

Ceftriaxone & Sulbactam for Injection IP

VARXON-S[®] 1.5 g

Each vial contains:

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Ceftriaxone Sodium IP eq. to Ceftriaxone	1gm
Sulbactam Sodium IP eq. to Sulbactam	500 mg

DESCRIPTION:

Ceftriaxone is a beta-lactam, third-generation cephalosporin antibiotic with bactericidal activity. The Chemical name of ceftriaxone is (6R,7R)-7-[[[(2Z)-2-(2-amino-1,3-thiazol-4-yl)-2-methoxyiminoacetyl]amino]-3-[(2-methyl-5,6-dioxo-1H-1,2,4-triazin-3-yl)sulfanyl]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid. The molecular formula is C₁₈H₁₈N₈O₇S₃ and molecular weight is 554.6g/mol.

Sulbactam is a β-lactamase inhibitor given in combination with β-lactam antibiotics to inhibit β-lactamase, an enzyme produced by bacteria that destroys antibiotic activity. The chemical name is (2S,5R)-3,3-dimethyl-4,4,7-trioxo-4A6-thia-1-azabicyclo [3.2.0] heptane-2-carboxylic acid. The molecular formula is C₈H₁₁NO₅S and its molecular weight is 233.24 g/mol.

THERAPEUTIC INDICATIONS

Ceftriaxone & Sulbactam for Injection is indicated in infections caused by Ceftriaxone sodium sensitive 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 gonorrhoea. Ceftriaxone & Sulbactam for Injection may also be used for Peri-operative Prophylaxis of Infections. A single dose given Preoperatively may reduce chances of Postoperative Infection.

POSODOLOGY AND METHOD OF ADMINISTRATION

Posology

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).

Generally, ceftriaxone therapy should be continued for at least 2 days after recovery indicated by disappearance of the signs and symptoms of infection. The usual duration of therapy is 4 to 14 days although in complicated infections, one may need to treat for a longer period. When treating infections caused by *Streptococcus pyrogens*, 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 renal and hepatic dysfunctions.

Method of administration

For intravenous or intramuscular administration.

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.

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 hyperbilirubinemia.

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 premature in particular. During prolonged treatment with Ceftriaxone & Sulbactam for Injection, blood profile should be checked at regular intervals. Dosage adjustments are not necessary in hepatic failure. However, in patients with hepatic dysfunction and significant renal malfunction, Ceftriaxone & Sulbactam for Injection doses should not exceed an equivalent of 2g/day of Ceftriaxone. Close serum monitoring is recommended. Extreme caution needs to be exercised in penicillin-sensitive patients. In case of serious hypersensitivity reactions, SC administration of epinephrine and other emergency measures are recommended. 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.

INTERACTION WITH OTHER MEDICINAL PRODUCTS

No impairment of renal function has been observed after concomitant administration of large doses of Ceftriaxone and potent diuretics. 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 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.

PREGNANCY, LACTATION AND FERTILITY

Reproductive studies on ceftriaxone have been performed in mice and rats at very high doses. No evidence of embryotoxicity, fetotoxicity or teratogenicity was observed. However, in absence of adequate and well-controlled studies in pregnant women, and since reproductive animal studies may not always reflect human response, this drug should be used during pregnancy only if clearly needed. As ceftriaxone is secreted in the breast-milk, albeit at low concentrations, caution should be exercised in nursing mothers.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

None stated.

UNDESIRABLE EFFECTS

The following side effects, reported to occur during Ceftriaxone therapy, may be seen with the combination as well:

Gastrointestinal: Diarrhoea, nausea & vomiting (less frequent), stomatitis, and glossitis.

Hepatic: Elevations of SGOT/SGPT.

Hematological: Eosinophilia, thrombocytopenia, leukopenia, granulocytopenia, hematoma or bleeding. Hemolytic anemia is observed less frequently. Agranulocytosis (< 500/mm³) has been reported occasionally at a total cumulative dose exceeding 20 g.

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. Anaphylactic shock may occur which requires immediate countermeasures.

Local reactions: Pain, induration, and tenderness may be encountered in a small number of patients. Inflammatory reactions in the vein wall may also occur after IV administration. These may be minimized by slow injection, given over 2 to 5 minutes.

OVERDOSE

Limited information is available on the acute toxicity of Ceftriaxone & Sulbactam for Injection. No specific antidote is available for the treatment of overdose. Hemodialysis does not remove the drug from system effectively. Hence, the treatment for Ceftriaxone & Sulbactam for Injection overdose is essentially supportive and symptomatic

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: Combinations of Cephalosporin and beta-lactamase inhibitors.

ATC Code: J01CG01 (Sulbactam Sodium), ATC code: J01DD04 (Ceftriaxone Sodium)

Mode of action Ceftriaxone is a beta-lactam antibiotic like the penicillins with bactericidal action. Penicillin-binding proteins (PBPs) are responsible for several steps in the synthesis of the cell wall of bacteria and are found in large quantities (several hundred to several thousand molecules/bacterial cell). Ceftriaxone inhibits the third and final stage of bacterial cell wall synthesis by preferentially binding to the specific PBPs located inside the bacterial cell wall. Ceftriaxone interferes with PBP-mediated cell wall synthesis leading to cell lysis, which is mediated by bacterial cell wall autolytic enzymes (autolysins), possibly through interference with an autolysin inhibitor. The presence of an aminothiazolylacetyl side chain with an alpha methoxyimino group at the 7-position of the beta-lactam ring provides Ceftriaxone with enhanced antibacterial activity, particularly against the Enterobacteriaceae (e.g., *E. coli*, *Klebsiella*, *Proteus*, and *Serratia*) and increased stability against many of the beta lactamases. Many strains of *Pseudomonas aeruginosa* are susceptible to Ceftriaxone. Other susceptible gram-negative organisms include *Enterobacter*, *Citrobacter*, *Morganella*, *Providencia*, *Moraxella* (*Branhamella*) *catarrhalis*, and *N. meningitidis*. Ceftriaxone has exceptional activity against *H. influenzae* and *N. gonorrhoeae* and is the drug of choice for uncomplicated *N. gonorrhoeae* infections. It has no activity against *B. fragilis* but is active against many other anaerobes.

However, recently it has been observed that the bacteria, through formation of beta lactamases hydrolyse the beta-lactam ring of cephalosporins to inactivate them, thereby developing resistance to the drug. Recently, such a development of resistance to ceftriaxone has been observed, which can be judged by an increase in the MIC. Sulbactam, by irreversibly binding to the beta-lactamases produced by the common gram positive or negative bacteria protects the beta-lactam ring of ceftriaxone, and conserves the activity. Thus, on combining ceftriaxone with sulbactam, the combination product - Ceftriaxone & Sulbactam for Injection extends its utility in the treatment of broad range of infections caused by organism resistant to the antibiotic alone, making them susceptible, possibly through lowering of MIC.

Pharmacokinetic properties

Ceftriaxone is completely absorbed with peak plasma concentrations of 40 mcg/ml and 80 mcg/ml at 2 to 3 hours after IM injection of 500 mg 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. 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 half-life of Ceftriaxone appreciably, severe renal impairment does, with a longer half-life, which is further increased if accompanied with liver impairment. Ceftriaxone at 1 - 2 g dose achieves concentrations above the MICs in the lung, heart, biliary tract/liver, tonsil, middle ear and nasal mucosa, bone; and cerebral, pleural, prostatic and synovial fluids for most of the pathogens responsible for infection, even after more than 24 hours. Urinary excretion by glomerular filtration accounts for 50-60% of the elimination. The intestinal flora has been shown to convert ceftriaxone into inactive metabolites. Biliary route accounts for 40-50% of excretion. In case of renal impairment, the biliary excretion may be the major pathway for excretion. In Infants & Children: Elimination half-life in neonates is prolonged which decreases with increasing postnatal age. In infants aged less than 8 days and in elderly persons aged over 75 years, the average elimination half-life is usually 2 - 3 times that seen in the adults. In patients with renal failure, non-renal elimination may compensate. Sulbactam has a half-life 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.

STORAGE

Store below 25 °C Protect from light & moisture.

Keep out of reach of children.

PRESENTATION:

Primary Pack:

Secondary Packing:

Mfd. By:

Bharat Parenterals Limited

Survey No. 144-A, Jarod-Samlaya Road,

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Marketed By:



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