tazobactam can be given up to 2 grams per day.

For Uncomplicated Gonococcal Infections: A single dose of 562.5 mg of EXTACEF-TAZO Injection (500 mg ceftriaxone + 62.5 mg tazobactam) to be administered by I.M. route.

For Preoperative Use (Surgical Prophylaxis): A single dose of 1.125 g of EXTACEF-TAZO Injection (1g ceftriaxone + 125 mg tazobactam) to be administered I.V. 30 minutes to 2 hours before surgery.

The usual duration of therapy is 4 to 14 days. In complicated infections, longer therapy may be required. or, as prescribed by the physician.

Dosage in Adult Patients with Renal Impairment and Hepatic Dysfunction

In patients with both hepatic dysfunction and significant renal disease, caution should be exercised and the ceftriaxone dosage should not exceed 2 gram daily. Tazobactam should be used with care in patients with renal impairment or in hemodialysis patients. The I.V. dose and administration interval should be adjusted to the degree of renal function impairment.

Dosage Recommendations in Pediatric Patients

For children with bodyweight above 50 kg or age over 12 years, the usual adult dosage should be administered. Although, ceftriaxone can be administered in neonates and infants, the safety and efficacy of this combination product (ceftriaxone + tazobactam injection) has not been established in children below 2 years of age. Thus, FERENS Injection is recommended only in children above 2 years of age.

Following doses in children are expressed in terms of ceftriaxone content of the formulation.

Usual Recommended Dosage: 50 to 75 mg/kg/day, given in divided doses every 12 hours. The total daily dose of ceftriaxone should not exceed 2 grams. In children, tazobactam can be given up to 12.5 mg/kg body weight per dose.

Treatment of Meningitis: The initial therapeutic dose should be 100 mg/kg body weight. Thereafter, daily dose of 100 mg/kg may be administered once a day or in equally divided doses every 12 hours. The total daily dose of ceftriaxone should not exceed 4 grams.

The usual duration of therapy is 7 to 14 days depending on the type and severity of infection.

Or, as prescribed by the physician.

Hypersensitivity: Before initiation of therapy, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to cephalosporins, penicillins and other beta-lactam agents or other drugs. As with all beta-lactam antibacterial agents, serious and occasionally fatal hypersensitivity reactions (i.e., anaphylaxis) have been reported. In case of severe hypersensitivity reactions, treatment with ceftriaxone must be discontinued immediately and adequate emergency measures must be initiated.

***Clostridium Difficile*-Associated Diarrhea (CDAD):** CDAD has been reported with use of nearlyall antibacterial agents, including ceftriaxone, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*. If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

Hemolytic Anemia: An immune mediated hemolytic anemia has been observed in patients receiving cephalosporin class of antibacterial drugs including ceftriaxone. 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.

Development of Drug-Resistant Bacteria: Prescribing ceftriaxone 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. Prolonged use of ceftriaxone may result in overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Pancreatitis: Cases of pancreatitis, possibly secondary to biliary obstruction, have been reported in patients treated with ceftriaxone. Most patients presented with risk factors for biliary stasis and biliary sludge (preceding major therapy, severe illness, and total parenteral nutrition). A cofactor role of ceftriaxone-related biliary precipitation cannot be ruled out.

Urolithiasis and Post-Renal Acute Renal Failure: Ceftriaxone-calcium precipitates in the urinary tract have been observed in patients receiving ceftriaxone. The probability of

such precipitates appears to be greatest in pediatric patients. Patients may be asymptomatic or may develop symptoms of urolithiasis, and ureteral obstruction and post-renal acute renal failure. The condition appears to be reversible upon discontinuation of ceftriaxone and institution of appropriate management. Ensure adequate hydration in patients receiving ceftriaxone. Discontinue ceftriaxone in patients who develop signs and symptoms suggestive of urolithiasis, oliguria or renal failure and/or the sonographic findings.

Gallbladder Pseudolithiasis: Ceftriaxone-calcium precipitates in the gallbladder have been observed in patients receiving ceftriaxone. The probability of such precipitates appears to be greatest in pediatric patients. Patients may be asymptomatic or may develop symptoms of gallbladder disease. The condition appears to be reversible upon discontinuation of ceftriaxone and institution of conservative management. Discontinue ceftriaxone sodium in patients who develop signs and symptoms suggestive of gallbladder disease and/or the sonographic findings.
Effect on Prothrombin Time: Alterations in prothrombin times have occurred in patients treated with ceftriaxone. Monitor prothrombin time during ceftriaxone treatment in patients with impaired vitamin K synthesis or low vitamin K stores (e.g., chronic hepatic disease and malnutrition). Vitamin K administration (10 mg weekly) may be necessary if the prothrombin time is prolonged before or during therapy.

Altered Laboratory Tests: Positive direct Coombs' test and galactosemia test, false-positive test for urinary glucose and elevated lactate dehydrogenase (LDH).

4.5 Drug Interactions

Ceftriaxone
Amsacrine, Vancomycin, Fluconazole, and Aminoglycosides: Ceftriaxone is incompatible with these drugs.
Oral Contraceptives: Ceftriaxone may adversely affect the efficacy of oral hormonal contraceptives. Consequently, it is advisable to use supplementary (non-hormonal) contraceptive measures during treatment and in the month following treatment.
Chloramphenicol: Caution is advised if concurrent administration of ceftriaxone with chloramphenicol is proposed.
Vitamin K Antagonist: Concomitant use of ceftriaxone with vitamin K antagonists may increase the risk of bleeding. Coagulation parameters should be monitored frequently, and the dose of the anticoagulant adjusted accordingly, both during and after treatment with ceftriaxone.

Tazobactam

Probenecid: When probenecid administered concomitantly with tazobactam, it prolongs the half-life of tazobactam by 71%. This is because probenecid inhibits tubular renal secretion of tazobactam. Probenecid should not be co-administered with tazobactam unless the benefit outweighs the risk.

4.6 Use in Special Populations

Pregnant Women

Ceftriaxone: Pregnancy Category B; Tazobactam: Pregnancy Category B.

Animal studies have revealed no evidence of impaired fertility or harm to the fetus. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, FERENS Injection should be used during pregnancy only if clearly needed.

Lactating Women

Low quantities of both ceftriaxone and tazobactam are excreted in human milk. Therefore, caution should be exercised when FERENS Injection is administered to a nursing woman. Women who are breast-feeding should be treated only if the expected benefit outweighs the possible risks to the woman and child.

Pediatric Patients

Safety and effectiveness of ceftriaxone has been established in pediatric patients. *In vitro* studies have shown that ceftriaxone, like some other cephalosporins, can displace bilirubin from serum albumin. Thus, ceftriaxone-containing preparations should not be administered to hyperbilirubinemic children. Safety and efficacy of FERENS Injection has not been established in children below 2 years of age.

Geriatric Patients

Dosage adjustments are not necessary for geriatric patients with ceftriaxone dosages up to 2 grams per day provided there is no severe renal and hepatic impairment.

4.7 Effect on Ability to Drive and Use Machines

During treatment with ceftriaxone and tazobactam combination, undesirable effects such as dizziness, headache, and convulsions may occur, which may influence the ability to drive and use machines. If affected by such events, patients should not drive or operate machinery.

4.8 Undesirable Effects

Clinical Trials Experience

Ceftriaxone-containing preparations are generally well tolerated. In clinical trials, the following adverse reactions were observed (related to ceftriaxone therapy or of uncertain etiology).

Local Reactions: Injection site pain, induration, tenderness, phlebitis, warmth, tightness.
Hypersensitivity: Rash, pruritus, fever or chills.
Infections and Infestations: Genital fungal infection.
Hematologic: Eosinophilia, thrombocytosis, leukopenia. Less frequently reported were anemia, hemolytic anemia, neutropenia, lymphopenia, thrombocytopenia and prolongation of the prothrombin time.
Blood and Lymphatic Disorders: Granulocytopenia, coagulopathy.
Gastrointestinal: Diarrhea/loose stools, nausea, vomiting, dysgeusia, pseudomembranous colitis.
Hepatic: Elevations of aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, and bilirubin.
Renal: Elevations of the blood urea nitrogen (BUN), creatinine and the presence of casts in the urine.
Central Nervous System: Headache, dizziness.
Genitourinary: Moniliasis, vaginitis.
Miscellaneous: Diaphoresis, flushing, increased blood creatinine.
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, decrease in the prothrombin time, renal precipitations, seizures, and serum sickness.

4.9 Overdose

Ceftriaxone
In the case of overdose nausea, vomiting, and diarrhea can occur. Ceftriaxone concentration cannot be reduced by haemodialysis or peritoneal dialysis. There is no specific antidote. Treatment should be supportive and symptomatic according the patient's clinical presentation.
Tazobactam
Limited information is available on the acute toxicity of tazobactam in humans. No specific antidote is known. Excessive serum concentration of tazobactam may be reduced by haemodialysis.

5. Pharmacological Properties

5.1 Mechanism of Action

Ceftriaxone
Ceftriaxone is a third generation cephalosporin class of beta-lactam antibiotic. Ceftriaxone inhibits bacterial cell wall synthesis and produces bactericidal effect. Ceftriaxone has

activity in the presence of some beta-lactamases, both penicillinases and cephalosporinases, of Gram-negative and Gram-positive bacteria.

Tazobactam

Beta-lactamases are the enzymes produced by certain bacteria to develop resistant to antibiotics. Tazobactam, a beta-lactam structurally related to penicillins, is an inhibitor of many beta-lactamases, which commonly cause resistance to penicillins and cephalosporins. Tazobactam has good inhibitory activity against the clinically important plasmid mediated beta-lactamases most frequently responsible for transferred drug resistance.

Ceftriaxone with Tazobactam Combination Therapy

Ceftriaxone has a high degree of stability against the beta-lactamases, both penicillinases and cephalosporinases produced by Gram-negative and Gram-positive bacteria but not against chromosomally and plasmid mediated ESBL's (Extended Spectrum Beta-Lactamases) produced by some strains of *Klebsiella, Escherichia coli, Enterobacter spp* and *Serratia spp*.

Tazobactam irreversibly blocks the destruction of beta-lactam ring of ceftriaxone by this wide variety of ESBLs and chromosomally mediated beta-lactamases. Tazobactam attach to these enzymes and act as a suicide substrate that forms a stable intermediate, rendering the enzyme inactive. Thus, tazobactam restores ceftriaxone activity against ESBL producing strains.

Tazobactam extends the antibiotic spectrum of ceftriaxone to include many ESBL-producing bacteria that have acquired resistance to ceftriaxone alone.

5.2 Pharmacodynamic Properties

The combination of ceftriaxone and tazobactam is active against wide variety of beta-lactamase producing gram-positive and gram-negative bacteria. In addition, it demonstrates synergistic activity (reduction in MICs of combination therapy versus ceftriaxone alone) in a variety of organisms which are sensitive to ceftriaxone.

FERENS Injection has been shown to be active against most isolates of the following bacteria, both *in vitro* and in clinical infections:

Gram-negative Bacteria

- *Acinetobacter calcoaceticus*
- *Enterobacter aerogenes*
- *Enterobacter cloacae*
- *Escherichia coli*
- *Haemophilus influenzae*

- *Haemophilus parainfluenzae*
- *Klebsiella oxytoca*
- *Klebsiella pneumoniae*
- *Moraxella catarrhalis*
- *Morganella morganii*
- *Neisseria gonorrhoeae*
- *Neisseria meningitidis*
- *Proteus mirabilis*
- *Proteus vulgaris*
- *Pseudomonas aeruginosa*
- *Serratia marcescens*

Gram-positive Bacteria

- *Staphylococcus aureus*
- *Staphylococcus epidermidis*
- *Streptococcus pneumoniae*
- *Streptococcus pyogenes*
- *Viridans group streptococci*

Anaerobic Bacteria

- *Bacteroides fragilis*
- *Clostridium species*
- *Peptostreptococcus species*

The following *in vitro* data are available, but their clinical significance is unknown. At least 90% of the following microorganisms exhibit an *in vitro* minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for ceftriaxone. However, the efficacy of ceftriaxone in treating clinical infections due to these microorganisms has not been established in adequate and well-controlled clinical trials.

Gram-negative Bacteria

- *Citrobacter diversus*
- *Citrobacter freundii*
- *Providencia species* (including *Providencia rettgeri*)
- *Salmonella species* (including *Salmonella typhi*)
- *Shigella species*

Gram-positive Bacteria

- *Streptococcus agalactiae*

Anaerobic Bacteria

- *Porphyromonas (Bacteroides) melaninogenicus*
- *Prevotella (Bacteroides) bivius*

5.3 Pharmacokinetic Properties

Ceftriaxone

Absorption: Following intramuscular injection, mean peak plasma ceftriaxone levels are approximately half those observed after intravenous administration of an equivalent dose. The maximum plasma concentration after a single intramuscular dose of 1 gram is about 81 mg/l and is reached in 2 to 3 hours after administration. The area under the plasma concentration-time curve after intramuscular administration is equivalent to that after intravenous administration of an equivalent dose.
After intravenous bolus administration of ceftriaxone 500 mg and 1 g, mean peak plasma ceftriaxone (Cmax) levels are approximately 120 and 200 mg/l respectively. After intravenous infusion of ceftriaxone 500 mg, 1 g and 2 g, the plasma ceftriaxone levels are approximately 80, 150 and 250 mg/l respectively. An 8 to 15 % increase in Cmax is seen on repeated administration; steady state is reached in most cases within 48 to 72 hours depending on the route of administration.

Distribution: The volume of distribution of ceftriaxone is 7 to 12 litre. Ceftriaxone is reversibly bound to albumin. Plasma protein binding is about 95 % at plasma concentrations below 100 mg/l. Binding is saturable and the bound portion decreases with rising concentration (up to 85 % at a plasma concentration of 300 mg/l).
Metabolism: Ceftriaxone is not metabolized systemically; but is converted to inactive metabolites by the gut flora.

Elimination: Plasma clearance of total ceftriaxone (bound and unbound) is 10 to 22 ml/min. Renal clearance is 5 to 12 ml/min. 50 to 60 % of ceftriaxone is excreted unchanged in the urine, primarily by glomerular filtration, while 40 to 50 % is excreted unchanged in the bile. The elimination half-life of total ceftriaxone in adults is about 8 hours.

Tazobactam
Peak plasma concentration is attained immediately after completion of an I.V. infusion. Plasma protein binding of tazobactam is approximately 23%. Tazobactam is widely distributed in tissues and body fluids including intestinal mucosa, gall bladder, lung and bile.
Approximately 20% of a dose of tazobactam is metabolized to a single metabolite that has been found to be microbiologically inactive. Tazobactam is eliminated by the kidney via glomerular filtration and tubular secretion. 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. In healthy subjects, plasma elimination half-life of tazobactam range from 0.7 to 1.2 hours following single or multiple doses.

6. Pharmaceutical Particulars

6.1 Shelf-life

24 months.

6.2 Packaging Information

The Ceftriaxone and Tazobactam For Injection 1.125 gm and Sterile Water For Injection USP 10 ml is packed in 20 ml USP Type III glass vial stoppered with 20 mm grey Bromo butyl rubber stopper and AL flip off seal Red colour.

6.3 Storage

Store below 25°C. Protect from light and moisture.
Keep out of reach of children.

7. Details of Manufacturer

Inject care parentrals Pvt.Ltd.
PLOT NO. 130, SILVASA ROAD, GIDC,
VAPI - 396 195, DIST.- VALSAD

8. Date of Revision

September 2023.