





<b>Brand Name : ROFIN</b>	
<b>Generic Name : Ceftriaxone for Injection USP 1 g</b>	

#### 4.3 Contraindications:

Ceftriaxone is contraindicated in patients with known hypersensitivity to beta-lactam antibiotics. In patients hypersensitive to penicillin, the possibility of allergic cross-reactions should be borne in mind. Hyperbilirubinaemic newborns and preterm newborns should not be treated with ceftriaxone. In-vitro studies have shown that ceftriaxone can displace bilirubin from its binding to serum albumin and bilirubin encephalopathy can possibly develop in these patients. Ceftriaxone is contraindicated in: • Premature newborns up to a corrected age of 41 weeks (weeks of gestation + weeks of life), • Full-term newborns (up to 28 days of age) with Jaundice, or who are hypoalbuminaemic or acidotic because these are conditions in which bilirubin binding is likely to be impaired or if they require calcium treatment, or calcium-containing infusions because of the risk of precipitation of ceftriaxone - calcium.

#### 4.4. Special warnings and special precautions for use

The stated dosage should not be exceeded.

Before therapy with ceftriaxone is instituted, careful inquiry should be made to determine whether the patient has had any previous hypersensitivity reactions to ceftriaxone, cephalosporins, penicillins, or other beta - lactam drugs.

In patients of any age ceftriaxone must not be mixed or administered simultaneously with any calcium-containing solutions, even via different infusion lines or at different infusion sites

Discontinuation of ceftriaxone treatment in symptomatic cases should be at the discretion of the physician. In children, doses greater than 80mg/kg body weight should be avoided because of the increased risk of biliary precipitates.

Cephalosporins may cause bleeding due to hypoprothrombinaemia and should be used with caution in patients with renal or hepatic impairment, malnourished patients or those with low vitamin K levels and also in patients receiving prolonged cephalosporin therapy who are at increased risk of developing hypoprothrombinaemia.

Ceftriaxone should be discontinued if severe and/or bloody diarrhoea occurs during treatment and appropriate therapy instituted. Ceftriaxone should be used with caution in individuals with a previous history of gastro - intestinal disease, particularly colitis.

#### 4.5 Interaction with other medicinal products and other form of interactions :

Do not use diluents containing calcium, such as Ringer's solution or Hartmann's solution, to reconstitute ceftriaxone vials or to further dilute a reconstituted vial for administration because a precipitate can form. Ceftriaxone must not be administered simultaneously with calcium-containing solutions.

Antibiotics: In an in vitro study, antagonistic effects have been observed with the combination of chloramphenicol and ceftriaxone.

Anticoagulants: As ceftriaxone has an N-methylthiotriazine side-chain, it might have the potential to cause hypoprothrombinaemia resulting in an increased risk of bleeding in patients treated with anticoagulants.

Oral Contraceptives: Ceftriaxone may adversely affect the efficacy of oral hormonal contraceptives.

<b>Brand Name : ROFIN</b>	
<b>Generic Name : Ceftriaxone for Injection USP 1 g</b>	

#### 4.6 Pregnancy and Lactation:

##### Pregnancy

Ceftriaxone crosses the placental barrier. Safety in human pregnancy has not been established. Reproductive studies in animals have shown no evidence of embryotoxicity, fetotoxicity, teratogenicity or adverse effects on male or female fertility, birth or perinatal and postnatal development. In primates, no embryotoxicity or teratogenicity has been observed. Therefore ceftriaxone should not be used in pregnancy unless absolutely indicated.

##### Breast-feeding

Low concentrations of ceftriaxone are excreted in human milk. Caution should be exercised when ceftriaxone is administered to a nursing woman.

#### 4.7 Effects on ability to drive and use machine:

Ceftriaxone has been associated with dizziness, which may affect the ability to drive or operate machinery.

#### 4.8 Undesirable effects:

The undesirable effects usually are mild and short-term. Rarely, severe, and in some cases fatal, adverse reactions have been reported in preterm and full term newborns (aged <28 days) who had been treated with intravenous ceftriaxone and calcium . The high risk of precipitation in newborns is due to their low blood volume and the longer half life of ceftriaxone compared with adults.

Ceftriaxone must not be mixed or administered simultaneously with calcium -

containing solutions or products, even via different infusion lines. Gastrointestinal Common ( $\geq 1\% - <10\%$ ): Loose stools or diarrhoea (diarrhoea may sometimes be a symptom of pseudomembranous colitis, see 4.4 Special warnings and precautions for use), nausea, vomiting, stomatitis and glossitis. Rare ( $\geq 0.01\% - <0.1\%$ ): Abdominal pain. Infections Superinfection caused by microorganisms non-susceptible to ceftriaxone such as yeasts, fungi (mycosis of the genital tract) or other resistant microorganisms may develop. Pseudomembranous colitis is a rare undesirable effect caused by infection with *Clostridium difficile* during treatment with ceftriaxone. Therefore, the possibility of the disease should be considered in patients who present with diarrhoea following antibacterial agent use. Hypersensitivity Uncommon ( $\geq 0.1\% - <1\%$ ): Maculopapular rash or exanthema, pruritus, urticaria, oedema, shivering and anaphylactic or anaphylactoid reactions (e.g. bronchospasm) and allergic dermatitis have occurred.

**Brand Name : ROFIN**

**Generic Name : Ceftriaxone for Injection USP 1 g**

Rare ( $\geq 0.01\%$  -  $< 0.1\%$ ): Drug fever, shivering. Anaphylactic-type reactions such as bronchospasm are rare. Very rare ( $< 0.01\%$ ): Isolated cases of severe cutaneous adverse reactions (erythema multiforme, Stevens Johnson Syndrome and Lyell's Syndrome/toxic epidermal necrolysis) have been reported. Blood and lymphatic system disorders Common ( $\geq 1\%$  -  $\leq 10\%$ ): Haematological reactions have included anaemia (all grades), haemolytic anaemia, granulocytopenia, leucopenia, neutropenia, thrombocytopenia and eosinophilia. Coagulation disorders have been reported as very rare side effects. Unknown frequency: Immune mediated haemolytic anaemia Unknown frequency of agranulocytosis ( $< 500/\text{mm}^3$ ) has been reported, mostly after 10 days of treatment and following total doses of 20g or more. There have been rare reports of fatal haemolysis in association with ceftriaxone. Ceftriaxone has rarely been associated with prolongation of prothrombin time, however, bleeding and bruising due to hypoprothrombinaemia may be more prevalent in patients with renal or hepatic impairment, malnourished patients or those with low vitamin K levels and patients receiving prolonged ceftriaxone therapy. Central Nervous system Rare ( $\geq 0.01\%$  -  $< 0.1\%$ ): Headache, vertigo and dizziness. Administration of high doses of cephalosporins, particularly in patients with renal insufficiency, may result in convulsions. Renal and Urinary Rare ( $\geq 0.01\%$  -  $< 0.1\%$ ): Glycosuria, oliguria, haematuria, increase in serum creatinine. Very rare ( $< 0.01\%$ ): Cases of renal precipitation have been reported, mostly in children older than 3 years and who have been treated with either high daily doses (e.g.  $\geq 80\text{mg/kg/day}$ ) or total doses exceeding 10 grams and presenting other risk factors (e.g. fluid restrictions, confinement to bed, etc.). The risk of precipitate formation is increased in immobilized or dehydrated patients. This event may be symptomatic or asymptomatic, may lead to renal insufficiency and anuria, and is reversible upon discontinuation of ceftriaxone. Acute renal tubular necrosis may occur rarely with ceftriaxone. Hepatobiliary system Rare ( $\geq 0.01\%$  -  $< 0.1\%$ ): Hepatitis and/or cholestatic jaundice, increase in liver enzymes. Transient elevations in liver function tests have been reported in a few cases. Shadows which have been mistaken for gallstones, but which are precipitates of calcium ceftriaxone, have been detected by sonograms. These abnormalities are commonly observed after an adult daily dose of two grams per day or more, or its equivalent in children; these abnormalities were particularly observed in children with an incidence of above 30% in isolated reports. At doses of two grams a day or above these biliary precipitates may occasionally cause symptoms. Should patients develop symptoms, non-surgical management is recommended and discontinuation of ceftriaxone should be considered. The evidence suggests biliary precipitates usually disappear once ceftriaxone has been stopped. The risk of biliary precipitates may be increased by treatment duration greater than 14 days, renal failure, dehydration or total parenteral nutrition. Pancreas Very rare ( $< 0.01\%$ ): There have been isolated reports of pancreatitis although a causal relationship to ceftriaxone has not been established. Local effects Rare ( $\geq 0.01\%$  -  $< 0.1\%$ ): Pain or discomfort may be experienced at the site of intramuscular injection immediately after administration but is usually well tolerated and transient. Intramuscular injection without lidocaine solution is painful. Local phlebitis has occurred rarely following intravenous administration but can be minimized by slow injection over at least 2-4 minutes.

<b>Brand Name : ROFIN</b>	
<b>Generic Name : Ceftriaxone for Injection USP 1 g</b>	

#### 4.9 Overdose:

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

### 5. PHARMACOLOGICAL PROPERTIES

#### 5.1 Pharmacodynamic properties

Ceftriaxone is a cephalosporin/cephamycin beta-lactam antibiotic used in the treatment of bacterial infections caused by susceptible, usually gram-positive, organisms. Ceftriaxone has in vitro activity against gram-positive and gram-negative aerobic and anaerobic bacteria. The bactericidal activity of Ceftriaxone results from the inhibition of cell wall synthesis and is mediated through Ceftriaxone binding to penicillin binding proteins (PBPs). Ceftriaxone is stable against hydrolysis by a variety of beta-lactamases, including penicillinases, and cephalosporinases and extended spectrum beta-lactamases.

##### Resistance

Bacterial resistance to ceftriaxone may be due to one or more of the following mechanisms: hydrolysis by beta-lactamases, including extended-spectrum beta-lactamases (ESBLs), carbapenemases and Amp C enzymes that may be induced or stably derepressed in certain aerobic Gram-negative bacterial species.

Reduced affinity of penicillin-binding proteins for ceftriaxone.

Outer membrane impermeability in Gram-negative organisms.

Bacterial efflux pumps.

Clinical efficacy against specific pathogens:

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections.

Commonly susceptible species may be Gram-positive aerobes like *Staphylococcus aureus*, *Streptococcus pyogenes* (Group A), *Streptococcus pneumoniae* etc.; Gram-negative aerobes like *Haemophilus influenzae*, *Neisseria meningitidis*, *Neisseria gonorrhoea*, *Treponema pallidum* and more.

#### 5.2 Pharmacokinetic properties

##### Absorption

##### Intramuscular administration

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 g is about 81 mg/l and is reached in 2 - 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.

<b>Brand Name : ROFIN</b>	
<b>Generic Name : Ceftriaxone for Injection USP 1 g</b>	

### Intravenous administration

After intravenous bolus administration of ceftriaxone 500 mg and 1 g, mean peak plasma ceftriaxone 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.

### Distribution

The volume of distribution of ceftriaxone is 7 – 12 l. Concentrations well above the minimal inhibitory concentrations of most relevant pathogens are detectable in tissue including lung, heart, biliary tract/liver, tonsil, middle ear and nasal mucosa, bone, and in cerebrospinal, pleural, prostatic and synovial fluids. An 8 - 15 % increase in mean peak plasma concentration ( $C_{max}$ ) is seen on repeated administration; steady state is reached in most cases within 48 - 72 hours depending on the route of administration.

### Penetration into particular tissues

Ceftriaxone penetrates the meninges. Penetration is greatest when the meninges are inflamed. Mean peak ceftriaxone concentrations in CSF in patients with bacterial meningitis are reported to be up to 25 % of plasma levels compared to 2 % of plasma levels in patients with uninflamed meninges. Peak ceftriaxone concentrations in CSF are reached approximately 4-6 hours after intravenous injection. Ceftriaxone crosses the placental barrier and is excreted in the breast milk at low concentrations (see section 4.6).

### Protein binding

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).

### Biotransformation

Ceftriaxone is not metabolised systemically; but is converted to inactive metabolites by the gut flora.

### Elimination

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

<b>Brand Name : ROFIN</b>	
<b>Generic Name : Ceftriaxone for Injection USP 1 g</b>	

#### Patients with renal or hepatic impairment

In patients with renal or hepatic dysfunction, the pharmacokinetics of ceftriaxone are only minimally altered with the half-life slightly increased (less than two fold), even in patients with severely impaired renal function.

The relatively modest increase in half-life in renal impairment is explained by a compensatory increase in non-renal clearance, resulting from a decrease in protein binding and corresponding increase in non-renal clearance of total ceftriaxone.

In patients with hepatic impairment, the elimination half-life of ceftriaxone is not increased, due to a compensatory increase in renal clearance. This is also due to an increase in plasma free fraction of ceftriaxone contributing to the observed paradoxical increase in total drug clearance, with an increase in volume of distribution paralleling that of total clearance.

#### Older people

In older people aged over 75 years the average elimination half-life is usually two to three times that of young adults.

#### Paediatric population

The half-life of ceftriaxone is prolonged in neonates. From birth to 14 days of age, the levels of free ceftriaxone may be further increased by factors such as reduced glomerular filtration and altered protein binding. During childhood, the half-life is lower than in neonates or adults.

The plasma clearance and volume of distribution of total ceftriaxone are greater in neonates, infants and children than in adults.

#### Linearity/non-linearity

The pharmacokinetics of ceftriaxone are non-linear and all basic pharmacokinetic parameters, except the elimination half-life, are dose dependent if based on total drug concentrations, increasing less than proportionally with dose. Non-linearity is due to saturation of plasma protein binding and is therefore observed for total plasma ceftriaxone but not for free (unbound) ceftriaxone.

#### Pharmacokinetic/pharmacodynamic relationship

As with other beta-lactams, the pharmacokinetic-pharmacodynamic index demonstrating the best correlation with *in vivo* efficacy is the percentage of the dosing interval that the unbound concentration remains above the minimum inhibitory concentration (MIC) of ceftriaxone for individual target species (i.e. %T > MIC).

### **5.3 Preclinical safety data**

There is evidence from animal studies that high doses of ceftriaxone calcium salt led to formation of concretions and precipitates in the gallbladder of dogs and monkeys, which proved to be reversible. Animal studies produced no evidence of toxicity to reproduction and genotoxicity. Carcinogenicity studies on ceftriaxone were not conducted.



<b>Brand Name : ROFIN</b>	
<b>Generic Name : Ceftriaxone for Injection USP 1 g</b>	

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

None

### 6.2. Incompatibilities

Solutions containing ceftriaxone should not be mixed with or added to other agents except those mentioned in section 6.6

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 including total parenteral nutrition

### 6.3. Shelf life

33 Months.

### 6.4 Special precautions for storage

Store at temperature below 30°C. In a dry place. Protect from direct sunlight. After reconstitution or dilution: From a microbiological point of view, once opened, the product should be used immediately.

### 6.5. Nature and contents of container

Ceftriaxone is supplied in Type II 15ml clear glass vials, closed with a Type I rubber stopper uncoated/coated in Omniflex and sealed with an aluminium/plastic cap, packed in a primary carton along with the Pack Insert

### 6.6. Instruction for use and handling

No special requirements.

## 7. MANUFACTURING AUTHORISATION HOLDER

**Name: SYNCOM FORMULATIONS I LTD.,**

**Plot no. 256-257, Sector-1, Pithampur (Dhar) 454775,**

**INDIA**