For the use of only a Registered Medical Practitioner or Hospital or Laboratory

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Ceftriaxone Injection IP 500mg/1g

SUPRAVA® 500mg/1g सुप्रवा ५००मि ग्रा / सुप्रवा १ ग्रा

Composition:
SUPRAVA® 500mg
Each Vial Contains:
Ceftriaxone Sodium IP (Sterile)
Eq. to Ceftriaxone 500 mg

SUPRAVA® 1g
Each Vial Contains:
Ceftriaxone Sodium IP (Sterile)
Eq. to Ceftriaxone 1000 mg

DESCRIPTION
Ceftriaxone Injection is a sterile, semisynthetic, broad-spectrum cephalosporin antibiotic for intravenous or intramuscular administration. Ceftriaxone sodium is (6R,7R)-7-[2-(2-Amino-4-thiazolyl) glyoxylamido]-8-oxo-3-[[(1,2,5,6-tetrahydro-2-methyl-5,6-dioxo-as-triazin-3-yl) thio]methyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7^2-(Z)-(O-methyloxime), disodium salt, sesquaterhydrate. The chemical formula of ceftriaxone sodium is $C_{18}H_{16}N_8Na_2O_7S_2 \bullet 3.5H_2O$ and has a calculated molecular weight of 661.60

CLINICAL PHARMACOLOGY
Mechanism of Action
Ceftriaxone binds to one or more of the penicillin-binding proteins (PBPs) which inhibits the final transpeptidation step of peptidoglycan synthesis in bacterial cell wall, thus inhibiting biosynthesis and arresting cell wall assembly resulting in bacterial cell death.

Pharmacokinetics
Absorption: Peak plasma concentrations after 2 hr (IM).
Distribution: Distributed widely into body tissues and fluids; CSF (therapeutic concentrations). Crosses the placenta and enters breast milk; bile (high concentrations). Protein-binding: 85-95%.
Excretion: Via the urine (40-65% as unchanged); via the bile to the faeces (remainder as unchanged and microbiologically inactive compounds); 6-9 hr (elimination half-life)

INDICATIONS AND USAGE
Ceftriaxone for Injection is indicated for the treatment of the following infections when caused by susceptible organisms:

LOWER RESPIRATORY TRACT INFECTIONS caused by *Streptococcus pneumoniae, Staphylococcus aureus, Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella pneumoniae, Escherichia coli, Enterobacter aerogenes, Proteus mirabilis or Serratia marcescens*.

ACUTE BACTERIAL OTITIS MEDIA caused by *Streptococcus pneumoniae, Haemophilus influenzae* (including beta-lactamase producing strains) or *Moraxella catarrhalis* .

SKIN AND SKIN STRUCTURE INFECTIONS caused by *Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pyogenes, Viridans group streptococci, Escherichia coli, Enterobacter cloacae, Klebsiella oxytoca, Klebsiella pneumoniae, Proteus mirabilis, Morganella morganii, Pseudomonas aeruginosa, Serratia marcescens, Acinetobacter calcoaceticus, Bacteroides fragilis* or *Peptostreptococcus species.*

URINARY TRACT INFECTIONS (complicated and uncomplicated) caused by *Escherichia coli, Proteus mirabilis, Proteus vulgaris, Morganella morganii* or *Klebsiella pneumoniae*.

PELVIC INFLAMMATORY DISEASE caused by *Neisseria gonorrhoeae*. Ceftriaxone, like other cephalosporins, has no activity against *Chlamydia trachomatis*. Therefore, when cephalosporins are used in the treatment of patients with pelvic inflammatory disease and *Chlamydia trachomatis* is one of the suspected pathogens, appropriate antichlamydial coverage should be added.

BACTERIAL SEPTICEMIA caused by *Staphylococcus aureus, Streptococcus pneumoniae, Escherichia coli, Haemophilus influenzae or Klebsiella pneumoniae*.

BONE AND JOINT INFECTIONS caused by *Staphylococcus aureus, Streptococcus pneumoniae, Escherichia coli, Proteus mirabilis, Klebsiella pneumoniae or Enterobacter species.*

INTRA-ABDOMINAL INFECTIONS caused by *Escherichia coli, Klebsiella pneumoniae, Bacteroides fragilis, Clostridium species* (Note: most strains of *Clostridium difficile* are resistant) or *Peptostreptococcus species.*

MENINGITIS caused by *Haemophilus influenzae, Neisseria meningitidis or Streptococcus pneumoniae.*

Ceftriaxone has also been used successfully in a limited number of cases of meningitis and shunt infection caused by *Staphylococcus epidermidis* and *Escherichia coli.*

SURGICAL PROPHYLAXIS: The preoperative administration of a single 1 g dose of ceftriaxone may reduce the incidence of postoperative infections in patients undergoing surgical procedures classified as contaminated or potentially contaminated (e.g., vaginal or abdominal hysterectomy or cholecystectomy for chronic calculous cholecystitis in high-risk patients, such as those over 70 years of age, with acute cholecystitis not requiring therapeutic antimicrobials, obstructive jaundice or common duct bile stones) and in surgical patients for whom infection at the operative site would present serious risk (e.g., during coronary artery bypass surgery). When administered prior to surgical procedures for which it is indicated, a single 1 g dose of ceftriaxone provides protection from most infections due to susceptible organisms throughout the course of the procedure.

CONTRAINDICATIONS: Ceftriaxone is contraindicated in patients with known allergy to the cephalosporin class of antibiotics.

NEONATES (<28 days): Hyperbilirubinemic neonates, especially prematures, should not be treated with Ceftriaxone for Injection. *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 for Injection must not be co-administered with calcium-containing IV solutions, including continuous calcium-containing infusions such as parenteral nutrition, in neonates because of the risk of precipitation of ceftriaxone-calcium salt. Cases of fatal reactions with ceftriaxone-calcium precipitates in lung and kidneys in neonates have been described. In some cases the infusion lines and the times of administration of ceftriaxone and calcium containing solutions differed.

WARNINGS
Hypersensitivity
BEFORE THERAPY WITH CEFTRIAXONE IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS, PENICILLINS OR OTHER DRUGS. THIS PRODUCT SHOULD BE GIVEN CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS. ANTIBIOTICS SHOULD BE ADMINISTERED WITH CAUTION TO ANY PATIENT WHO HAS DEMONSTRATED SOME FORM OF ALLERGY, PARTICULARLY TO DRUGS. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE THE USE OF SUBCUTANEOUS EPINEPHRINE AND OTHER EMERGENCY MEASURES.

Interaction with Calcium-Containing Products
There are no reports to date of intravascular or pulmonary precipitations in patients, other than neonates, treated with ceftriaxone and calcium-containing IV solutions. However, the theoretical possibility exists for an interaction between ceftriaxone and IV calcium-containing solutions in patients other than neonates. Therefore, Ceftriaxone for Injection and calcium-containing solutions, including continuous calcium-containing infusions such as parenteral nutrition, should not be mixed or co-administered to any patient irrespective of age, even via different infusion lines at different sites.

Clostridium difficile
Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including ceftriaxone, and may range in severity from mild diarrhea to fatal colitis. 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 *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

PRECAUTIONS:
General: Prescribing Ceftriaxone for Injection 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.
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 cephalosporins. 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, dosage 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, ceftriaxone dosage should not exceed 2 g 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 treatment. Vitamin K administration (10 mg 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. If superinfection occurs during therapy, appropriate measures should be taken.
Ceftriaxone for Injection should be prescribed with caution in individuals with a history of gastrointestinal disease, especially colitis.
There have been reports of sonographic abnormalities in the gallbladder of patients treated with ceftriaxone; some of these patients also had symptoms of gallbladder disease. These abnormalities appear on sonography as an echo without acoustical shadowing suggesting sludge or as an echo with acoustical shadowing which may be misinterpreted as gallstones. The chemical nature of the sonographically detected material has been determined to be predominantly a ceftriaxone-calcium salt.
The condition appears to be transient and reversible upon discontinuation of Ceftriaxone for Injection and institution of conservative management. Therefore, ceftriaxone should be discontinued in patients who develop signs and symptoms suggestive of gallbladder disease and/or the sonographic findings described above.
Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenesis: Considering the maximum duration of treatment and the class of the compound, carcinogenicity studies with ceftriaxone in animals have not been performed. The maximum

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duration of animal toxicity studies was 6 months.
Mutagenesis: Genetic toxicology 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 for mutagenic activity in these studies.
Impairment of Fertility: Ceftriaxone produced no impairment of fertility when given intravenously to rats at daily doses up to 586 mg/kg/day, approximately 20 times the recommended clinical dose of 2 g/day.
Pregnancy: Teratogenic Effects: Pregnancy Category B. Reproductive studies have been performed in mice and rats at doses up to 20 times the usual human dose and have no evidence of embryotoxicity, fetotoxicity or teratogenicity. In primates, no embryotoxicity or teratogenicity was demonstrated at a dose approximately 3 times the human dose. There are, however, no adequate and 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. Caution should be exercised when ceftriaxone is administered to a nursing woman.
Pediatric Use: Safety and effectiveness of ceftriaxone in neonates, infants and pediatric patients have been established for the dosages described in the DOSAGE AND ADMINISTRATION section. *In vitro* studies have shown that ceftriaxone, like some other cephalosporins, can displace bilirubin from serum albumin. Ceftriaxone should not be administered to hyperbilirubinemic neonates, especially prematures.

ADVERSE REACTIONS: Ceftriaxone is generally well tolerated. In clinical trials, the following adverse reactions, which were considered to be related to ceftriaxone therapy or of uncertain etiology, were observed:
Local reactions - pain, induration , tenderness and phlebitis
Hypersensitivity - rash ,pruritus, fever or chills.
Hematologic - eosinophilia, thrombocytosis and leukopenia Less frequently reported (<1%) were anemia, hemolytic anemia, neutropenia, lymphopenia, thrombocytopenia and prolongation of the prothrombin time.
Gastrointestinal - diarrhea . Less frequently reported (<1%) were nausea or vomiting, and dysgeusia. The onset of pseudomembranous colitis symptoms may occur during or after antibacterial treatment.
Hepatic - elevations of SGOT or SGPT. Less frequently reported (<1%) were elevations of alkaline phosphatase and bilirubin.
Renal - elevations of the BUN . Less frequently reported (<1%) were elevations of creatinine and the presence of casts in the urine.
Central nervous system - headache or dizziness were reported occasionally (<1%).
Genitourinary - moniliasis or vaginitis were reported occasionally (<1%).
Miscellaneous - diaphoresis and flushing were reported occasionally (<1%).
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, a decrease in prothrombin time, renal precipitations, seizures, and serum sickness.
Cases of fatal reactions with ceftriaxone-calcium precipitates in lung and kidneys in neonates have been described.

OVERDOSAGE:
In the case of overdosage, drug concentration would not be reduced by hemodialysis or peritoneal dialysis. There is no specific antidote. Treatment of overdosage should be symptomatic.

DOSAGE AND ADMINISTRATION:
Do not use diluents containing calcium, such as Ringer's solution to reconstitute Ceftriaxone for Injection. Particulate formation can result. Ceftriaxone for Injection and calcium-containing solutions, including continuous calcium-containing infusions such as parenteral nutrition, should not be mixed or co-administered to any patient irrespective of age, even via different infusion lines at different sites.
NEONATES: Hyperbilirubinemic neonates, especially prematures, should not be treated with Ceftriaxone for Injection.

PEDIATRIC PATIENTS:
For the treatment of skin and skin structure infections, the recommended total daily dose is 50 to 75 mg/kg given once a day (or in equally divided doses twice a day). The total daily dose should not exceed 2 gram.
For the treatment of acute bacterial otitis media, a single intramuscular dose 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 is 50 to 75 mg/kg, given in divided doses every 12 hours. The total daily dose should not exceed 2 gram.
In the treatment of meningitis, it is recommended that the initial therapeutic dose be 100 mg/kg (not to exceed 4 gram). Thereafter, a total daily dose of 100 mg/kg/day (not to exceed 4 gram daily) is recommended. The daily dose may be administered once a day or in equally divided doses every 12 hours. The usual duration of therapy is 7 to 14 days.

ADULTS:
The usual adult daily dose is 1 to 2 gram given once a day or in equally divided doses twice a day depending on the type and severity of infection. The total daily dose should not exceed 4 gram.

For preoperative use (surgical prophylaxis), a single dose of 1 gram administered intravenously half an hour to 2 hours before surgery is recommended. 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 infections, longer therapy may be required. When treating infections caused by *Streptococcus pyogenes*, 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 (e.g., dialysis patients) and in patients with both renal and hepatic dysfunctions.

DIRECTIONS FOR USE:
Intravenous Administration: Ceftriaxone should be administered intravenously by infusion over a period of 30 minutes.
Intramuscular Injection: Reconstituted solution should be administered by intragluteal injection. More than 1 g of Suprava should not be injected at a single site.
Reconstitution Method:
For IM use: Reconstitute with an appropriate diluent (1% Lidocaine solution, sterile water for Injections, 0.9% w/v sodium chloride solution, 5% Dextrose solution) as per below table:

Vial Dosage size	Amount of Diluent to be added
500 mg	1.8 mL
1 g	3.6 mL

For IV use: Reconstitute only with sterile water for Injections or other diluents like - 0.9% sodium chloride injection, 5% Dextrose solution for intravenous infusion as per below table:

Vial Dosage size	Amount of Diluent to be added
500 mg	4.8 mL
1 g	9.6 mL

After reconstitution, each mL of solution contains 100mg (approx.) equivalent to ceftriaxone. This reconstituted solution can be administered by slow IV injection over approximately 5 minutes, or further diluted and administered as short intravenous infusion.
For short IV infusion, concentrations between 10mg/mL and 40mg/mL are recommended, however, lower concentrations may be used if desired.
Withdraw entire content and dilute to the desired concentrations with the appropriate IV diluent.
Diluents which can be used for Intravenous infusion are: 5% Dextrose + 0.9% Sodium Chloride solution, 0.9% Sodium Chloride Injection, 5% Dextrose Injection, 10% Dextrose solution.

COMPATIBILITY AND STABILITY:
Ceftriaxone has been shown to be compatible with metronidazole hydrochloride. The concentration should not exceed 5 to 7.5 mg/mL metronidazole hydrochloride with ceftriaxone 10 mg/mL as an admixture. Vancomycin and fluconazole are physically incompatible with ceftriaxone in admixtures. When either of these drugs is to be administered concomitantly with ceftriaxone by intermittent intravenous infusion, it is recommended that they should be given sequentially, with thorough flushing of the intravenous lines with one of the compatible fluids between the administrations.

Do not use diluents containing calcium, such as Ringer's solution or Hartmann's solution, to reconstitute Ceftriaxone for Injection. Particulate formation can result.

Shelf Life: Please refer carton/label.

STORAGE
Store protected from light at a temperature not exceeding 30°C.
Keep out of reach of children.

How supplied
SUPRAVA®500mg: Powder filled in glass vial
SUPRAVA®1g: Powder filled in glass vial

Special Precautions for Disposal and Other Handling
Any unused medicinal product should be disposed off in accordance with the local requirements.

Marketed by:
Biocon Biologics India Limited
Biocon House, Semicon Park,
Electronics City, Phase - II,
Bengaluru - 560 100, India.

BF/LL/3861/01

Leaflet revised on August 2019

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