FREDACEF

ROENTGEN IMPEX

Module 1: - Administrative information and prescribing information:

1.3.1Summary of Product Characteristics (SmPC):

Summary Product Characteristics (SPC)

1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT

FREDACEF (Combipack of Ceftriaxone and Sulbactam For Injection 1.5 gm & Sterilised Water For Injections BP 10 ml)

Strength
Each Combipack contains
1. Each Vial contains
   Sterile Ceftriaxone Sodium USP
   eq. to Ceftriaxone 1000 mg
   Sterile Sulbactam Sodium USP
   eq. to Sulbactam 500 mg

2. One Ampoule of Sterilised water for injections BP 10 ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Bath size: 1,00,000 vials

Sr. No.	Ingredients	Spec	Qty/ (mg)	(%) Overage[$]	Qty Per Batch (Kg)	Category
1.	Ceftriaxone Sodium eq. to Ceftriaxone	USP	1080.00 mg1000.00 mg	2 %	110.00 kg	Active
2.	Sulbactam Sodium eq. to Sulbactam	USP	547.12mg 500.00mg	2 %	55.80 kg	Active

USP=United States Pharmacopoeia
BP = British Pharmacopoeia

[$]Overages are added to compensate loss during manufacturing & quantity may be varied Based on Potency of API

3. PHARMACEUTICAL FORM

Powder for Injection

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ceftriaxone & Sulbactam for Injection is indicated in infections caused by Ceftriaxone sodiumsensitive pathogens and may be used in the clinical settings in Sepsis, Meningitis, Abdominal Infections (e.g. Peritonitis, infection of the biliary tract), infections of the Bones, Joints, Soft tissue, Skin and of wounds, Renal and Urinary Tract Infections, Respiratory tract Infections, particularly Pneumonia, and Ear, Nose and Throat Infections, and uncomplicated gonorrhea.

4.2 Posology and method of administration

Adults: The usual adult daily dose in adults with normal renal function is equivalent to ceftriaxone 1 to 2 grams given once a day (or in two equally divided doses given 12 hr apart). The dose depends upon the type of infection and its severity. (The total daily Ceftriaxone dose should never exceed 4 grams) Dosage of Ceftriaxone & Sulbactam in patients with renal impairment: Dosage regimens of Ceftriaxone & Sulbactam For Injection should be adjusted in patients with marked decrease in renal function (creatinine clearance of less than 30ml / min) to compensate for the reduced clearance of Sulbactam.
Patients with creatinine clearance between 15 and 30 ml/min should receive a maximum of 1g of Sulbactam every 12 hours (maximum daily dosage of 2g Sulbactam). Patients with creatinine clearance of less than 15ml /min should receive 500mg Sulbactam every 12 hours.
Paediatric Patients: For the treatment of skin and skin structure infections: The recommended total daily ceftriaxone (equivalent) dose is 50 to 75 mg/kg, once a day (or in two equally divided doses 12 hrs apart). The total daily dose should not exceed 1G. For the treatment of acute bacterial otitis media, a single IM ceftriaxone equivalent dose is 50 mg/kg (not to exceed 1 G).
For the treatment of other serious infections (other than meningitis), the recommended total daily dose (equivalent to ceftriaxone) is 50 to 75 mg/kg, in two equally divided doses given every 12 hours.
The total daily dose (equivalent to ceftriaxone) should not exceed 2G.
Meningitis: It is recommended that the initial therapeutic dose (equivalent to Ceftriaxone) be 100 mg/kg (not to exceed 4 grams). The daily dose (in terms of ceftriaxone) may be administered once a day (or in two equally divided doses every 12 hours).

4.3 Contraindications
Ceftriaxone & Sulbactam for Injection is contraindicated in patients with known allergy to Cephalosporin group of antibiotics.
Hypersensitivity to penicillin may pre-dispose the patient to the possibility of allergic cross-reactions.

4.4 Special warnings and precautions for use
Superinfections with non-susceptible microorganisms may occur. Since pseudo-membranous colitis has been reported to occur with ceftriaxone, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of Ceftriaxone & Sulbactam For Injection. Ceftriaxone, if given at higher than standard doses, may get precipitated as its calcium salt in the gall bladder, the shadows of which seen under

sonography, could be mistaken for gallstones. However, it is largely asymptomatic and the shadows disappear on discontinuation of therapy or in due course after the completion of therapy. Even in the case of symptomatic cases surgical interventions are not required, and they may be treated conservatively.
Discontinuation of Ceftriaxone & Sulbactam For Injection treatment in symptomatic cases is at the discretion of the clinician. Like other cephalosporins, ceftriaxone is known to displace bilirubin from serum albumin. Hence caution needs to be exercised when considering Ceftriaxone & Sulbactam For Injection for the treatment of neonates with hyper-bilirubinemia.
In order to avoid the risk of development of bilirubin encephalopathy, use of Ceftriaxone & Sulbactam For Injection is best avoided in neonates in general and prematures in particular. During prolonged treatment with Ceftriaxone & Sulbactam For Injection, blood profile should be checked at regular intervals.
The allergic reaction is the indication for the interruption of Ceftriaxone & Sulbactam For Injection therapy.
Ceftriaxone & Sulbactam For Injection should not be administered to neonates in general, hyperbilirubinemic neonates in particular, and to premature babies.

4.5 Interaction with other medicinal products and other forms of interaction
No impairment of renal function has been observed after concurrent administration of large doses of Ceftriaxone and potent diurectics.
There is no evidence to suggest that Ceftriaxone increases renal toxicity of aminoglycosides. The elimination of Ceftriaxone is not altered by probenecid. Ceftriaxone and chloramphenicol have been shown to be antagonistic in in vitro studies. In cases of concomitant severe renal and hepatic dysfunction, the plasma concentrations of ceftriaxone should be determined at regular intervals. Coombs test may show false-positive results during Ceftriaxone therapy. Non-enzymatic urinary glucose estimation methods may give false-positive results.

4.6 Fertility, pregnancy and lactation
Pregnancy: Category B: Either animal-reproduction studies have not demonstrated a foetal risk but there are no controlled studies in pregnant women or animal-reproduction studies have shown an adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies in women in the 1st trimester (and there is no evidence of a risk in later trimesters).
Lactation: Caution when used during lactation.
Fertility: Reproductive studies have shown no evidence of adverse effects on male or female fertility

4.7 Effects on ability to drive and use machines
During treatment with ceftriaxone and sulbactam 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
Gastrointestinal: Diarrhoea, nausea & vomiting (less frequent), stomatitis, and glossitis.

Hepatic: Elevations of SGOT/SGPT.
Hematological: Eosinophilia, thrombocytopenia, leukopenia, granulocytopenia, hematoma or bleeding.
Skin reactions: Exanthema, allergic dermatitis, pruritis, urticaria, edema, erythema multiforme.
Other side effects such as headache, dizziness, increase in serum creatinine, mycosis of the genital tract, oliguria, fever, and shivering have been observed.

4.9 Overdose.
Symptoms: In the case of Ceftriaxone overdose nausea, vomiting, diarrhoea, can occur. Ceftriaxone concentration cannot be reduced by haemodialysis or peritoneal dialysis.
Treatment: There is no specific antidote. Treatment is symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

Pharmacotherapeutic group: Cephalosporin and beta-lactamase inhibitors.
ATC code: J01DD54
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. Sulbactam does not possess any useful antibacterial activity, except against Neisseriaceae and Acinetobacter. As Sulbactam also binds with some penicillin-binding proteins, sensitive strains are also often rendered more susceptible to Sulbactam/Ceftriaxone than to Ceftriaxone alone. The combination of Sulbactam and Ceftriaxone is active against all organisms sensitive to ceftriaxone.

5.2 Pharmacokinetic properties
Ceftriaxone Sodium
Absorption: Ceftriaxone is completely absorbed with peak plasma concentrations of 40mcg/ml and 80mcg/ml at 2 to 3 hours after IM injection of 500mg and 1g dose of Ceftriaxone respectively. It follows a dose dependent non-linear pharmacokinetic because of the high (80-85%) plasma protein. A similar AUC is observed after administration of an equivalent dose of Ceftriaxone by the IM or IV route.
Distribution: Widely distributed in body tissues and fluid, it crosses the inflamed as well as non-inflamed meninges and may achieve therapeutic concentrations in the CSF. Irrespective of the dose Ceftriaxone has a half-life of between 6 to 9 hours. The half-life may be prolonged in neonates. While moderate renal impairment may not affect the halflife of

Ceftriaxone appreciably, severe renal impairment does, with a longer half-life, which is further increased if accompanied with liver impairment.

Metabolism and Excretion: Elimination half-life is about 8.7 hours; 33-67% removed as unchanged drug.

Sulbactam Sodium

Metabolism and Excretion: About 75-85% of Sulbactam is excreted in the urine during the first eight hours of administration.

Sulbactam has a halflife of about 1 hour in healthy volunteers. Serum concentrations reached are proportional to the dose administered. It is predominantly eliminated through kidney in the unchanged form.

5.3 Preclinical safety data

Clinical studies revealed that the combination of Ceftriaxone and Sulbactam had no major problem after intravenous use. Incidence of side-effects due to Ceftriaxone is very negligible.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water For injection	BP

6.2 Incompatibilities

None

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store below 30° C. Protect from light.

6.5 Nature and contents of container

10 X1ml Ampoule

6.6 Special precautions for disposal and other handling

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.

7. APPLICANT/MANUFACTURER

APPLICANT

FREDAN PHARMACEUTICAL NIGERIA LTD.

No. 8Frist Avenue, New Haven, Enugu State, Nigeria

MANUFACTURED

Makcur Laboratories Limited

46/4-7, Dehgam Road Zak Village, Tal. – Dehgam,
Dist.: Gandhinagar-30, GUJARAT, INDIA