SUMMARY OF PRODUCT CHARACTERISTICS
(PRODUCT DATA SHEET)

1. Name of the Medicinal Product:

1.1 Product Name :

CORCEF IV (Ceftriaxone for Injection USP 1 gm)

1.2 Strength:

Sterile Ceftriaxone Sodium USP eq. to Anhydrous Ceftriaxone 1gm
Sterilised Water For Injection BP 10 ml

1.3 Pharmaceutical Dosage Form :

Sterile dry powder for Injection

2. Quality and Quantitative Composition

Combipack of Ceftriaxone for Injection USP I gm and Sterilised Water For Injection BP 10 ml

1. Ceftriaxone for Injection USP 1gm Each vial contains:
   Sterile Ceftriaxone Sodium USP eq. to Anhydrous Ceftriaxone 1gm
2. Sterilised Water For Injection BP 10 ml

2.1 Qualitative Declaration:

For Excipients see section 6.1

2.2 Quantitative Declaration:

Combipack of Ceftriaxone for Injection USP I gm and Sterilised Water For Injection BP 10 ml

1. Ceftriaxone for Injection USP 1gm Each vial contains:
   Sterile Ceftriaxone Sodium USP eq. to Anhydrous Ceftriaxone 1gm
2. Sterilised Water For Injection BP 10 ml

3. Pharmaceutical Form: Sterile dry powder for Injection

4. Clinical Particulars

4.1 Therapeutic indications :

Ceftriaxone injection is used to treat certain infections caused by bacteria such as gonorrhea (a sexually transmitted disease), pelvic inflammatory disease (infection of the female reproductive organs that may cause infertility), meningitis (infection of the

membranes that surround the brain and spinal cord), and infections of the lungs, ears, skin, urinary tract, blood, bones, joints, and abdomen. Ceftriaxone injection is also sometimes given before certain types of surgery to prevent infections that may develop after the operation. Ceftriaxone injection is in a class of medications called cephalosporin antibiotics. It works by killing bacteria.

4.2 Posology and method of administration :

Posology

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 hepatic function 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 (see *Special warning and precautions for use*).

Paediatric Population

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.

Hepatic impairment

Available data do not indicate the need for dose adjustment in mild or moderate liver function impairment provided renal function is not impaired.

There are no study data in patients with severe hepatic impairment.

Renal impairment:

In patients with impaired renal function, there is no need to reduce the dosage of ceftriaxone provided hepatic function is not impaired. Only in cases of preterminal renal failure (creatinine clearance < 10 ml/min) should the ceftriaxone dosage not exceed 2 g daily.

In patients undergoing dialysis no additional supplementary dosing is required following the dialysis. Ceftriaxone is not removed by peritoneal- or haemodialysis. Close clinical monitoring for safety and efficacy is advised.

Patients with severe hepatic and renal impairment

In patients with both severe renal and hepatic dysfunction, close clinical monitoring for safety and efficacy is advised.

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Method of administration

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 3.6ml of BP. The solution should be administered by deep intramuscular injection. Doses greater than 1g should be divided and injected at more than one site.

Intravenous injection: 1g ceftriaxone should be dissolved in 10ml of Water for Injections PhEur. The injection should be administered over at least 2-4 minutes, directly into the vein or via the tubing of an intravenous infusion.

4.3 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. In vitro studies have shown that ceftriaxone can displace bilirubin from its binding to serum albumin, leading to a possible risk of bilirubin encephalopathy in these patients.

Ceftriaxone is contraindicated in neonates if they require (or are expected to require) treatment with calcium-containing IV solutions, including continuous calcium-containing infusions such as parenteral nutrition because of the risk of precipitation of ceftriaxone - calcium.

A small number of cases of fatal outcomes in which a crystalline material was observed in the lungs and kidneys at autopsy have been reported in neonates receiving ceftriaxone and calcium-containing fluids. In some of these cases, the same intravenous infusion line was used for both ceftriaxone and calcium-containing fluids and in some a precipitate was observed in the intravenous infusion line. At least one fatality has been reported in a neonate in whom ceftriaxone and calcium-containing fluids were administered at different time points via different intravenous lines; no crystalline material was observed at autopsy in this neonate. There have been no similar reports in patients other than neonates.

4.4 Special warning and precautions for use:

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 penicillinsensitive 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.

As with other cephalosporins, anaphylactic reactions with fatal outcome have been reported, even if a patient is not known to be allergic or previously exposed.

Interaction with Calcium-Containing Products

Do not use diluents containing calcium, such as Ringer's solution or Hartmann's

solution, 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. Ceftriaxone must not be administered simultaneously with calcium-containing IV solutions, including continuous calcium-containing infusions such as parenteral nutrition via a Y-site. However, in patients other than neonates, Ceftriaxone and calcium-containing solutions may be administered sequentially of one another if the infusion lines are thoroughly flushed between infusions with a compatible fluid. In vitro studies using adult and neonatal plasma from umbilical cord blood demonstrated that neonates have an increased risk of precipitation of ceftriaxone-calcium.

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. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of C. difficile.
C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of C. difficile cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.
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 of C. difficile, and surgical evaluation should be instituted as clinically indicated.

Hemolytic Anemia
An immune mediated hemolytic anemia has been observed in patients receiving cephalosporin class antibacterials including Ceftriaxone . Severe cases of hemolytic anemia, including fatalities, have been reported during treatment in both adults and children. If a patient develops anemia while on ceftriaxone, the diagnosis of a cephalosporin associated anemia should be considered and ceftriaxone stopped until the etiology is determined.

Precaution
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 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.
Dosage adjustments should not be necessary in patients with hepatic dysfunction; however, in patients with both hepatic dysfunction and significant renal disease, caution should be exercised and the Ceftriaxone dosage should not exceed 2 gm daily.
Alterations in prothrombin times have occurred rarely in patients treated with Ceftriaxone. Patients with impaired vitamin K synthesis or low vitamin K stores (eg, 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 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 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.

Cases of pancreatitis, possibly secondary to biliary obstruction, have been reported rarely in patients treated with Ceftriaxone. Most patients presented with risk factors for biliary stasis and biliary sludge (preceding major therapy, severe illness, total parenteral nutrition). A cofactor role of Ceftriaxone -related biliary precipitation cannot be ruled out.

4.5 Drug Interaction:

No impairment of renal function has so far been observed after concurrent administration of large doses of Ceftriaxone and potent diuretics (e.g. furosemide).

No interference with the action or increase in nephrotoxicity of aminoglycosides has been observed during simultaneous administration with Ceftriaxone.

No effect similar to that of disulfiram has been demonstrated after ingestion of alcohol subsequent to the administration of Ceftriaxone. Ceftriaxone does not contain an N-methylthiotetrazole moiety associated with possible ethanol intolerance and bleeding problems of certain other cephalosporins. The elimination of Ceftriaxone is not altered by probenecid.

In an in-vitro study antagonistic effects have been observed with the combination of chloramphenicol and ceftriaxone. The clinical relevance of this finding is unknown, but caution is advised if concurrent administration of ceftriaxone with chloramphenicol is proposed.

Do not use diluents containing calcium, such as Ringer's solution or Hartmann's solution, 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. Ceftriaxone must not be administered simultaneously with calcium-containing IV solutions including continuous calcium-containing infusions such as parenteral nutrition via a Y-site. However, in patients other than neonates, Ceftriaxone and calcium-containing solutions may

be administered sequentially, of one another, if the infusion lines are thoroughly flushed between infusions with a compatible fluid. In vitro studies using adult and neonatal plasma from umbilical cord blood demonstrated that neonates have an increased risk of precipitation of ceftriaxone-calcium.

Based on literature reports ceftriaxone is incompatible with amsacrine, vancomycin, fluconazole and aminoglycosides.

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.

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.

4.6 Pregnancy and lactation:

Pregnancy

Ceftriaxone crosses the placental barrier. There are limited amounts of data from the use of ceftriaxone in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to embryonal/foetal, perinatal and postnatal development. Ceftriaxone should only be administered during pregnancy and in particular in the first trimester of pregnancy if the benefit outweighs the risk.

Breastfeeding

Ceftriaxone is excreted into human milk in low concentrations but at therapeutic doses of ceftriaxone no effects on the breastfed infants are anticipated. However, a risk of diarrhoea and fungal infection of the mucous membranes cannot be excluded. The possibility of sensitisation should be taken into account. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from ceftriaxone therapy, taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

4.6 Effect on ability to drive and use machines

During treatment with ceftriaxone, undesirable effects may occur (e.g. dizziness), which may influence the ability to drive and use machines.Patients should be cautious when driving or operating machinery.

4.7 Undesirable effects :

The most frequently reported adverse reactions for ceftriaxone are eosinophilia, leucopenia, thrombocytopenia, diarrhoea, rash, and hepatic enzymes increased.
Data to determine the frequency of ceftriaxone ADRs was derived from clinical trials.
The following convention has been used for the classification of frequency:

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Very common (≥ 1/10)
Common (≥ 1/100 - < 1/10)
Uncommon (≥ 1/1000 - < 1/100)
Rare (≥ 1/10000 - < 1/1000)
Not known (cannot be estimated from the available data)

System Organ Class	Common	Uncommon	Rare	Not Known [a]
Infections and infestations		Genital fungal infection	Pseudomembranous colitis[b]	Superinfection[b]
Blood and lymphatic system disorders	Eosinophilia Leucopenia Thrombocytopenia	Granulocytopenia Anaemia Coagulopathy		Haemolytic anaemia[b] Agranulocytosis
Immune system disorders				Anaphylactic shock Anaphylactic reaction Anaphylactoid reaction Hypersensitivity[b]
Nervous system disorders		Headache Dizziness		Convulsion
Ear and labyrinth disorders				Vertigo
Respiratory, thoracic and mediastinal disorders			Bronchospasm	
Gastrointestinal disorders	Diarrhoea[b] Loose stools	Nausea Vomiting		Pancreatitis[b] Stomatitis Glossitis
Hepatobiliary disorders	Hepatic enzyme increased			Gall bladder precipitation[b] Kernicterus
Skin and subcutaneous tissue disorders	Rash	Pruritus	Urticaria	Stevens Johnson Syndrome[b] Toxic epidermal necrolysis[b] Erythema multiforme Acute generalised exanthematous pustulosis
Renal and urinary disorders			Haematuria Glycosuria	Oliguria Renal precipitation

				(reversible)
General disorders and administration site conditions		Phlebitis Injection site pain Pyrexia	Oedema Chills	
Investigations		Blood creatinine increased		Coombs test false positive[b] Galactosaemia test false positive[b] Non enzymatic methods for glucose determination false positive[b]

[a] *Based on post-marketing reports. Since these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorised as not known.*

Description of selected adverse reactions

Infections and infestations

Reports of diarrhoea following the use of ceftriaxone may be associated with *Clostridium difficile*. Appropriate fluid and electrolyte management should be instituted.

Ceftriaxone-calcium salt precipitation

Rarely, severe, and in some cases, fatal, adverse reactions have been reported in pre-term and full-term neonates (aged < 28 days) who had been treated with intravenous ceftriaxone and calcium. Precipitations of ceftriaxone-calcium salt have been observed in lung and kidneys post-mortem. The high risk of precipitation in neonates is a result of their low blood volume and the longer half-life of ceftriaxone compared with adults.

Cases of ceftriaxone precipitation in the urinary tract have been reported, mostly in children treated with high doses (e.g. ≥ 80 mg/kg/day or total doses exceeding 10 grams) and who have other risk factors (e.g. dehydration, confinement to bed). This event may be asymptomatic or symptomatic, and may lead to ureteric obstruction and postrenal acute renal failure, but is usually reversible upon discontinuation of ceftriaxone.

Precipitation of ceftriaxone calcium salt in the gallbladder has been observed, primarily in patients treated with doses higher than the recommended standard dose. In children, prospective studies have shown a variable incidence of precipitation with intravenous application - above 30 % in some studies. The incidence appears to be lower with slow infusion (20 - 30 minutes). This effect is usually asymptomatic, but the precipitations have been accompanied by clinical symptoms such as pain, nausea and vomiting in rare cases. Symptomatic treatment is recommended in these cases. Precipitation is usually reversible upon discontinuation of ceftriaxone.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme www.mhra.gov.uk/yellowcard.

4.8 Overdose :

In overdose, the symptoms of nausea, vomiting and diarrhoea can occur. Ceftriaxone concentrations cannot be reduced by haemodialysis or peritoneal dialysis. There is no specific antidote. Treatment is symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC classification
Pharmacotherapeutic group: cephalosporins and related substances, ATC code: J01DA13

Mode of action
Ceftriaxone has bactericidal activity resulting from the inhibition of bacterial cell wall synthesis ultimately leading to cell death. Ceftriaxone is stable to a broad range of bacterial β-lactamases and is active against a broad spectrum of bacterial pathogens including both Gram-positive and Gram-negative species.

Mechanism of resistance
Ceftriaxone is stable to a wide range of both Gram-positive and Gram-negative beta-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 beta-lactam hydrolysing enzymes (including carbapenemases and some ESBLs) especially in Gram-negative organisms. For Gram-positive organisms such as S. aureus and S. pneumoniae, acquired resistance is mainly encoded by cell wall target site alterations.
Outside of the advanced generation parenteral cephalosporins, cross-resistance to other drug classes is generally not encountered.
Breakpoints
Current MIC breakpoints used to interpret ceftriaxone susceptibility data are shown below. The use of NCCLS breakpoints predominate and are the breakpoints used in data presented in the Table. Values quoted comprise mg/L (MIC testing) or mm (disk diffusion testing) using a 30mg/L drug concentration.
National Committee for Clinical Laboratory Standards (NCCLS) (M100-S12) – 2002

	Susceptible	Intermediate	Resistant
Enterobacteriaceae, P. aeruginosa and other non-Enterobacteriaceae, Staphylococcus spp.	≤ 8 Disk: < 13	16-32 Disk: 14 – 20	≥ 64 Disk: ≥ 21
Haemophilus spp.	≤ 2 Disk: ≥ 26	-	-
Neisseria spp.	≤ 0.25 Disk: ≥ 35	-	-
Streptococcus pneumoniae *	≤ 0.5	1	≥ 2

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Other Streptococcus spp.**	Beta strep ≤ 0.5 Disk: ≥ 24 Viridans group: ≤ 0.5 Disk: ≥ 27	- Viridans group: 1 Disk: 25-26	- Viridans group: ≥ 2 Disk: ≤ 24

* Recent 2002 S. pneumoniae breakpoints (NCCLS M100-S12) defined as ≤ 1 (Sensitive), 2 (Intermediate) and ≥ 4 (Resistant) for non-meningitis specimens and ≤ 0.5 (Sensitive), 1 (Intermediate), and > 2 (Resistant) for meningitis specimens.
** Recent 2002 Streptococcus viridans group breakpoints (NCCLS M100-S12) defined ≤ 1 (Sensitive), 2 (Intermediate), and ≥ 4 (Resistant)

Susceptibility

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Ceftriaxone susceptibility among Gram-positive and Gram-negative bacterial species in Europe from January 1999-December 2001:

Commonly susceptible species (i.e. resistance < 10% in all EU Member States)
Gram-Positive aerobes: MSa coagulase negative Staphylococcus spp. (including S. epidermis)* MSb Staphylococcus aureus* Group B (Streptococcus agalactiae) Streptococcus bovis Streptococcus pneumoniae* Group A Streptococcus (Streptococcus pyogenes)* Streptococcus viridans* Gram-Negative aerobes: Citrobacter spp. (including C.freundii) Escherichia coli* Haemophilus influenzae (including beta-lactamase positive isolates)c* Haemophilus para-influenzae* Klebsiella spp. (including K. pneumoniae and K. oxytoca)* Moraxella catarrhalis* Morganella morganii* Neisseria gonorrhoea (including penicillin-resistant isolates)* Neisseria meningitidis* Proteus spp. (including P. mirabilis and P. vulgaris)* Salmonella spp. (including S. typhimurium) Serratia spp. (including Serratia marsescens)* Shigella spp. Anaerobes: Clostridium spp.*
Species for which acquired resistance may be a problem (i.e. resistance ≥ 10% in at least one EU Member State)
Gram-Negative aerobes:

Pseudomonas aeruginosa + Enterobacter spp. (including E. aerogenes and E. cloacae)*+ Acinetobacter spp. (including A. baumanii and A. calcoaceticus)*+ Anaerobes: Bacteroides spp.* Peptostreptococcus spp.*
Inherently resistant organisms
Gram-Positive aerobes: MRd coagulase negative Staphylococcus spp. (including S. epidermidis) MRe Staphylococcus aureus Enterococcus spp. Gram-Negative aerobes: Listeria monocytogenes Mycoplasma spp. Stenotrophomonas maltophilia Ureaplasma urealyticum Others: Chlamydia spp.

aMethicillin-susceptible Coagulase-Negative Staphylococcus
bMethicillin-susceptible Staphylococcus aureus
cNon-susceptible range (no resistant breakpoints defined)
dMethicillin-resistant Coagulase-Negative Staphylococcus
eMethicillin-resistant Staphylococcus aureus
* Species for which the efficacy of ceftriaxone has been demonstrated both in vitro and in vivo
+ Species for which high rates of resistance have been observed in one or more regions within the EU approximate guidance on probabilities whether micro-organisms will be susceptible. The table above comprises current levels of susceptibility according to routinely produced susceptibility test results in France, Germany, Greece, Italy, the Netherlands, Spain, and the United Kingdom. All data is presented using contemporary NCCLS derived susceptibility breakpoints except France (CA-SFM). Data is derived from The Surveillance Network™ (TSN) Databases in each respective region. The prevalence of resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. This information gives only approximate guidance on probabilities whether microorganisms will be susceptible to ceftriaxone or not.

5.2 Pharmacokinetic properties

Absorption

The maximum plasma concentration after a single IM dose of 1.0 gm is about 81 mg/L and is reached in 2-3 hours after the dose. The area under the plasma concentration-time curve after IM administration is equivalent to that after IV administration of an equivalent dose, indicating 100% bioavailability of intramuscularly administered ceftriaxone.

Distribution

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The volume of distribution of ceftriaxone is 7-12 L. Ceftriaxone has shown excellent tissue and body fluid penetration after a dose of 1-2 gm; concentrations well above the minimal inhibitory concentrations of most pathogens responsible for infection are detectable for more than 24 hours in over 60 tissues or body fluids including lung, heart, biliary tract/liver, tonsil, middle ear and nasal mucosa, bone; and cerebrospinal, pleural, prostatic and synovial fluids. On intravenous administration, ceftriaxone diffuses rapidly into the interstitial fluid, where bactericidal concentrations against susceptible organisms are maintained for 24 hours.

Metabolism

Ceftriaxone is not metabolized systemically; only the intestinal flora transforms the agent into inactive metabolites.

Clearance

The total plasma clearance is 10-22 mL/min. The renal clearance is 5-12 mL/min. 50-60% of ceftriaxone is excreted unchanged in the urine, while 40-50% is excreted unchanged in the bile into the faeces as microbiologically inactive metabolites.

The elimination half-life in adults is about eight hours. Over a 0.15 to 3 g dose range, the values of elimination half-life range from 6 – 9 hours. Total plasma clearance from 0.6 – 1.4 l/h and renal clearance from 0.3 – 07 l/ h.

Ceftriaxone concentrates in the urine. The urine concentrations are 5-10 times higher than those found in the plasma.

Ceftriaxone cannot be removed by dialysis. This applies to both haemodialysis and peritoneal dialysis.

Urinary excretion is via glomerular filtration. No tubular secretion takes place.

The pharmacokinetics of Ceftriaxone are non-linear with respect to the dose.

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:

Nil

6.2 Incompatibilities: None

6.3 Shelf life: 24 Months

6.4 Special precautions for storage:

Store below 30°C. Protect from light and moisture.

Keep medicine out of reach of children.

6.5 Nature and contents of container:

Almost white crystalline powder filled in USP type III clear glass vials, sealed with rubber plug and flip off aluminium seal.

6.6 Special precautions for disposal

None

7. Marketing Authorization Holder:

Signature Healthcare Limited
Cape Business Park,
Along Thika Super Highway,
P.O. Box 66172-00800,
Nairobi, KENYA.

8. Marketing Authorization Numbers:

9. Date of first authorization/renewal of the authorization: ---

10. Date of revision of the text: ---

11. Name and address of Manufacture

Company Name: CORAL LABORATORIES LTD.

Address : **Plot No. 130, silvasa road, GIDC**
Vapi-396195, Dist –Valsad, Gujarat state, India

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