1.3 Product Information

1.3.1 Summary of Product Characteristics (SmPC)

Enclosed Overleaf

Prescribing Information (Summary of Product Characteristics)

1. Name of the finished pharmaceutical product
2. Qualitative and quantitative composition
3. Pharmaceutical form
4. Clinical particulars
4.1 Therapeutic indications
4.2 Posology and method of administration
4.3 Contraindications
4.4 Special warnings and special precautions for use
4.5 Interaction with other FPPs and other forms of interaction
4.6 Pregnancy and lactation
4.7 Effects on ability to drive and use machines
4.8 Undesirable effects
4.9 Overdose
5. Pharmacological properties
5.1 Pharmacodynamic properties
5.2 Pharmacokinetic properties
5.3 Preclinical safety data
6. Pharmaceutical particulars
6.1 List of excipients
6.2 Incompatibilities
6.3 Shelf life
6.4 Special precautions for storage
6.5 Nature and contents of container
6.6 Special precautions for disposal and other handling
7. 0 Marketing authorisation holder
8.Marketing authorization number
9.Date of first autorization/renewal of authorization

1. Name of the medicinal product

OFRAMAX S (Ceftriaxone and Sulbactam for Injection 2:1 (1000:500))

Dosage Form: Dry Powder for Injection

2. Qualitative and quantitative composition

Each vial contains:

Sterile blend of Ceftriaxone Sodium USP equivalent to anhydrous Ceftriaxone 1000mg and Sulbactam Sodium USP equivalent to anhydrous Sulbactam 500mg

Sr. No	Raw Material	Specification	Quantity/Vial in mg	Function
1	Ceftriaxone sodium(sterile)*	USP	1248.0	Active Pharmaceutical Ingredient
2.	Sulbactam sodium(sterile)**	USP	624.0	Active Pharmaceutical Ingredient

Remarks:

* Standard quantity of Ceftriaxone sodium is based on 90.0 % w/w assay value as Ceftriaxone and 11.0 % water content.

** Standard quantity of Sulbactam based on 2:1 Ratio.

3. Pharmaceutical form: Dry powder for Injection

Description: Sterile, off white to yellow coloured free flowing powder, distributed in sealed containers and which, when shaken with the prescribed volume of sterile liquid, rapidly form clear and practically particle - free solution.

4. Clinical particulars

4.1 Therapeutic indications

Lower Respiratory Tract Infections

Acute Bacterial Otitis Media

Skin and Skin Structure infections

Urinary Tract Infections (complicated and uncomplicated)

Pelvic inflammatory Disease

Bacterial Septicemia

Bone and Joint infections

Intra-Abdominal infections

Meningitis

Sexually transmitted diseases

Surgical Prophylaxis

The preoperative administration of Ceftriaxone/ Sulbactam Injection 2:1 (1000:500) may reduce the incidence of postoperative infections in patients undergoing surgical procedures

4.2 Posology and method of administration

Ceftriaxone/Sulbactam may be administered by deep intramuscular injection, or as a slow intravenous injection**,** after reconstitution of the solution. The dosage and mode of administration should be determined by the severity of the infection, susceptibility of the causative organism and the patient's condition.

Adults

The usual daily dose [in terms of ceftriaxone] is 1-2 grams given once a day {or in equally divided doses twice a day} depending upon the type and severity of infection. The total daily dose should not exceed 4 grams.

Dosage regimen of Ceftriaxone/Sulbactam should be adjusted in patients with marked decrease in renal function (creatinine clearance of less than 30 ml/min) to compensate for the reduced clearance less than 15 ml/min should receive a maximum of 500 mg of Sulbactam every 12 hours (maximum dosage of 1 gm of Sulbactam).

Pediatric Patients

For the treatment of skin and skin and skin structure infections, the recommended total daily dose {in terms of ceftriaxone} is 50 to 75 mg/kg given once a day (or in equally divided doses twice a day). The total daily doses should not exceed 1 gram. For treatment of acute bacterial otitis media, a single intramuscular dose {in terms of ceftriaxone} of 50 mg/kg (not to exceed 1 gram) is recommended.

For the treatment of serious miscellaneous infections other than meningitis, the recommended total daily dose {in terms of ceftriaxone} is 50 to 75 mg/kg given in divided dose every 12 hours. The total daily dose {in terms of ceftriaxone} should not exceed 2 grams.

In treatment of meningitis, it is recommended that the initial therapeutic dose (in terms of 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 equally divided dose every 12 hours). The usual duration of therapy is 7 to 14 days. Generally, ceftriaxone 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 therapy, longer therapy may be required.

When treating infections caused by Streptococcus pyrogenes, therapy should be continued for at least 10 days. No dosage adjustment is necessary for patients with impairment of renal or hepatic function; however, blood levels should be monitored in patients with severe renal impairment [eg. Dialysis] patient and in patients with both renal and hepatic dysfunctions.

4.3 Contraindications

Ceftriaxone/Sulbactam is contraindicated in patients with known allergy to penicillins and cephalosporins

4.4 Special warnings and precautions for use

Warnings

Serious or occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving beta-lactam therapy. These reactions are more likely to occur in individuals with a history of hypersensitivity reactions to multiple allergens. If an allergic reaction develops, the drug should be discontinued and appropriate therapy instituted. Pseudomembranous colitis has been reported with the use of Cephalosporins (and other broad-spectrum antibiotics), therefore, it is important to consider its diagnosis in patients who develop diarrhoea in association with antibiotic use.

Treatment with broad-spectrum antibiotics alters the normal flora of the colon and may permit overgrowth of *clostridia.* Studies indicate a toxin produced by *Clostridium difficile* is the primary cause of antibiotic-associated colitis. Mild cases of colitis may respond to drug discontinuance alone. Moderate to severe cases should be managed with fluid, electrolyte, and protein supplementation as indicated

Precautions

General

Although transient elevations of BUN and serum creatinine have been observed, at the recommended dosages, the nephrotoxic potential of ceftriaxone is similar to that of other Cephalsosporins. Ceftriaxone is excreted via both biliary and renal excretion. Therefore, patients with renal failure normally require no adjustment in dosage when usual doses of ceftriaxone are administered but concentrations of drug in the serum should be monitored periodically. If evidence of accumulation exists, dosages should be decreased accordingly. Dosage adjustments should not be necessary in patients with hepatic dysfunction; however, in patients with both hepatic dysfunction and significant renal disease, dosage should not exceed 2 gm daily without close monitoring of serum concentrations.

Alterations in prothrombin times have occurred rarely in patients treated with ceftriaxone. Patients with impaired vitamin K synthesis or low vitamin K stores (e.g. chronic hepatic disease and malnutrition) may require monitoring of prothrombin time during Ceftriaxone/Sulbactam treatment. Vitamin K administration (10mg weekly) may be necessary if the prothrombin time is prolonged before or during therapy. Prolonged use of ceftriaxone may result in overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. Ceftriaxone/ Sulbactam Injection 2:1 (1000:500) should be prescribed with caution in individuals with a history of gastrointestinal disease, especially colitis.

4.5 Interaction with other medicinal products and other forms of interaction

Solutions containing ceftriaxone should not be mixed with or added to solutions containing other agents except 1% Lidocaine Injection BP (for intramuscular injection only). In particular, diluents containing calcium, (e.g. Ringer's solution, Hartmann's solution) should not be used to reconstitute ceftriaxone vials or to further dilute a reconstituted vial for IV administration because a precipitate can form. Ceftriaxone must not be mixed or administered simultaneously with calcium containing solutions (see section 4.2, 4.3, 4.4 and 4.8). Based on literature reports, ceftriaxone is not compatible with amsacrine, vancomycin, fluconazole, aminoglycosides, pentamidine, clindamycin phosphate and labetalol.

4.6 Pregnancy and lactation

Pregnancy

Teratogenic effects: Pregnancy category B. Reproductive studies have been performed in mice and rats at doses upto 20 times the usual human dose and no evidence of embryo toxicity, fetotoxicity or teratogenicity. In primates no teratogenicity or embryogenicity was demonstrated at a dose approximately 3 times the human dose.

There is however no well controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

Low concentrations of Ceftriaxone are excreted in human milk. No risk to nursing infants have been reported but caution should be exercised when ceftriaxone-sulbactam is administered to nursing women.

4.7 Effects on ability to drive and use machines

There is no evidence that Ceftriaxone sulbactam impairs the ability to drive or operate machines.

4.8 Undesirable effects

The most frequently reported adverse reactions for ceftriaxone are eosinophilia, leucopenia, thrombocytopenia, diarrhoea, rash, and hepatic enzymes increased.

Data to determine the frequency of ceftriaxone ADRs was derived from clinical trials.

The following convention has been used for the classification of frequency:

Very common (≥ 1/10)

Common (≥ 1/100 - < 1/10)

Uncommon (≥ 1/1000 - < 1/100)

Rare (≥ 1/10000 - < 1/1000)

Not known (cannot be estimated from the available data)

System Organ Class	Common	Uncommon	Rare	Not Known [a]
Infections and infestations		Genital fungal infection	Pseudo-membranous colitis[b]	Superinfection
Blood and lymphatic system disorders	Eosinophilia Leucopenia Thrombocytopenia	Granulocytopenia Anaemia Coagulopathy		Haemolytic anaemia Agranulocytosis
Immune system disorders				Anaphylactic shock Anaphylactic reaction Anaphylactoid reaction Hypersensitivity Jarisch-Herxheimer reaction
Nervous system disorders		Headache Dizziness		Convulsion
Ear and labyrinth disorders				Vertigo
Respiratory, thoracic and mediastinal disorders			Bronchospasm	

Gastrointestinal disorders	Diarrhoea Loose stools	Nausea Vomiting		Pancreatitis Stomatitis Glossitis
Hepatobiliary disorders	Hepatic enzyme increased			Gall bladder precipitation Kernicterus
Skin and subcutaneous tissue disorders	Rash	Pruritus	Urticaria	Stevens Johnson Syndrome Toxic epidermal necrolysis Erythema multiforme Acute generalised exanthematous pustulosis Drug reaction with eosinophilia and systemic symptoms (DRESS)
Renal and urinary disorders			Haematuria Glycosuria	Oliguria Renal precipitation (reversible)
General disorders and administration site conditions		Phlebitis Injection site pain Pyrexia	Oedema Chills	
Investigations		Blood creatinine		Coombs test false

		increased		positive Galactosaemia test false positive Non enzymatic methods for glucose determination false positive

Description of selected adverse reactions

Infections and infestations

Reports of diarrhoea following the use of ceftriaxone may be associated with *Clostridium difficile*. Appropriate fluid and electrolyte management should be instituted

Ceftriaxone-calcium salt precipitation

Rarely, severe, and in some cases, fatal, adverse reactions have been reported in pre-term and full-term neonates (aged < 28 days) who had been treated with intravenous ceftriaxone and calcium. Precipitations of ceftriaxone-calcium salt have been observed in lung and kidneys post-mortem. The high risk of precipitation in neonates is a result of their low blood volume and the longer half-life of ceftriaxone compared with adults

Cases of ceftriaxone precipitation in the urinary tract have been reported, mostly in children treated with high doses (e.g. ≥ 80 mg/kg/day or total doses exceeding 10 grams) and who have other risk factors (e.g. dehydration, confinement to bed). This event may be asymptomatic or symptomatic, and may lead to ureteric obstruction and postrenal acute renal failure, but is usually reversible upon discontinuation of ceftriaxone

Precipitation of ceftriaxone calcium salt in the gallbladder has been observed, primarily in patients treated with doses higher than the recommended standard dose. In children, prospective studies have shown a variable incidence of precipitation with intravenous application - above 30 % in some studies. The incidence appears to be lower with slow infusion (20 - 30 minutes). This effect is usually asymptomatic, but the precipitations have been accompanied by clinical symptoms such as pain, nausea and vomiting in rare cases. Symptomatic treatment is recommended in these cases. Precipitation is usually reversible upon discontinuation of ceftriaxone.

4.9 Overdose

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

5. Pharmacological properties

5.1 Pharmacodynamic properties

The antibacterial activity of Ceftriaxone/Sulbactam Injection 2:1 (1000:500) due to the inhibition of cell wall synthesis is attained by the ceftriaxone. Ceftriaxone has a high degree of stability in the presence of beta-lactamases, both *penicillinases* and *cephalosporinases* of gram-negative and positive bacteria. But chromosomally mediated enzymes though less common can be induced in some strains of *Klebsiella*, *Enterobacter* and *Serratia* species.

Sulbactam in Ceftriaxone/Sulbactam Injection 2:1 (1000:500) is a potent, highly specific inhibitor of a wide variety of beta lactamases produced by common gram-negative and gram-positive aerobes and anaerobes. By forming a protein complex with beta-lactamases, Sulbactam irreversibly blocks their hydrolytic activity. Thus, the full potential of ceftriaxone against *Enterobacter* and *Pseudomonas* species is restored by the addition of Sulbactam.

The combination of Sulbactam and ceftriaxone sodium is active against all the organisms' sensitive to Ceftriaxone. In addition, it demonstrates synergistic activity (reduction in minimum inhibitory concentrations for the combination versus those of each component) in a variety of organisms.

5.2 Pharmacokinetic properties

Following intramuscular administration, peak serum concentrations of Sulbactam and ceftriaxone are seen between 15 minutes to 2 hours. The maximum plasma concentration of ceftriaxone after a single IM dose of 1.0g is about 81mg/L and is reached in 2-3hours after the dose, while that of Sulbactam sodium is 6-24 mcg/ml and is reached approximately in 1 hour in

healthy volunteers. Serum concentrations have shown to be proportional to the dose administered.

The area under the plasma concentration-time curve after IM administration is equivalent to that after IV administration of an equivalent dose, indicating 100% bioavailability of intramuscularly administered ceftriaxone. On intravenous administration, ceftriaxone diffuses into the tissue fluid, where, if it is given in the recommended dosage range, bactericidal concentrations lasting up to 24 hours may be maintained. Ceftriaxone is reversibly bound to albumin, and the binding decreases with the increase in concentration e.g. from 95% binding at plasma concentrations of < 100 mg/L to 85% binding at 300 mg/L. Owing to the lower albumin content, the proportion of free ceftriaxone in intestitial fluid is correspondingly higher than in plasma.

The volume of distribution of ceftriaxone is 7-12 L and that of Sulbactam is 18-27.6L. Both are widely distributed into body tissues and fluids. Ceftriaxone crosses placenta and is distributed in the amniotic fluid. It is also distributed in milk. In healthy, young adult volunteers, the total plasma clearance is 10-22mL/min. The renal clearance is 5-12 ml/min. Approximately 75-85% of Sulbactam and 50-60% of ceftriaxone is excreted unchanged in the urine, while the remaining dose is excreted in the bile.

The mean plasma elimination half-life of ceftriaxone is 8 hours in healthy, young adult volunteers. In neonates, urinary recovery accounts for about 70% of the dose. In Infants aged less than eight days and in elderly persons aged over 75years, the average elimination half-life is usually 2-3 times that in the young adult group. The mean serum half- life of sulbactam is approximately 1 hour.

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the Summary of Product Characteristics.

6. Pharmaceutical particulars

6.1 List of excipients

Not Applicable.

6.2 Incompatibilities

None

6.3 Shelf life

24 months

6.4 Special precautions for storage

Before Opening

Store at temperature below 30°C. Keep out of reach of children.

Reconstituted Solution

Reconstituted solution can be stored for 24 hours at 2^0C-8^0C. Discard unused contents appropriately

6.5. Nature and contents of container:

15ml USP Type – III glass vials sealed with 20mm Grey Butyl Rubber stopper and 20mm Flip off Seal (Taxim blue). Such 10ml vial is packed in Carton along with SWFI & package insert.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

7.Marketing authorization holder: -

Sun Pharmaceuticals Ind. Ltd.
Sun House, 201 B/1,
Western Express Highway,
Goregaon (East), Mumbai – 400063, India.

8. Marketing authorization number(s):

C4-0168

9. Date of first authorization/renewal of the authorization:

November, 2019