1.16 Local Technical Representative

1.17 Summary Product Characteristics (SPC)

Ceftriaoxne for injection 1g

1. Name of the medicinal product

Ceftriaxone for injection 1g

2. Qualitative and quantitative composition

Each vial contains ceftriaxone sodium equivalent to 1g of ceftriaxone.

3. Pharmaceutical form

Powder for injection.

White to pale yellow crystalline powder.

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 (see sections 4.3, 4.4 and 6.2).

Intramuscular injection: 1g ceftriaxone should be dissolved in 3.5ml of 1% Lidocaine Injection 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.

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 (see below).

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*).

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 patients with 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 patients hypersensitive to penicillin, the possibility of allergic 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

	o jaundice, or who are hypoalbuminaemic or acidotic because these are conditions in which bilirubin binding is likely to be impaired o if they require (or are expected to require) IV calcium treatment, or calcium-containing infusions because of the risk of precipitation of ceftriaxone-calcium (see sections 4.4, 4.8 and 6.2).

Contraindications of lidocaine must be excluded before intramuscular injection of ceftriaxone when lidocaine is used as a solvent.

4.4 Special warnings and precautions for use

The stated dosage should not be exceeded.

If lidocaine is used as a solvent ceftriaxone solutions should only be used for intramuscular injection.

As with other cephalosporins, anaphylactic shock cannot be ruled out even if a thorough patient history is taken.

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. Ceftriaxone is contraindicated in patients who have had a previous hypersensitivity reaction to any cephalosporin. It is also contraindicated in patients who have had a previous immediate and/or any severe hypersensitivity reaction to any penicillin or to any other beta-lactam drug (see section 4.3, Contra-indications). Ceftriaxone should be given with caution to patients who have had any other type of hypersensitivity reaction to a penicillin or any other beta-lactam drug. Care is required when administering ceftriaxone to patients who have previously shown hypersensitivity to penicillins or other non-cephalosporin beta-lactam antibiotics, as occasional instances of cross allergenicity between cephalosporins and these antibiotics have been recorded. Anaphylactic shock requires immediate counter measures.

In severe renal impairment accompanied by hepatic insufficiency, dosage reduction is required as outlined under *Posology and method of administration.*

Safety and effectiveness of ceftriaxone in neonates, infants and children have been established for the dosages described under Dosage and administration. *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 neonates (especially prematures) at risk of developing bilirubin encephalopathy.

Cases of fatal reactions with calcium-ceftriaxone precipitates in lungs and kidneys in premature and full-term newborns aged less than 1 month have been described. At least one of them had received

ceftriaxone and calcium at different times and through different intravenous lines. In the available scientific data, there are no reports of confirmed intravascular precipitations in patients, other than newborns, treated with ceftriaxone and calcium-containing solutions or any other calcium-containing products. In vitro studies demonstrated that newborns have an increased risk of precipitation of ceftriaxone-calcium compared to other age groups.

In patients of any age ceftriaxone must not be mixed or administered simultaneously with any calcium-containing IV solutions, even via different infusion lines or at different infusion sites. However, in patients older than 28 days of age ceftriaxone and calcium-containing solutions may be administered sequentially one after another if infusion lines at different sites are used or if the infusion lines are replaced or thoroughly flushed between infusions with physiological salt-solution to avoid precipitation. In patients requiring continuous infusion with calcium-containing TPN solutions, healthcare professionals may wish to consider the use of alternative antibacterial treatments which do not carry a similar risk of precipitation. If use of ceftriaxone is considered necessary in patients requiring continuous nutrition, TPN solutions and ceftriaxone can be administered simultaneously, albeit via different infusion lines at different sites. Alternatively, infusion of TPN solution could be stopped for the period of ceftriaxone infusion, considering the advice to flush infusion lines between solutions. (see sections 4.3, 4.8, 5.2 and 6.2).

Shadows which have been mistaken for gallstones, have been detected on sonograms of the gallbladder, usually following doses of higher than the standard recommended dose (see section 4.8). These shadows are, however, precipitates of calcium ceftriaxone which disappear on completion or discontinuation of ceftriaxone therapy. Rarely have these findings been associated with symptoms. In symptomatic cases, conservative nonsurgical management is recommended.

Discontinuation of ceftriaxone treatment in symptomatic cases should be at the discretion of the physician. These shadows can appear in patients of any age, but are more likely in infants and small children who are usually given a larger dose of ceftriaxone on a body weight basis. In children, doses greater than 80mg/kg body weight should be avoided because of the increased risk of biliary precipitates. There is no clear evidence of gallstones or of acute cholecystitis developing in children or infants treated with ceftriaxone.

Cephalosporins as a class tend to be absorbed onto the surface of the red cell membranes and react with antibodies directed against the drug to produce a positive Coombs' test and occasionally a rather mild haemolytic anaemia. In this respect, there may be some cross-reactivity with penicillins.

Regular blood counts (haemoglobin, erythrocyte, leucocyte and platelet counts and screening for prolongation of prothrombin time) should be carried out during treatment.

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.

Cases of pancreatitis, possibly of biliary obstruction aetiology, have been rarely reported in patients treated with ceftriaxone. Most patients presented with risk factors for biliary stasis and biliary sludge, e.g. preceding major therapy, severe illness and total parenteral nutrition. A trigger or cofactor role of ceftriaxone-related biliary precipitation cannot be ruled out.

Superinfections with non-susceptible micro-organisms (such as yeasts, fungi) may occur as with other anti-bacterial agents. A rare side-effect is pseudomembranous colitis which has resulted from infection with *Clostridium difficile* during treatment with ceftriaxone.

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.

An immune mediated haemolytic anaemia has been observed in patients receiving cephalosporin class antibacterials including ceftriaxone. Severe cases of haemolytic anaemia, including fatalities, have been reported during treatment in both adults and children. If a patient develops anaemia while on ceftriaxone, the diagnosis of a cephalosporin associated anaemia should be considered and ceftriaxone discontinued until the aetiology is determined.

Antibiotic-associated diarrhoea, colitis and pseudomembranous colitis have all been reported with the use of ceftriaxone. These diagnoses should be considered in any patient who develops diarrhoea

during or shortly after treatment. Ceftriaxone should be discontinued if severe and/or bloody diarrhoea occurs during treatment and appropriate therapy instituted.

Ceftriaxone should be used with caution in individuals with a previous history of gastro-intestinal disease, particularly colitis.

Each gram of ceftriaxone sodium contains approximately 3.6mmol sodium.

This should be taken into account for patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

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.

The elimination of ceftriaxone is not altered by probenecid.

Aminoglycoside antibiotics and diuretics: No impairment of renal function has so far been observed after concurrent administration of large doses of ceftriaxone and potent diuretics (e.g.furosemide). There is no evidence that ceftriaxone increases renal toxicity of aminoglycosides.

Alcohol: 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.

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 hypoprothrombinaemia (Refer to section 4.8, Undesirable effects) resulting in an increased risk of bleeding in patients treated with anticoagulants.

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.

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

Interference with Laboratory Tests:

In patients treated with ceftriaxone, the Coombs' test may in rare cases be false-positive.

Ceftriaxone, like other antibiotics, may result in false-positive tests for galactosaemia. Likewise, non-enzymatic methods such as copper reduction methods (Benedict's, Fehling's or Clinitest) for glucose determination in urine may give false-positive results. For this reason, urine-glucose determination during therapy with ceftriaxone should be carried out enzymatically.

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.

Lactation: 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 machines

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. Precipitations of ceftriaxone-calcium salt have been observed in lung and kidneys post-mortem. The high risk of precipitation in newborns is due to their low blood volume and the longer half life of ceftriaxone compared with adults (see sections 4.3, 4.4 and 5.2).

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 of pseudomembranous 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-type reactions such as bronchospasm are rare.

Very rare (< 0.01%): Isolated cases of severe cutaneous adverse reactions (erythema multiforme, Stevens Johnson Syndrome and Lyell's Syndrome/toxic epidermal necrolysis) have been reported.

Blood and lymphatic system disorders

Common (≥1% - ≤10%):

Haematological reactions have included anaemia (all grades), haemolytic anaemia, granulocytopenia, leucopenia, neutropenia, thrombocytopenia and eosinophilia. Coagulation disorders have been reported as very rare side effects.

Unknown frequency: Immune mediated haemolytic anaemia

Unknown frequency of agranulocytosis (<500/mm3) has been reported, mostly after 10 days of treatment and following total doses of 20g or more.

There have been rare reports of fatal haemolysis in association with ceftriaxone. Ceftriaxone has rarely been associated with prolongation of prothrombin time, however, bleeding and bruising due to hypoprothrombinaemia may be more prevalent in patients with renal or hepatic impairment, malnourished patients or those with low vitamin K levels and patients receiving prolonged ceftriaxone therapy.

Central Nervous system

Rare (≥ 0.01% - < 0.1%): Headache, vertigo and dizziness.

Administration of high doses of cephalosporins, particularly in patients with renal insufficiency, may result in convulsions.

Renal and Urinary

Rare (≥ 0.01% - < 0.1%): Glycosuria, oliguria, haematuria, increase in serum creatinine.

Very rare (< 0.01%): Cases of renal precipitation have been reported, mostly in children older than 3 years 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, confinement 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 mould necrosis may occur rarely with ceftriaxone.

Hepatobiliary system

Rare (≥ 0.01% - < 0.1%): Hepatitis and/or cholestatic jaundice, increase in liver enzymes.Transient elevations in liver function tests have been reported in a few cases.

Shadows which have been mistaken for gallstones, but which are precipitates of calcium ceftriaxone, have been detected by sonograms. These abnormalities are commonly observed after an adult daily dose of two grams per day or more, 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 grams a day or above these biliary precipitates may occasionally cause symptoms. Should patients develop symptoms, non-surgical management is recommended and discontinuation of ceftriaxone should be considered. The evidence suggests biliary precipitates usually disappear once ceftriaxone has been stopped. The risk of biliary precipitates may be increased by treatment duration greater 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 may be experienced at the site of intramuscular injection immediately after administration but is usually well tolerated and transient. Intramuscular injection without lidocaine solution is painful. Local phlebitis has occurred rarely following intravenous administration but can be minimised by slow injection over at least 2-4 minutes.

Influence on diagnostic tests

In patients treated with ceftriaxone the Coombs' test rarely may become false-positive. Ceftriaxone, like other antibiotics, may result in false-positive tests for galactosemia.

Likewise, nonenzymatic methods for the glucose determination in urine may give false-positive results. For this reason, urine-glucose determination during therapy with ceftriaxone should be done enzymatically.

4.9 Overdose

In the case of overdose nausea, vomiting, diarrhoea, can occur. Ceftriaxone concentration can not be reduced by haemodialysis or peritoneal dialysis. There is no specific antidote. Treatment is symptomatic.

5. Pharmacological properties

5.1 Pharmacodynamic properties

General Properties

ATC classification: JO1D A13

Mode of action