1.3.1 Summary of product characteristics

Enclosed

INJECT CARE PARENTERALS PVT. LTD.
Plot No. 130, Silvassa Road , GIDC ,Vapi – 396195

Summary of Product Characteristic

1. Name of the medicinal product

Ceftriaxone and Sulbactam for Injection 1.5 gm

2. Qualitative and quantitative composition

Each combipack contains:

1. Ceftriaxone and Sulbactam for Injection 1.5 gm
Each vial contains
Sterile Ceftriaxone Sodium USP
Equivalent to Ceftriaxone……. 1000 mg
Sulbactam Sodium USP
Equivalent to Sulbactam…….500 mg
2. Sterile water for Injection ..10 ml

3. Pharmaceutical form

Dry powder for injection

An off White to pale yellow crystalline powder

4. Clinical particulars

4.1 Therapeutic indications

Infections caused by pathogens sensitive to Ceftriaxone Injection, e.g.:
- sepsis;
- meningitis;
- abdominal infections (peritonitis, infections of the biliary and gastrointestinal tracts);
- infections of the bones, joints, soft tissue, skin and of wounds;
- infections in patients with impaired defence mechanisms;
- renal and urinary tract infections;
- respiratory tract infections, particularly pneumonia, and ear, nose and throat infections;
- genital infections, including gonorrhoea.
- Perioperative prophylaxis of infections.

4.2 Posology and method of administration

The recommended adult dosage is 1.5 g (1Ceftriaxone as the sodium salt plus 0.5 g sulbactam as the sodium salt)to 3 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 (utop14 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 Body weight should be given by infusion over at least 30 minutes.

4.3 Contraindications

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.

4.4 Special warnings and precautions for use

WARNINGS:

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. Pseudomembranous colitis has been reported with nearly all-antibacterial agents including ceftriaxone, and may range In severity from mild to life threatening. Therefore, It is Important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents. Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by Clostridium difficile Is one primary cause of "antibiotic-associated colitis"

After the diagnosis of pseudomembranous colitis has been established, appropriate therapeutic measures should be initiated. Mild cases of Pseudomembranous colitis usually respond to drug

discontinuation alone, in moderate to severe cases, consideration should be given to management with effective against clostridium difficile colitis.

In vivo and In vitro studies have shown that ceftriaxone, like some other cephalosporins, can displace bilirubin from serum albumin. Clinical data obtained in neonates have confirmed this finding. Ceftriaxone should therefore not be used In Jaundiced new-born or in those who are hypoalbuminaemic or acidotic, in whom bilirubin binding is likely to be impaired. Particular caution should be exercised in babies born prematurely.

PRECAUTIONS:

General

Prescribing ceftriaxone 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 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 billiary 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 dally without dose 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 and sulbactam for injection treatment. Vitamin K administration (10 mg weekly) may be necessary if the prothrombin time is prolonged before or during therapy.

Prolong use of ceftriaxone may result in overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If Superinfections occurs during therapy, appropriate measures should be taken.

Ceftriaxone sodium and sulbactam sodium 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 sodium; 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 b The condition appears to be transient and reversible upon discontinuation of ceftriaxone sodium and Institution of conservative management.

Therefore, Ceftriaxone should be discontinued in patients who develop signs and symptoms suggestive of gallbladder disease and/or the sonographlc findings described above. Cases of pancreatitis, possibly secondary to biliary obstruction, have been rarely reported in patients treated with ceftriaxone. Most patients presented with risk factors for billiary stasis and billiary sludge (e.g. preceding major therapy, severe Illness, total parenteral nutrition). A trigger or cofactor role of ceftriaxone-related billiary precipitation cannot be ruled out.

4.5 Interaction with other medicinal products and other forms of interaction

Diuretics: No impairment of renal function has been observed in man after simultaneous administration of ceftriaxone with diuretics.

Aminoglycosides: No interference with the action or increase in nephrotoxicity of aminoglycoside has been observed during simultaneous administration with ceftriaxone.

Alcohol: The ceftriaxone molecule does not contain the N-methylthio-tetrazole substituent, which has been associated with a disulfiram-like effect, when alcohol is taken during therapy with certain cephalosporins.

Chloramphenicol: In vitro, chloramphenicol has been shown to be antagonistic with respect to ceftriaxone and other cephalosporins. The clinical relevance of this finding is unknown, but caution is advised if concurrent administration of ceftriaxone with Chloramphenicol is proposed.

Coombs' test: In patients treated with ceftriaxone, the Coombs' test may rarely become false positive. Ceftriaxone, like other antibiotics, may result in false-positive tests for galactosaemia. Likewise, non-enzymatic methods for glucose determination in urine may

give false-positive results. For this reason, urine-glucose determination during therapy with ceftriaxone should be done enzymatically.

Oral contraceptives: 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.

Probenecid: Probenecid decreases the renal tubular secretion of sulbactam, concurrent use of probenecid with Ceftriaxone sodium & sulbactam sodium Injection may result in increased and prolonged blood levels of sulbactam.

4.6 Fertility, pregnancy and lactation

• Pregnancy

There is no available information about the use of Ceftriaxone and Sulbactam combination during pregnancy either in human or in animals.

Ceftriaxone

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. 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.

Sulbactam

There is no Information on available about the use of Sulbactam alone during pregnancy. Below Is the Information available with the ampicillin and Sulbactam parenteral combination. Reproduction studies have been performed in mice, rats, and rabbits at doses up to ten (10)

times the human dose and have revealed no evidence of impaired fertility or harm to the fetus

due to ampicillin and sulbactam parenteral combination. There are, however, no adequate and

welt-controlled studies ln pregnant women.

Because the available animal reproduction studies with ceftriaxone and sulbactam (In combination with ampicillin) are not always predictive of human response, ceftriaxone sodium & sulbactam sodium Injection should be used during pregnancy only if clearly needed.

• Lactation

Low concentration of ceftriaxone and sulbactam are excreted in human milk. Caution should be exercised when ceftriaxone sodium & sulbactam sodium injection is administered to a nursing woman.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Ceftriaxone

Ceftriaxone is generally well tolerated. In clinical trials, the following adverse reactions, which were considered to be related to ceftriaxone sodium therapy or of uncertain etiology, were observed:

Local Reactions-pain, induration and tenderness was 1% overall. Phlebitis was reported in

<1% after IV administration.

Hypersensitivity-rash (1.7%), Less frequently reported (<1%) were pruritus, fever or chills. Hematologic-eosinophilia (6%), thrombocytosis (5.1%) and leukopenia (2.1%). Less

frequently reported (<1%) were anemia, hemolytic anemia, neutropenia, lymphopenia,

thrombocytopenia and prolongation of the prothrombin time. Gastrointestinal-diarrhea (2.7%).

Less frequently reported (<1%) were nausea or vomiting, and dysgeusia. The onset of Pseudomembranous colitis symptoms may occur during or after antibacterial treatment (see WARNINGS).

Hepatic-elevations of SGOT (3.1%) or SGPT (3.3%). Less frequently reported (<1%) were elevations of alkaline phosphatase and bilirubin.

Renal-elevations of the BUN (1.2%). 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, billiary lithiasis, bronchospasm, colitis, dyspepsia, epistaxis, flatulence, gallbladder sludge, glycosuria, haematuria, jaundice, teukocytosis, lymphocytosis, monocytosis, nephrolithiasis, palpitations, a decrease in the prothrombin time, renal precipitations, seizures, and serum sickness.

Other reported adverse events are stomatitis , glossitis, Pseudomembranous colitis(mostly caused by Clostridium difficile), pancreatitis(possibly caused by obstruction of bile ducts), allergic skin reactions such as maculopapular rash or exanthema, urticaria, dermatitis, pruritus, edema, Erythema multiforme, Stevens Johnson Syndrome, Lyeli's Syndrome/toxic epidermal necrolysis, oliguria, dehydration or immobilization, anuria, renal impairment and rigors.

Sulbactam

The only side effect observed after the parenteral administration of sulbactam to humans was pain the site of i.m. injection. the pain subsided rapidly and disappeared completely within 1 hour.

4.9 Overdose

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.
Neurological adverse reactions, including convulsions, may occur with the attainment of high CSF levels of beta-lactams. The molecular weight, degree of protein binding and pharmacokinetics profile of sulbactam suggest that this compound may also be removed by hemodialysis.

5. Pharmacological properties

5.1 Pharmacodynamic properties

The combination of Ceftriaxone sodium and Sulbactam sodium is active against all the organisms sensitive to Ceftriaxone. In addition it demonstrates

synergistic activity (reduction in minimum inhibitory concentrations, for the combination versus those of each component) in a variety of organisms. Gram-Negative Aerobes Acinetobacter calcoaceticus

Enterobacter aerogenes

Enterobacter cloacae

Escherichia coli

Haemophilus influenzae (including ampicillin-resistant and beta-lactamase producing strains)

Haemophilus parainfluenzae

Klebsiella oxytoca

Klebsiella pneumoniae

Moraxella catarrhalis (including beta-lactamase producing strains)

Morganella morganii

Neisseria gonorrhoeae (including penicillinase - and nonpenicillinaseproducing strains)

Neisseria meningitides

Proteus mirabilis

Proteus vulgaris

Serratia marcescens

Ceftriaxone is also active against many strains of Pseudomonas aeruginosa.

Many strains of the above organisms that are resistant to other antibiotics, eg,penicillins, cephalosporins and aminoglycosides, are susceptible to Ceftriaxone.

Ceftriaxone also demonstrates in vitro activity against most strains of the following microorganism like Citrobacter diversus , Citrobacter freundii,Providencia species (including Providencia rettgeri , almonella species (including S. typhi), Shigella species

Gram-Positive Aerobes

Staphylococcus aureus (including penicillinase-producing strains and methicillin sensitive strains but not methicillin resistant strains)

Staphylococcus epidermidis

Streptococcus pneumoniae

Streptococcus pyogenes

Viridans group streptococci

Anaerobes:

Bacteroides fragilis, Clostridium species , Peptostreptococcus species.

5.2 Pharmacokinetic properties

It can be administered IM or IV.

Following intramuscular administration, peak serum concentrations of Ceftriaxone and

Sulbactam are seen between 15 minutes to 2 hrs.

The maximum plasma conc of Ceftriaxone after a single IM dsoe of 1.0 g is about 81mg/L and is reached 2-3 hrs after the dose while that of Sulbactam sodium is 6-24 mg/L and is reached approximately 1 hr after the dose. Hence effective amount of beta-lactamases are destroyed by the time peak concentration of Ceftriaxone is reached allowing full potential of action of Ceftriaxone against ESBL producing Klebsiella, E coli spp. Serum concentrations

have been shown to be proportional to the amount of dose administered.

The area under curve (AUC)after IM administration is equivalent to that after IV administration of an equivalent dose, indicating 100% bioavailability of intramuscularly administered Ceftriaxone sodium.

On intravenous administration Ceftriaxone sodium diffuses into the tissue fluid where if given in the recommended doses bactericidal concentrations are maintained for upto 24 hrs. Ceftriaxone is highly bound to human serum protein by about 83-90%.

Distribution

The volume of distribution of Ceftriaxone sodium is 7-12 L and that of Sulbactam is 18-27.6L.

Ceftriaxone sodium penetrates well into the extravascular spaces, tissue fluid and the synovial fluid of inflamed joints. The concentrations in most extracellular foci reach or exceed several times the MIC of most pathogens for at least 24 hours after a single administration.

Ceftriaxone sodium reaches therapeutically effective concentrations in patients with bacterial meningitis which are at least ten-fold the MICs of common pathogens such as, Enterobacteriaceae, H.influenzae, Meningococci, Pneumococci and Group B Streptococci. Ceftriaxone crosses placenta and is distributed in the amniotic fluid. It is also distributed in the milk.

Metabolism and excretion

Ceftriaxone is not metabolised in the body and is eliminated unchanged via two pathways, urine and bile. 40-50% of parenterally administered dose is excreted into the urine within 48 hours as active drug. Thus, high concentrations are attained in urine, whatever is not excreted via kidney is excreted through bile.

Metabolism of sulbactam is less than 25%. 70-80% of Sulbactam is excreted by the kidney biliary excretion is minimal and. renal excretion is blocked by probenecid. Sulbactam and Ceftriaxone can be removed by hemodialysis.

Impaired renal function and Hepatic insufficiency: Ceftriaxone is excreted via both renal and biliary pathways therefore patients with renal failure normally require no adjustments of dose however concentration of the drug should be monitored in such patients and if there is evidence of drug accumulation then dosage adjustments should be made accordingly. Dosage adjustments are not necessary in patients with hepatic dysfunction, however in patients with

both hepatic dysfunction and significant renal failure, dosage should not exceed more than 2 gm daily with close monitoring of serum concentrations.

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

None

6.2 Incompatibilities

None known

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store below 25°

6.5 Nature and contents of container

20 ml, USP type III, clear glass vial closed with bromo butyl rubber stopper and sealed with flip off seal

6.6 Special precautions for disposal and other handling

After 24 hours any unused solution should be discarded.

The reconstituted solution should be clear. Do not use if particles are present.

For single use only. Discard any unused contents

Add the recommended volume of reconstitution solution and shake well until the contents of the vial have dissolved completely.

7. Marketing authorisation holder

Inject Care Parenterals Pvt. Ltd.
Plot no. 130, Silvassa Road G.I.D.C. Vapi-396195
Gujarat, India.

NAGAR LIFE SCIENCE NIGERIA LTD,
FATAI IRAWO STREET, OFF LATEEF
SALAMI STREET, AJAO ESTATE
ISOLO LAGOS NIGERIA

8. Marketing authorisation number(s)

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9. Date of first authorisation/renewal of the authorisation

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10. Date of revision of the text
