1.3 Product Information

1.3.1 Summary of Product Characteristics (SmPC)

Enclosed.

Summary Product Characteristics

1. Name of the proprietary product: SASTRIAXONE

Name of the nonproprietary International Product: Ceftriaxone for Injection USP 1gm

Route of Administration: Intramuscular Only

2. Qualitative and Quantitative composition:

Sr. No.	Ingredient	Specification	Qty / Vial (mg)	Reason on inclusion
1.	Ceftriaxone Sodium (Sterile)	USP	*1000 mg	Active

Where, USP = United States Pharmacopoeia.

Note:
*Value of Target weight will vary accordingly to the Water Content and Assay of Ceftriaxone sodium.

3. Pharmaceutical Form: Powder for Injection

4. Clinical Particulars:

4.1 Therapeutic indications:
Ceftriaxone sodium is a broad-spectrum bactericidal cephalosporin antibiotic. Ceftriaxone is active in vitro against a wide range of Gram-positive and Gram-negative organisms, which include β-lactamase producing strains.
Ceftriaxone is indicated in the treatment of the following infections either before the infecting organism has been identified or when known to be caused by bacteria of established sensitivity.
Pneumonia
Septicaemia
Meningitis
Skin and soft tissue infections
Infections in neutropenic patients
Gonorrhoea
Peri-operative prophylaxis of infections associated with surgery.

4.2 Posology and method of administration:
Ceftriaxone may be administered by deep intramuscular injection, or as a slow intravenous injection**,** after reconstitution of the solution according to the directions given below. 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. Under most circumstances a

once-daily dose or, in the specified indications, one dose will give satisfactory therapeutic results.

Diluents containing calcium, (e.g. Ringer's solution or 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. Precipitation of ceftriaxone-calcium can also occur when ceftriaxone is mixed with calcium-containing solutions in the same IV administration line. Therefore, ceftriaxone and calcium-containing solutions must not be mixed or administered simultaneously.

Intramuscular injection: 1g ceftriaxone should be dissolved in 3.5ml of 1% Lidocaine Injection BP. The solution should be administered by deep intramuscular injection. Doses greater than 1g should be divided and injected at more than one site.

Intravenous injection: 1g ceftriaxone should be dissolved in 10ml of Water for Injections. The injection should be administered over at least 2-4 minutes, directly into the vein or via the tubing of an intravenous infusion.

Adults and children 12 years and over:

Standard therapeutic dosage: 1g once daily.

Severe infections: 2-4 g daily, normally as a once daily dose.

The duration of therapy varies according to the course of the disease. As with antibiotic therapy in general, administration of ceftriaxone should be continued for a minimum of 48 to 72 hours after the patient has become afebrile or evidence of bacterial eradication has been obtained.

Acute, uncomplicated gonorrhoea: One dose of 250mg intramuscularly should be administered. Simultaneous administration of probenecid is not indicated.

Peri-operative prophylaxis: Usually one dose of 1g given by intramuscular or slow intravenous injection. In colorectal surgery, 2g should be given intramuscularly (in divided doses at different injection sites), by slow intravenous injection or by slow intravenous infusion**,** in conjunction with a suitable agent against anaerobic bacteria.

Elderly: These dosages do not require modification in elderly patients provided that renal and hepatic function are satisfactory.

In the neonate, the intravenous dose should be given over 60 minutes to reduce the displacement of bilirubin from albumin, thereby reducing the potential risk of bilirubin encephalopathy.

Children under 12 years

Standard therapeutic dosage: 20-50mg/kg body-weight once daily.

Up to 80mg/kg body-weight daily may be given in severe infections, except in premature neonates where a daily dosage of 50mg/kg should not be exceeded. For children with body weights of 50kg or more, the usual dosage should be used. Doses of 50mg/kg or over should be given by slow intravenous infusion over at least 30 minutes. Doses greater than 80mg/kg body weight should be avoided because of the increased risk of biliary precipitates.

Renal and hepatic impairment: In patients with impaired renal function, there is no need to reduce the dosage of ceftriaxone provided liver function is intact. Only in cases of pre-terminal renal failure (creatinine clearance <10ml per minute) should the daily dosage be limited to 2g or less.

In patients with liver damage there is no need for the dosage to be reduced provided renal function is intact.

In severe renal impairment accompanied by hepatic insufficiency, the plasma concentration of ceftriaxone should be determined at regular intervals and dosage adjusted.

In patients undergoing dialysis, no additional supplementary dosage is required following the dialysis. Plasma concentrations should be monitored, however, to determine whether dosage adjustments are necessary, since the elimination rate in these patients may be reduced.

4.3 Contraindications:
Ceftriaxone should not be given to patients with a known history of hypersensitivity to cephalosporin antibiotics. Ceftriaxone should not be given to neonates with jaundice or those who are hypoalbuminaemic or acidotic or have other conditions, such as prematurity, in which bilirubin binding is likely to be impaired.

4.4 Special warnings and precautions for use:
The stated dosage should not be exceeded.
Care is required when administering Ceftriaxone to patients who have previously shown hypersensitivity (especially anaphylaxis) to penicillins or other B-lactam antibiotics, as occasional instances of cross-antigenicity between cephalosporins and these antibiotics have been reported. If an allergic reaction is displayed to Ceftriaxone, use of the drug should be immediately discontinued. Care should be used in the presence of renal or hepatic impairment.

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 diuretics (e.g. Furosemide). There is no evidence that ceftriaxone increases renal toxicity of aminoglycosides. No effect similar to that of disulfiram has been demonstrated after administration of alcohol with Ceftriaxone. Ceftriaxone does not contain an N-methylthiotetrazole moeity associated with possible ethanol intolerance and bleeding problems.
The elimination of Ceftriaxone is not altered by probenecid. In an in vitro-study antagonistic effects have been observed with the combination of Chloramphenicol & Ceftriaxone.
In patients treated with Ceftriaxone the Coombs test may become false positive . Ceftriaxone, like other antibiotics , may result in false – positive tests for galactosemia.
Likewise , non enzymatic methods for the glucose determination in urine may give false – positive results. For this reason, urine – glucose determination during therapy with Ceftriaxone should be done enzymatically.

4.6 Fertility, pregnancy and lactation:
Teratogenic effects:
Pregnancy category B. Reproductive studies have been performed in mice and rats , at a dose up to 20times the usual human dose and have no evidence of embryotoxicity**,** fatotoxicity and teratogenecity to primates , no embryotoxicity or teratogenecity was remonstrated at a dose approximately 3 times a human dose.

Nonteratogenic effects
In rats in the segment I (fertility and general reproduction) and segment III (perinatal and postnatal) studies with intravenously administered Ceftraixone, no adverse effects were noted on various reproductive parameters during gestation and lactation, including post natal growth , functional behavior and reproductive ability of the offspring, at doses of 586 mg/kg/day or less.
There are, however, no adequate and well controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, these drugs should be used during pregnancy only if clearly needed.

Nursing mothers
Low concentration of Ceftriaxone are excreted in human milk, No risk to nursing infants has been reported but caution should be exercised when Ceftriaxone is administrated to a nursing women.

Safety in human pregnancy has not been established.

4.7 Effects on ability to drive and use machines:
None.

4.8 Undesirable effects:
Ceftriaxone 1000 generally well tolerate
Local reactions: Pain, induration and tendemess at site of injection, phlebitis.
Hypersensitivity: Less frequently reported were rash, pruritus, fever or chills
Hematologic: Eosinophilia, thrombocytosis and leucopenia
Gastrointestinal: Diarrhoea, Nausea, vomiting
Hepatic: elevations of AST or ALT
Less frequently reported were elevations of alkaline phosphatase and bilirubin.
Renal: elevations of BUN
CNS: headache or dizziness were reported occasionally.
GENITOURINARY moniliasis or vaginitis were reported occasionally.
MISCELLANEOUS diaphoresis and flushing were reported occasionally.
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.
Other rare adverse reactions include, hematuria, jaundice, leukocytosis,lymphocytosis, monocytosis, nephrolithiasis, palpitations, a decrease in the prothrombin time, renal precipitations, seizures, and serum sickness.

4.9 Overdose:
In the case of overdosage, plasma concentrations would not be reduced by haemodialysis or peritoneal dialysis. There is no specific antidote. Treatment of overdosage should be symptomatic.

5. Pharmacological properties:
5.1 Pharmacodynamic properties:
Pharmacotherapeutic group: Antibacterial, cephalosporin.

ATC code: J01DD04

Ceftriaxone has potent bactericidal activity against a wide range of Gram-positive and, especially, Gram-negative organisms. The spectrum of activity includes both aerobic and some anaerobic species. It has considerable resistance to degradation by most bacterial β-lactamases.
Ceftriaxone kills bacteria by interfering with the synthesis of the bacterial cell wall. Ceftriaxone binds with high affinity to penicillin binding proteins in the bacterial cell wall, thus interfering with peptidoglycan synthesis. The final stage in the synthesis or peptidoglycan involves the completion of the cross-linking, and the terminal glycine residue of the pentaglycine bridge is linked to the fourth residue of the pentapeptide (D-alanine). The transpeptidase enzyme that performs this step is inhibited by cephalosporins and penicillins. As a result the bacterial cell wall is weakened, and the cell swells and then ruptures.

5.2 Pharmacokinetic properties:
The pharmacokinetics of Ceftriaxone are largely determined by its concentration-dependent binding to plasma albumin. Plasma concentrations: Mean peak concentrations after bolus

intravenous injection are about 120mg/l following a 500mg dose and about 200mg/l following a 1g dose; mean levels of 250mg/l are achieved after infusion of 2g over 30 minutes. Intramuscular injection of 500mg Ceftriaxone in 1% lignocaine produces mean peak plasma concentrations of 40-70 mg/l within one hour. Bioavailability after intramuscular injection is 100%.

Excretion: Ceftriaxone is eliminated mainly as unchanged drug, approximately 60% of the dose being excreted in the urine (almost exclusively by glomerular filtration) and the remainder via the biliary and intestinal tracts. The total plasma clearance is 10-22 ml/min. The renal clearance is 5-12 ml/min. A notable feature of Ceftriaxone is its relatively long plasma elimination half-life of approximately eight hours which makes single or once daily dosage of the drug appropriate for most patients. The half-life is not significantly affected by the dose, the route of administration or by repeated administration.

5.3 Preclinical safety data:

Carcinogenesis

Considering the maximum duration of treatment and the class of the compound,carcinogenic studies with Ceftriaxone in animals have not been performed. The maximum duration of animal toxicity studies was 6 months.

Mutagenesis

Genetic toxicological 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 mutagenic activity in these studies

Impairment of fertility

Ceftriaxone produced no impairment in fertility when given intravenously to rats at daily doses upto 586 mg/kg/day, approximately 20 times the recommended dose of 2 gm/day.

6. Pharmaceutical Particulars:

6.1 List of Excipients:

No Excipients are used.

6.2 Incompatibilities:

Nil.

6.3 Shelf Life: Unopened – 24 months.

After reconstitution: The reconstituted solution should be used within 24 hour when stored at 2-8^0C.

6.4 Special Precautions for storage:

This medicinal product does not require any special storage conditions.

Stored the reconstituted solution at 2-8^0C, do not freeze.

Store the unopened vial below 30° C, protected from light.

6.5 Nature and contents of container:

White to yellowish-orange crystalline powder filled in a 10 ml Clear glass vial, plugged with grey butyl rubber plug with flip-off seal, packed in a carton along with 10ml Water for Injection BP and Pack insert.

6.6 Special precautions for disposal and other handling:
No special requirements.

7. Marketing Authorization Holder: M/S. SASTEK MEGA PHARMA & CHEMICAL CO.LTD

8. Marketing Authorization Number: ---

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

10. Date of revision of text: February 2021