1.3 PRODUCT INFORMATION

1.3.1 Summary of Product Characteristics (SmPC)

1. NAME OF THE MEDICINAL PRODUCT

1.1 Name of the Medicinal Product

MACKCEFTRA

(Ceftriaxone for Injection USP 1 g.)

1.2 Strength

1 g

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains:
Ceftriaxone Sodium USP eq. to
Anhydrous Ceftriaxone .....1 g

3. PHARMACEUTICAL FORM

Powder for solution for injection (Powder for injection).

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Ceftriaxone sodium is a broad-spectrum bactericidal cephalosporin antibiotic. Ceftriaxone is active *in vitro* against a wide range of Gram -positive and Gram-negative organisms, which include β-lactamase producing strains.

Ceftriaxone is indicated in the treatment of the following infections either before the infecting organism has been identified or when known to be caused by bacteria of established sensitivity.

Pneumonia
Septicaemia
Meningitis
Skin and soft tissue infections
Infections in neutropenic patients
Gonorrhoea
Peri-operative prophylaxis of infections associated with surgery

Treatment may be started before the results of susceptibility tests are known.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2. Posology and method of administration

Ceftriaxone may be administered by deep intramuscular injection, or as a slow intravenous injection, after reconstitution of the solution according to the directions given below. The dosage and mode of administration should be determined by the severity of the infection, susceptibility of the causative organism and the patient's condition. Under most circumstances a once-daily dose or, in the specified indications, one dose will give satisfactory therapeutic results. Diluents containing calcium, (e.g. Ringer's solution or 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. Precipitation of ceftriaxone-calcium can also occur when ceftriaxone is mixed with calcium-containing solutions in the same IV administration line. Therefore, ceftriaxone and calcium-containing solutions must not be mixed or administered simultaneously. Intramuscular injection:1g ceftriaxone should be dissolved in 3.5ml of 1% Lidocaine Injection B P. The solution should be administered by deep intramuscular injection. Doses greater than 1g should be divided and injected at more than one site.
ntravenous injection:1g ceftriaxone should be dissolved in 10ml of Water for Injections. The injection should be administered over at least 2-4 minutes, directly into the vein or via the tubing of an intravenous infusion.
Adults and children 12 years and over: Standard therapeutic dosage:1g once daily. Severe infections:2-4 g daily, normally as a once daily dose. The duration of therapy varies according to the course of the disease. As with antibiotic therapy in general, administration of ceftriaxone should be continued for a minimum of 48 to 72 hours after the patient has become afebrile or evidence of bacterial eradication has been obtained. Acute, uncomplicated gonorrhoea:One dose of 250mg intramuscularly should be administered. Simultaneous administration of probenecid is not indicated. Peri-operative prophylaxis:Usually one dose of 1g given by intramuscular or slow intravenous injection. In colorectal surgery, 2g should be given intramuscularly (in divided doses at different injection sites), by slow intravenous injection or by slow intravenous infusion,in conjunction with a suitable agent against anaerobic bacteria. Elderly:These dosages do not require modification in elderly patients provided that renal and hepaticfunction are satisfactory. In the neonate, the intravenous dose should be given over 60 minutes to reduce the displacement of bilirubin from albumin, thereby reducing the potential risk of bilirubin encephalopathy. Children under 12 years Standard therapeutic dosage: 20-50mg/kg body-weight once daily. Up to 80mg/kg body-weight daily may be given in severe infections, except in premature neonates where a daily dosage of 50mg/kg should not be exceeded. For children with body weights of 50kg or more, the usual dosage should be used. Doses of 50mg/kg or over should be given by slow intravenous infusion over at least 30 minutes. Doses greater than 80mg/kg body weight should be avoided because of the increased risk of biliary precipitates. Renal and hepatic impairment: In patients with impaired renal function, there is no need to reduce the dosage of ceftriaxone provided liver function is intact. Only in cases of pre-terminal renal failure (creatinine clearance <10ml per minute) should the daily dosage be limited to 2g or less. In patientswith liver damage there is no need for the dosage to be reduced provided renal function is intact. In severe renal impairment accompanied by hepatic insufficiency, the plasma concentration of ceftriaxone should be determined at regular intervals and dosage adjusted.
In patients undergoing dialysis, no additional supplementary dosage is required following the dialysis.Plasma concentrations should be monitored, however, to determine whether dosage adjustments are necessary, since the elimination rate in these patients may be reduced.

4.3 Contraindications:

Ceftriaxone is contraindicated in patients with known hypersensitivity to beta-lactam antibiotics. In patien ts hypersensitive to penicillin, th e possibility of allerg ic 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 m ixed or adm inistered 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 80m g/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 th erapy instituted. Ceftriaxone should be used with caution in in dividuals 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 recon stituted vial for adm inistration because a precip itate can for m. Ceftriaxone m ust not be adm inistered 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 hypoprothrom binaemia resu lting in an increased risk of bleeding in patients treated with anticoagulants.
Oral Contraceptives: Ceftriaxone may adversely affect the efficacy of oral hormonal contraceptives.

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 (≥ 1% - <10%): Loose stools or diarrhoea (diarrhoea may sometimes be a symptom ofpseudomembranous colitis, see 4.4 Special warnings and precautions for use), nausea, vomiting, stomatitis and glossitis. Rare (≥ 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 (≥ 0.1% - < 1%): Maculopapular rash or exanthema, pruritus, urticaria, oedema, shivering and anaphylactic or anaphylactoid reactions (e.g. bronchospasm) and allergic dermatitis have occurred.

Rare (≥ 0.01% - < 0.1%): Drug fever, shivering. Anaphylactic-t ype reactions such as bronchospasm are rare. Very r are (< 0.01%): Isolated cases of severe cutaneous adverse reactions (erythema multiform e, Stevens Johnson Syndrome and Lyell' s Syndrome/toxic epidermal necrolysis) have been reported. Blood and lymphatic system disorders Common (≥1% - ≤10%): Haem atological reactions have in cluded anaemia (all grades), haemolytic anaemia, granulocytopenia, leucopenia, neutropenia, throm bocytopenia and eosinophilia. Coagulation disorders have been reported as very rare side effects. Unknown frequency: Immune mediated haemolytic anaem ia Unknown frequency of agranulocytosis (<500/mm3) has been reported, m ostly after 10 days of treatm ent and following total doses of 20g or more. There have been ra re reports of fatal haem olysis in association with ceftriaxone. Ceftriaxone has rarely been associated with prolongation of prothrombin time, however, bleeding and bruising due to hypoprothrom binaemia may be m ore prevalent in patients with renal or hepatic impairm ent, malnourished patients or those with low vitam in K levels and patients receiving prolonged ceftriaxone therapy. Central Nervous system Rare (≥ 0.01% - < 0.1%): Headache, vertigo and dizziness. Adm inistration of high doses of cephalosporins, particularly in patients with renal insufficiency, m ay result in convulsions. Renal and Urinary Rare (≥ 0.01% - < 0.1%): Glycosuria, oliguria, haem aturia, increase in serum creatinine. Very rare (< 0.01%): Cases of renal precipitation have been reported, m ostly in children older than 3 year s and who have been treated with either high daily doses (e.g. ≥ 80mg/kg/day) or total doses exceeding 10 grams and presenting other risk factors (e.g. fluid restrictions, confinem ent 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 (≥ 0.01% - < 0.1%): Hepatitis and/or cholestatic jaundice, increase in liver enzym es.Transient elevations in liver function tests have been reported in a few cases. Shado ws which have been m istaken for gallstones, but which are precipitates of calcium ceftriaxone, have been dete cted by sonograms. These abnormalities are commonly observed after an adult daily dose of two gram s per day or m ore, 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 gram s a day or above these biliary precipitates m ay occasionally cause symptoms. Should patien ts develop symptoms, non-surgical management is recommended and discontinuation of ceftriaxone should be considered. The evidence suggests biliary precipitates usu ally disappear once ceftriaxone has been stopped. The risk of biliary precipitates may be increas ed by treatment duration g reater 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 (≥ 0.01% - < 0.1%): Pain or discomfort m ay be experienced at the site of intramuscular injection im mediately after adm inistration but is usually well tolerated and transient. Intramuscular injection witho ut lidocaine solution is p ainful. Local phlebitis has occurred rarely following intravenous adm inistration but can be m inimised by slow injection over at least 2-4 minutes.

4.9 Overdose:

In overdose, the sym ptoms of nausea, vom iting and diarrhoea can occur. Ceftriaxone concentrations cannot be reduced by haem odialysis or peritoneal dialys is. There is no specific antidote. Treatment is symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Ceftriaxone is a cephalosporin/cepham ycin beta-lactam antibiotic used in the treatm ent of bacterial infections caused by susceptible, usually gram -positive, organisms. Ceftriaxone has in vitro activity against g ram-positive and gram -negative aerobic and anaerob ic bacteria. The bactericidal activity of Ceftriaxon e results from the inhibition of cell wall sy nthesis 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 m ay vary geographically and with time for selected species and local infor mation on resistance is desirable, particularly when treating severe infections.
Commonly susceptible species m ay be Gram-positive aerobes like Staphylococcus aureus, Streptococcus pyogenes (Group A), Streptococcus pneumonia etc.; Gram-negative aerobes like Haemophilus influenza, Neisseria m eningitides, Neisseria gonorrhea, Treponema pallidum and more.

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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 u nder the p lasma concentration-time curve after intram uscular administration is equivalent to that after intravenous administration of an equivalent dose.

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.

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 concrements 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None

6.2. Incompatibilities

Solutions containing ceftriaxone should not be m ixed 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 precip itate can form. Ceftriaxone m ust not be m ixed or adm inistered 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 m icrobiological point of view, once opened, the product should be used immediately.

6.5. Nature and contents of container

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

6.6. Instruction for use and handling

No special requirements.

7. MANUFACTURING AUTHORISATION HOLDER

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