1.3.1 SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

1.3.1.1 NAME OF THE MEDICINAL PRODUCT

International Non– Proprietary Name (INN): Ceftriaxone & Sulbactam for Injection 1.5 gm.

1.3.1.2 ATC AND FORENSIC CLASSIFICATION

ATC Classification: Cephalosporin antibiotic with enzyme inhibitor.

ATC Code: ATC code: J01DD54

1.3.1.3 QUALITATIVE AND QUANTITATIVE COMPOSITION

Label Claim:

Each Vial contains:
Ceftriaxone Sodium USP (Sterile)
Eq. to Anhydrous Ceftriaxone.....1000 mg
Sulbactam Sodium USP (Sterile)
Eq. to Anhydrous Sulbactam..... 500 mg

1.3.1.4 PHARMACEUTICAL FORM

Powder for Injection
A white to pale yellow crystalline powder, filled in 20ml clear glass vial USP T-III.

1.3.1.5 CLINICAL PARTICULARS

1.3.1.5.1 Therapeutic Indications

Ceftriaxone with Sulbactam is indicated in the treatment of the following infections caused by susceptible organisms:

- *Lower resipiratory tract infections*
- *Acute otitis media*
- *Skin and skin structure infections*
- *Urinary tract infections*
- *Bone and joint infections*
- *Intra-abdominal infections*
- *Septicaemia.*
- *Meningitis.*
- *Gonorrhoea.*

The pre-operative administration of the combination reduces the incidence of postoperative infections in patients undergoing surgical procedures.

1.3.1.5.2 Posology and Method of Administration

Adult dose:

The recommended adult dosage is 1.5 g (1 g Ceftriaxone as the sodium salt plus 0.5 g sulbactam as the sodium salt) to 3 g (2 g Ceftriaxone as the sodium salt plus 1 g Sulbactam as the sodium salt) every six hours. This 1.5 to 3 g range represents the total of Ceftriaxone content plus the sulbactam content and corresponds to a range of 1 g Ceftriaxone /0.5 g sulbactam to 2 g Ceftriaxone /1 g sulbactam.

The total dose of Sulbactam should not exceed 4 grams per day.

Neonates, infants and children up to 12 years:

The following dosage schedules are recommended for once daily administration. Neonates (up to 14 days): 20 to 50 mg/kg bodyweight once daily. The daily dose should not exceed 50 mg/kg. It is not necessary to differentiate between premature and term infants. Infants and children (15 days to 12 years): 20 to 80 mg/kg once daily. For children with bodyweights of 50 kg or more, the usual adult dosage should be used. Intravenous doses of NLT 50 mg/kg bodyweight should be given by infusion over at least 30 minutes.

1.3.1.5.3 Contraindications

Ceftriaxone Injection is contraindicated in patients with known hypersensitivity to cephalosporin antibiotics. In patients hypersensitive to penicillin, consider the possibility of allergic cross-reactions.

The use of Sulbactam is contraindicated in individuals with a history of hypersensitivity reactions to any of the penicillins.

1.3.1.5.4 Special warnings and precautions for use

Serious or occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving β -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 alter 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-asociated colitis. Mild cases of colitis may respond to drug discontinuance alone. Moderate to serious cases should be managed with fluid, electrolyte and protein supplementation as indicated.

Although transient elevations of BUN and serum creatinine nave been observed, at the recommended dosages, the nephrotoxic potential of ceftriaxone with sulbactam is simitar to that of the cephalosporins. Ceftriaxone is excreted via both biliary and renat excretion. Therefore,

patients with renal failure normally require no adjustment of dosage when usual doses of ceftriaxone and sulbactam 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 is not be necessary in patients with hepatic dysfunction; however, in patients with both hepatic dysfunction and significant renal disease, ceftriaxone and sulbactam dosage should not exceed 3.0gm daily without close monitoring of serum concentrations.

Alterations in prothrombin time have occured rarely in patients treated with ceftriaxone and sulbactam. Patients with impaired vitamin K stores (e.g., chronic hepatic disease and malnutrition) may require monitoring of prothrombin time during treatment. Vitamin K administration (10 mg weekly) may be necessary if prothrombin time is prolonged before or during therapy.

Ceftriaxone and sulbactam should be prescribed with caution in individuals with a history of gastrointestinal disease, especially colitis.

1.3.1.5.5 Interaction with other medicinal products and other forms of interaction

The elimination of ceftriaxone is not altered by probenecid but tubular secretion of sulbactam is reduced by probenecid.

Ceftriaxone may adversely affect the efficacy of oral hormonal contraceptives. Consequently, it is advisable to use supplementary (non-hormonal) contraceptive measures during treatment and in the month following treatment.

1.3.1.5.6 Pregnancy and lactation

Usage in pregnancy

The use of ceftriaxone and sulbactam has not been well studied in pregnant women. Hence the combination should be used in pregnancy only if clearly needed.

Usage in nursing mothers

Low concentrations of ceftriaxone and sulbactam are secreted in human milk. Hence the combination should be used with due caution in nursing mothers.

1.3.1.5.7 Effects on ability to drive and use machines

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

1.3.1.5. Undesirable effects

Ceftriaxone and sulbactam have been generally well tolerated. Adverse reactions are usually mild and transient.
The most common side-effects are gastrointestinal, consisting mainly of loose stools and diarrhoea or occasionally, nausea and vomiting, stomatitis and glossitis. Cutaneous reactions, including maculopapular rash or exanthema, pruritus, urticaria, oedema and allergic dermatitis have occurred. Isolated cases of severe cutaneous adverse reactions (erythema multiforme, Stevens Johnson Syndrome and Lyell's Syndrome/toxic epidermal necrolysis) have been reported.
Haematological reactions have included anaemia (all grades), haemolytic anaemia, leucopenia, neutropenia, thrombocytopenia, eosinophilia, agranulocytosis and positive Coombs' test. Regular blood counts should be carried out during treatment.
Headache and dizziness, drug fever, shivering and transient elevations in liver function tests have been reported in a few cases. Other rarely observed adverse reactions include glycosuria, oliguria, haematuria, increase in serum creatinine, mycosis of the genital tract and anaphylactic-type reactions such as bronchospasm.
Very rarely, reversible symptomatic urinary precipitates of calcium ceftriaxone have occurred after ceftriaxone administration. Patients who are very young, immobilised or who are dehydrated are at increased risk. There have been a few reports of anuria and renal impairment following this reaction.
Shadows which have been mistaken for gallstones, but which are precipitates of calcium ceftriaxone, have been detected by sonograms.
Superinfections with yeasts, fungi or other resistant organisms may occur. A rare side-effect is pseudomembranous colitis which has resulted from infection with Clostridium difficile during treatment. Therefore it is important to consider this diagnosis in patients who present with diarrhoea subsequent to the administration of antibacterial agents.
Pain or discomfort may be experienced at the site of intramuscular injection immediately after administration but is usually well tolerated and transient. Local phlebitis has occurred rarely following intravenous administration but can be minimised by slow injection over at least 2-4 minutes.

1.3.1.5.9 Overdose

Limited data is available on the acute toxicity of ceftriaxone and sulbactam. There are no specific antidote. In the event of acute overdosage, supportive and symptomatic treatment should be initiated.

1.3.1.6 PHARMACOLOGICAL PROPERTIES

1.3.1.6.1 Pharmacodynamic properties

General Properties
ATC classification: J01DD54

Ceftriaxone, like other cephalosporins and penicillins, kills bacteria by interfering with the synthesis of the bacterial cell wall. Ceftriaxone is bactericidal against a broad spectrum of bacteria at easily achievable plasma concentrations.
Ceftriaxone is stable to a wide range of both Gram-positive and Gram-negative β-lactamases, including those which are able to hydrolyse advanced generation penicillin derivatives and other cephalosporins. Resistance to ceftriaxone is encoded mainly by the production of some β-lactam hydrolysing enzymes especially in Gram-negative organisms. Sulbactam is a penicillanic acid sulfone with β-lactamase inhibitory properties. It is an irreversible inhibitor of many plasmid-mediated and some chromosomal beta-lactamases. Sulbactam in combination with ceftriaxone protects ceftriaxone against destruction by β-lactamases. Sulbactam can therefore enhance the activity of ceftriaxone against many resistant strains of bacteria.

Spectrum

Gram-positive aerobes: Staphylococcus aureus (including penicillinase-producing strains) Streptococcus pneumoniae, Streptococcus group A (Streptococcus pyogenes), Streptococcus group B (Streptococcus agalactiae), Streptococcus viridans and Streptococcus bovis.
Gram-Negative Aerobes : Acinetobacter calcoaceticus, Enterobacter aerogenes, Enterobacter cloacae, Escherichia coli, Haemophilus influenzae (including ampicillin-resistant and β-lactamase producing strains), Haemophilus para-influenzae, Klebsiella oxytoca, Klebsiella pneumoniae, Moraxella catarrhalis (including β-lactamase producing strains), Morganella morganii, Neisseria gonorrhoeae (including penicillinase and nonpenicillinase-producing strains), Neisseria meningitidis, Proteus mirabilis, Proteus vulgaris, Serratia marcescens. It is also active against many strains of Pseudomonas aeruginosa.

Anaerobes: Clostridium species, Peptococcus species, Bacteroides species, including B.fragilis

1.3.1.6.2 Pharmacokinetic properties

Following intramuscular administration, peak serum concentrations of sulbactam and ceftriaxone are seen between 15 mins. To 2 hours.

The plasma concentration of ceftriaxone after a single IM dose of 1.5 gm is about 81 mg/L and is reached approx. 1 hour in healthy volunteers. Serum concentration have shown to be proporyional to the dose administered. Bioavailability after intramuscular injection is 100%.

Ceftriaxone crosses non-inflamed and inflamed meninges, attaining concentrations 4-17% of the simultaneous plasma concentration. The volume of distribution of ceftriaxone is 7-12 L while that of sulbactam is 18-27.6 L.Both are widely distributed in tissues and body fluids.

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. The serum half life of sulbactam is about 1 hour and approximately 75-85% of sulbactam is excreted unchanged in urine.

In patients with renal or hepatic dysfunction, the pharmacokinetics of ceftriaxone are only minimally altered and the elimination half-life is only slightly increased. If kidney function alone is impaired, biliary elimination of ceftriaxone is increased; if liver function alone is impaired, renal elimination is increased.

1.3.1.6.3 Preclinical safety data

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 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 gm/day.

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.

Nonteratogenic Effects

In rats, in the Segment I (fertility and general reproduction) and Segment III (perinatal and postnatal) studies with intravenously administered ceftriaxone, no adverse effects were noted on various reproductive parameters during gestation and lactation, including postnatal growth, functional behavior and reproductive ability of the offspring, at doses of 586 mg/kg/day or less.

1.3.1.7 PHARMACEUTICAL PARTICULARS

1.3.1.7.1 Incompatibilities

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. Based on literature reports, ceftriaxone is not compatible with amsacrine, Vancomycin, fluconazole, aminoglycosides, pentamidine, clindamycin phosphate and labetalol.

1.3.1.7 2 Shelf life

24 Months

1.3.1.7.3 Special precautions for storage

Store below 30°C. The product should be used immediately after opening. Discard any unused portion.

1.3.1.7.4 Nature and contents of container

Ceftriaxone & Sulbactam for Injection is supplied in 20 ml clear glass vials, closed with a rubber stopper and sealed with an aluminium cap.

1.3.1.7.5 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

1.3.1.8 Registrant

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