SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

CEFTRIAXONE 500 IV iPHARMA (powder and solvent for solution for intravenous injection)

CEFTRIAXONE 1 000 IV iPHARMA (powder and solvent for solution for intravenous injection)

CEFTRIAXONE 500 IM iPHARMA (powder and solvent for solution for intramuscular injection)

CEFTRIAXONE 1 000 IM iPHARMA (powder and solvent for solution for intramuscular injection)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

CEFTRIAXONE 500 IV iPHARMA and IM vials contain ceftriaxone disodium equivalent to 500 mg ceftriaxone.

CEFTRIAXONE 1 000 IV and IM iPHARMA vials contain ceftriaxone disodium equivalent to 1 000 mg ceftriaxone.

Solvent for CEFTRIAXONE 500 IV and 1 000 IV iPHARMA: each ampoule contains 5 ml water for injection.

Solvent for CEFTRIAXONE 500 IM iPHARMA: each 2 ml ampoule contains lidocaine (lignocaine) hydrochloride (20 mg), sodium chloride and water for injection.

Solvent for CEFTRIAXONE 1 000 IM iPHARMA: each 3,5 ml ampoule contains lidocaine (lignocaine) hydrochloride (35 mg), sodium chloride and water for injection.

Each gram CEFTRIAXONE iPHARMA contains 3,6 mmol sodium.

Sugar free.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Intravenous (IV) injection:

CEFTRIAXONE 500 IV and 1 000 IV iPHARMA: almost white to yellowish crystalline sterile powder filled in a colourless glass vial.

Solvent: clear sterile solution filled in a clear, colourless glass ampoule.

Intramuscular (IM) injection:

CEFTRIAXONE 500 IM and 1000 IM iPHARMA: almost white to yellowish crystalline sterile powder filled in a colourless glass vial.

Solvent: clear sterile solution filled in an amber glass ampoule.

Reconstituted solutions:

Clear, straw yellow colour solutions free from particulate matter.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

CEFTRIAXONE iPHARMA is indicated for the treatment of the following infections when caused by susceptible organisms:

Bacterial septicaemia caused by Methicillin Sensitive *Staphylococcus aureus* (MSSA), *Streptococcus pneumoniae, Escherichia coli, Haemophilus influenzae* or *Klebsiella pneumoniae.*

Meningitis caused by *Haemophilus influenzae, Neisseria meningitidis* or *Streptococcus pneumoniae.*

Intra-abdominal infections caused by *Escherichia coli, Klebsiella pneumoniae, Clostridium species* (Note that most strains of *Clostridium difficile* are resistant) or *Peptostreptococcus* species.

Skin and skin structure infections caused by Methicillin Sensitive *Staphylococcus aureus (MSSA), Streptococcus pyogenes, Streptococcus viridans group, Escherichia coli, Enterobacter cloacae, Klebsiella oxytoca, Klebsiella pneumoniae, Proteus mirabilis, Morganella morganii, Pseudomonas aeruginosa, Serratia marcescens* or *Peptostreptococcus* species.

Bone- and joint infections caused by Methicillin Sensitive *Staphylococcus aureus (MSSA), Streptococcus pneumoniae, Escherichia coli, Proteus mirabilis, Klebsiella pneumoniae* or *Enterobacter* species.

Renal and urinary tract infections (complicated and uncomplicated) caused by *Escherichia coli, Proteus mirabilis, Proteus vulgaris, Morgonella morganii* or *Klebsiella pneumoniae.*

Respiratory tract infections caused by *Streptococcus pneumoniae*,

Methicillin Sensitive *Staphylococcus aureus* (MSSA), *Haemophilus influenzae, Haemophilus para-influenzae, Klebsiella pneumoniae, Escherichia coli, Enterobacter aerogenes, Proteus mirabilis* or *Serratia marcescens.*

Ear, nose and throat infections (acute bacterial otitis media) caused by *Streptococcus pneumoniae, Haemophilus influenza* (including beta-lactamase producing strains) or *Moraxella catarrhalis* (including beta-lactamase producing strains).

Uncomplicated gonorrhoea (cervical/urethral and rectal) caused by *Neisseria gonorrhoeae*, including both penicillinase- and non-penicillinase-producing strains, and pharyngeal gonorrhoea caused by non-penicillinase producing strains of *Neisseria gonorrhoeae.*

Surgical prophylaxis: The pre-operative administration of a single 1 g dose of CEFTRIAXONE iPHARMA may reduce the incidence of post-operative infections.

In the treatment of infections caused by *Pseudomonas aeruginosa*, an aminoglycoside should be administered concomitantly.

4.2 Posology and method of administration

Prescribers must adhere to the principles of antibiotic stewardship.

Posology

Standard dosage

Adults and children over the age of 12 years:

The usual dosage is 1 to 2 g CEFTRIAXONE iPHARMA once daily (every 24 hours). In severe cases or in infections caused by moderately sensitive organisms, the dosage may be raised to 4 g, once daily.

Neonates, infants and children up to 12 years of age:

The following dosage schedules are recommended for once daily administration.

Neonates (up to 14 days of age):

20 – 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 – 80 mg/kg once daily.

For children with bodyweights of 50 kg or more, the usual adult dose should be used.

Intravenous doses of ≥ 50 mg/kg bodyweight should be given by infusion over at least 30 minutes.

Elderly patients:

The dosages recommended for adults require no modification in the case of geriatric patients.

Duration of therapy

The duration of therapy varies according to the course of the disease.

Administration of CEFTRIAXONE iPHARMA 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.

Special dosage instructions

Meningitis:

In bacterial meningitis in neonates, infants and children, treatment begins with doses of 100 mg/kg (not to exceed 4 g), once daily. As soon as the causative organism has been identified and its sensitivity determined, the dosage can be adjusted accordingly.

For bacterial meningitis in adults, the recommended dose is 4 g daily.

Gonorrhoea:

For the treatment of uncomplicated gonorrhoea (penicillinase-producing and non-penicillinase-producing strains), a single intramuscular dose of 125 mg CEFTRIAXONE iPHARMA IM is recommended.

Peri-operative prophylaxis:

A single dose of 1 to 2 g CEFTRIAXONE iPHARMA administered 30 - 90 minutes prior to surgery. In colorectal surgery, administration of CEFTRIAXONE iPHARMA with or without a 5-nitroimidazole, e.g. ornidazole, (separate administration: see Method of administration below) has been proven effective.

Impaired renal and hepatic function:

In patients with impaired renal function, there is no need to reduce the dosage of CEFTRIAXONE iPHARMA, provided that the hepatic function is intact.

In cases of severe renal failure (creatinine clearance <10 ml/min) the CEFTRIAXONE iPHARMA dosage should not exceed 2 g daily. In patients with liver damage, there is no need for the dosage to be reduced, provided renal function is intact.

Method of administration

CEFTRIAXONE iPHARMA must be reconstituted prior to use. Reconstituted solutions retain their physical and chemical stability for 6 hours at room temperature (or 24 hours in the refrigerator at 2 – 8 °C). As a general rule, however, the solutions should be used immediately after preparation. The solutions range in colour from pale yellow to amber, depending on the concentration and length of storage. The colouration of the solutions is of no significance for the efficacy or tolerance of the medicine.

Intramuscular administration

CEFTRIAXONE iPHARMA can be administered by deep intramuscular injection. Intramuscular injections should be injected well within the bulk of a relatively large muscle and not more than 1 g should be injected at one site. For IM injection, CEFTRIAXONE iPHARMA 500 mg is dissolved in 2 ml and CEFTRIAXONE iPHARMA 1 000 mg in 3,5 ml, of water for injection. CEFTRIAXONE iPHARMA dissolved in a 1 % lidocaine solution instead of water for injection can reduce pain at the site of injection. If the solvent used is lidocaine (lignocaine), the resulting solution should never be administered intravenously (see section 4.3)

Intravenous administration

For IV injection, CEFTRIAXONE iPHARMA 500 mg is dissolved in 5 ml, and CEFTRIAXONE iPHARMA 1 000 mg in 10 ml sterile water for injection. The intravenous administration should be given over 2 - 4 minutes.

Intravenous Infusion

The infusion should be given over a period of at least 30 minutes.

For incompatibilities, see section 6.2.

For instructions on reconstitution of the CEFTRIAXONE iPHARMA before administration, see section 6.6.

4.3 Contraindications

- Hypersensitivity to ceftriaxone, to any other cephalosporin or to any of the excipients listed in section 6.1.
- History of severe hypersensitivity (e.g. anaphylactic reaction) to any other type of beta-lactam antibacterial medicine (penicillins, monobactams and carbapenems).
- Premature neonates up to a postmenstrual age of 41 weeks (gestational age + chronological age)*
- Full-term neonates (up to 28 days of age):
    - with hyperbilirubinaemia, jaundice, or who are hypoalbuminaemic or acidotic because these are conditions in which bilirubin binding is likely to be impaired*
    - if they require (or are expected to require) intravenous calcium treatment, or calcium-containing infusions due to the risk of precipitation of a ceftriaxone-calcium salt (see sections 4.4, 4.5 and 4.8)

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

Contraindications to lidocaine (lignocaine) must be excluded before CEFTRIAXONE iPHARMA IM reconstituted with lidocaine (lignocaine) is given to patients (see section 4.4). Lidocaine (lignocaine) is contraindicated in patients with:

- hypersensitivity to lidocaine (lignocaine) or amide-type local anaesthetics
- hypovolaemia, heart block, other conduction disturbances, bradycardia, cardiac decompensation or hypotension
- sino-atrial disorders
- all grades of atrioventricular block
- severe myocardial depression
- patients with porphyria
- CEFTRIAXONE iPHARMA IM solutions containing lidocaine (lignocaine) should never be administered intravenously.

4.4 Special warnings and precautions for use

Hypersensitivity reactions

As with all beta-lactam antibacterial medicines, serious and occasionally fatal hypersensitivity reactions have been reported (see section 4.8). In case of severe hypersensitivity reactions, treatment with CEFTRIAXONE iPHARMA must be discontinued immediately and adequate emergency measures must be initiated. Before beginning treatment, it should be established whether the patient has a history of severe hypersensitivity reactions to ceftriaxone, as contained in CEFTRIAXONE iPHARMA, to other cephalosporins or to any other type of beta-lactam medicine. Caution should be used if CEFTRIAXONE iPHARMA is given to patients with a history of non-severe hypersensitivity to other beta-lactam medicines.

Severe cutaneous adverse reactions (SCAR), such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalised exanthematous pustulosis (AGEP) have been reported in patients taking beta-lactam antibiotics. When SCAR is suspected CEFTRIAXONE iPHARMA should be discontinued

Interaction with calcium containing products

Cases of fatal reactions with calcium-ceftriaxone precipitates in lungs and kidneys in premature and full-term neonates 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 neonates, treated with ceftriaxone and calcium-containing solutions or any other calcium-containing products. *In-vitro* studies demonstrated that neonates have an increased risk of precipitation of ceftriaxone-calcium compared to other age groups.

In patients of any age CEFTRIAXONE iPHARMA must not be mixed or administered simultaneously with any calcium-containing intravenous solutions, even via different infusion lines or at different infusion sites. However, in patients older than 28 days of age CEFTRIAXONE iPHARMA 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 total parenteral nutrition (TPN) solutions, healthcare professionals may wish to consider the use of alternative antibacterial treatments which do not carry a similar risk of precipitation. If the use of CEFTRIAXONE iPHARMA is considered necessary in patients requiring continuous nutrition, TPN solutions and CEFTRIAXONE iPHARMA 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 iPHARMA infusion and the infusion lines flushed between solutions (see sections 4.3, 4.8, 5.2 and 6.2)

Paediatric population

Safety and effectiveness of CEFTRIAXONE iPHARMA in neonates, infants and children have been established for the dosages described under Posology and Method of Administration (see section 4.2). Studies have shown that ceftriaxone, like some other cephalosporins, can displace bilirubin from serum albumin.

CEFTRIAXONE iPHARMA is contraindicated in premature and full-term neonates at risk of developing bilirubin encephalopathy (see section 4.3).

Immune mediated haemolytic anaemia

An immune mediated haemolytic anaemia has been observed in patients receiving cephalosporin class antibacterials including ceftriaxone, as contained in CEFTRIAXONE iPHARMA (see section 4.8). Severe cases of haemolytic anaemia, including fatalities, have been reported during treatment with ceftriaxone, as contained in CEFTRIAXONE iPHARMA in both adults and children.

If a patient develops anaemia while on CEFTRIAXONE iPHARMA, the diagnosis of a cephalosporin-associated anaemia should be considered and CEFTRIAXONE iPHARMA discontinued until the aetiology is determined.

Long term treatment

During prolonged treatment complete blood count should be performed at regular intervals.

Colitis/Overgrowth of non-susceptible microorganisms

Antibacterial medicine-associated colitis and pseudo-membranous colitis have been reported with nearly all antibacterial medicines, 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 diarrhoea during or subsequent to the administration of ceftriaxone (see section 4.8). Discontinuation of therapy with CEFTRIAXONE iPHARMA and the administration of specific treatment for *Clostridium difficile* should be considered. Medicines that inhibit peristalsis should not be given.

Superinfections with non-susceptible microorganisms may occur as with other antibacterial medicines.

Severe renal and hepatic insufficiency

In severe renal and hepatic insufficiency, close clinical monitoring for safety and efficacy is advised (see section 4.2).

Interference with serological testing

Interference with Coombs tests may occur, as CEFTRIAXONE iPHARMA may lead to false-positive test results. CEFTRIAXONE iPHARMA can also lead to false-positive test results for galactosaemia (see section 4.8).

Non-enzymatic methods for the glucose determination in urine may give false-positive results. Urine glucose determination during therapy with CEFTRIAXONE iPHARMA should be done enzymatically (see section 4.8).

The presence of ceftriaxone may falsely lower estimated blood glucose values obtained with some blood glucose monitoring systems. Please refer to instructions for use for each system. Alternative testing methods should be used if necessary.

Sodium

Each gram of CEFTRIAXONE iPHARMA contains 3,6 mmol sodium. This should be taken into consideration in patients on a controlled sodium diet.

Antibacterial spectrum

Ceftriaxone as contained in CEFTRIAXONE iPHARMA has a limited spectrum of antibacterial activity and may not be suitable for use as a single medicine for the treatment of some types of infections unless the pathogen has already been confirmed. In polymicrobial infections, where suspected pathogens include organisms resistant to ceftriaxone, administration of an additional antibiotic should be considered.

Use of lidocaine (lignocaine)

In case a lidocaine (lignocaine) solution is used as a solvent, ceftriaxone solutions must only be used for intramuscular injection. The lidocaine (lignocaine) solution should never be administered intravenously.

Facilities for resuscitation should be available when administering lidocaine (lignocaine).

Lidocaine (lignocaine) should be used with caution in patients with epilepsy, shock, myasthenia gravis, congestive cardiac failure or respiratory depression, including where medicines are known to interact with lidocaine (lignocaine) either to increase its availability or additive effects e.g., phenytoin or prolong its elimination e.g., hepatic or end renal insufficiency where the metabolites of lidocaine (lignocaine) may accumulate.

The effect of lidocaine (lignocaine) may be reduced if the injection is made into an inflamed or infected area.

Intramuscular lidocaine (lignocaine) may increase creatinine phosphokinase concentrations which can interfere with the diagnosis of acute myocardial infarction.

Biliary lithiasis

When shadows are observed on sonograms, consideration should be given to the possibility of precipitates of calcium ceftriaxone. Shadows, which have been mistaken for gallstones, have been detected on sonograms of the gallbladder and have been observed more frequently at ceftriaxone doses of 1 g per day and above. Caution should be particularly considered in the paediatric population. Such precipitates disappear after discontinuation of CEFTRIAXONE iPHARMA therapy. Precipitates of calcium ceftriaxone have been associated with symptoms. In symptomatic cases, conservative nonsurgical management is recommended and discontinuation of CEFTRIAXONE iPHARMA treatment should be considered by the medical practitioner based on specific benefit risk assessment (see section 4.8).

Biliary stasis

Cases of pancreatitis, possibly of biliary obstruction aetiology, have been reported in patients treated with ceftriaxone, as contained in CEFTRIAXONE iPHARMA, (see section 4.8). 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 of CEFTRIAXONE iPHARMA-related biliary precipitation cannot be ruled out.

Renal lithiasis

Cases of renal lithiasis have been reported, which is reversible upon discontinuation of CEFTRIAXONE iPHARMA (see section 4.8). In symptomatic cases, sonography should be performed. Use in patients with history of renal lithiasis or with hypercalciuria should be considered by the medical practitioner based on specific benefit risk assessment.

Jarisch-Herxheimer reaction (JHR)

Some patients with spirochete infections may experience a Jarisch-Herxheimer reaction (JHR) shortly after CEFTRIAXONE iPHARMA treatment is started. JHR is usually a self - limiting condition or can be managed by symptomatic treatment. The antibiotic treatment should not be discontinued if such reaction occurs.

4.5 Interaction with other medicines and other forms of interaction

Calcium-containing diluents, such as Ringer's solution or Hartmann's solution, should not be used to reconstitute CEFTRIAXONE iPHARMA vials or to further dilute a reconstituted vial for intravenous administration because a precipitate can form. Precipitation of ceftriaxone-calcium can also occur when CEFTRIAXONE iPHARMA is mixed with calcium-containing solutions in the same intravenous administration line. CEFTRIAXONE iPHARMA must not be administered simultaneously with calcium-containing intravenous solutions, including continuous calcium-containing infusions such as parenteral nutrition via a Y-site. However, in patients other than neonates, CEFTRIAXONE iPHARMA 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 (see sections 4.3, 4.4, 4.8 and 6.2).

Concomitant use with oral anticoagulants may increase the anti-vitamin K effect and the risk of bleeding. It is recommended that the International Normalised Ratio (INR) is monitored frequently and the posology of the anti-vitamin K medicine adjusted accordingly, both during and after treatment with CEFTRIAXONE iPHARMA (see section 4.8).

There is conflicting evidence regarding a potential increase in renal toxicity of aminoglycosides when used with cephalosporins. The recommended monitoring of aminoglycoside levels (and renal function) in clinical practice should be closely adhered to in such cases.

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.

In patients treated with CEFTRIAXONE iPHARMA, the Coombs' test may lead to false-positive test results.

CEFTRIAXONE iPHARMA may result in false-positive tests for galactosaemia

Likewise, non-enzymatic methods for glucose determination in urine may yield false-positive results. For this reason, glucose level determination in urine during therapy with CEFTRIAXONE iPHARMA should be carried out enzymatically.

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

Simultaneous administration of probenecid does not reduce the elimination of CEFTRIAXONE iPHARMA.

Use of lidocaine (lignocaine) as solvent

Interactions with lidocaine (lignocaine) must be considered before CEFTRIAXONE iPHARMA IM reconstituted with lidocaine (lignocaine) is given to patients.

While adrenaline when used in conjunction with lidocaine (lignocaine) might decrease vascular absorption, it greatly increases the danger of ventricular tachycardia and fibrillation if accidentally injected intravenously.

Lidocaine (lignocaine) reduces the seizure threshold to fentanyl. Opioid-antiemetic combination sometimes used for sedation in children could reduce the convulsant threshold to lidocaine (lignocaine) and increase the CNS depressant effect.

Cimetidine and propranolol reduce the clearance of lidocaine (lignocaine), thus enhancing its toxicity if concomitantly administered with these medicines. Increase in serum levels of lidocaine (lignocaine) may also occur with anti-viral agents (e.g. amprenavir, atazanavir, darunavir, lopinavir).

Hypokalaemia caused by diuretics may antagonize the action of lidocaine (lignocaine) if administered concomitantly.

Cardiovascular collapse has been reported following the use of bupivacaine in patients on treatment with verapamil and timolol; lidocaine (lignocaine) is closely related to bupivacaine.

Lidocaine (lignocaine) should be used with caution in patients receiving other local anaesthetics or medicines related structurally to amide-type local anaesthetics (e.g. anti-dysrhythmics, such as mexiletine), since the systemic toxic effects are additive. Specific interaction studies with lidocaine (lignocaine) and class III anti-dysrhythmic medicines (e.g. amiodarone) have not been performed, but caution is advised.

There may be an increased risk of ventricular dysrhythmia in patients treated concurrently with antipsychotics which prolong or may prolong the QT interval (e.g. pimozide, sertindole, olanzapine, quetiapine, zotepine) or 5HT3 antagonists (e.g. tropisetron, dolasetron). Concomitant use of quinupristin/dalfopristin should be avoided.

There may be an increased risk of enhanced and prolonged neuromuscular blockade in patients treated concurrently with muscle relaxants (e.g. suxamethonium).

Inhibition of CYP1A2 by fluvoxamine considerably reduces elimination of lidocaine (lignocaine) and increases the risk of lidocaine (lignocaine) toxicity. Concomitant use of both fluvoxamine and a CYP3A4 inhibitor such as erythromycin can further increase lidocaine (lignocaine) concentrations. Conversely, reduced serum lidocaine (lignocaine) concentrations may result from medicines that may stimulate the hepatic metabolism of lidocaine (lignocaine) (e.g. phenytoin, oral hormone replacement therapy [HRT]).

Lidocaine (lignocaine) is markedly bound to α-l-acid glycoprotein (AAG). AAG concentrations may be reduced by oestrogens leading to a higher free fraction of lidocaine (lignocaine) in women than in men and the free fraction is further increased during pregnancy and in women taking oral contraceptives or HRT.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety in human pregnancy has not been established. CEFTRIAXONE iPHARMA, and the solvent lidocaine (lignocaine), crosses the placental barrier.

Breastfeeding

CEFTRIAXONE iPHARMA, and the solvent lidocaine (lignocaine), is excreted into human milk in low concentrations. Caution is advised in nursing mothers.

Fertility

Reproductive studies have shown no evidence of adverse effects on male or female fertility.

4.7 Effects on ability to drive and use machines

During treatment with CEFTRIAXONE iPHARMA, undesirable effects may occur (e.g. dizziness), which may influence the ability to drive and use machines (see section 4.8). Patients should be cautious when driving or operating machinery.

4.8 Undesirable effects

The most frequently reported adverse reactions for ceftriaxone as contained in CEFTRIAXONE iPHARMA are eosinophilia, leukopenia, thrombocytopenia, diarrhoea, rash, and hepatic enzymes increased.

Data to determine the frequency of ceftriaxone ADRs was derived from clinical trials.

System Organ Class	*Frequent*	*Less frequent*	*Unknown frequency*
Infections and infestations		Genital fungal infection, Pseudomembranous colitis[b]	Superinfection[b]
Blood and lymphatic system disorders	Eosinophilia, leukopenia, thrombocytopenia	Granulocytopenia, anaemia, coagulopathy	Haemolytic anaemia[b], Agranulocytosis
Immune system disorders			Anaphylactic shock, anaphylactic reaction, anaphylactoid reaction, hypersensitivity[b] Jarisch-Herxheimer reaction[b]
Nervous system disorders		Headache, dizziness	Convulsion
Ear and labyrinth disorders			Vertigo

System Organ Class	*Frequent*	*Less frequent*	*Unknown frequency*
Respiratory, thoracic and mediastinal disorders		Bronchospasm	
Gastrointestinal disorders	Diarrhoea[b], loose stools	Nausea, vomiting	Pancreatitis[b], stomatitis, glossitis
Hepato-biliary disorders	Increased hepatic enzyme		Gall bladder precipitation[b], Kernicterus, hepatotoxicity
Skin and subcutaneous tissue disorders	Rash	Pruritus, urticaria	Stevens Johnson Syndrome[b], toxic epidermal necrolysis[b] (TEN), erythema multiforme, acute generalized exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS)b, petechiae, purpura, diaphoresis, flushing, urticaria, exfoliative dermatitis
Renal and urinary disorders		Haematuria, glycosuria	Oliguria, renal precipitation (reversible)
General disorders and administration site conditions		Phlebitis, chills injection site pain, pyrexia, oedema	
Investigations		Increased blood creatinine	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.

[b] See section 4.4

Adverse events reported for lidocaine (lignocaine) solvent

Adverse reactions reported for lidocaine (lignocaine) are usually the result of raised plasma concentrations due to accidental intravascular injection, excessive dosage or rapid absorption from highly vascular areas, or may result from a hypersensitivity, idiosyncrasy or diminished tolerance on the part of the patient.

System Organ Class	*Unknown frequency*
Blood and lymphatic system disorders	Methaemoglobinaemia
Immune system disorders	Hypersensitivity reactions (allergic or anaphylactoid reactions, anaphylactic shock)
Nervous system disorders	Neurological signs of systemic toxicity include restlessness, excitement, dizziness or lightheadedness, nervousness, tremor, circumoral paraesthesia, numbness of the tongue and perioral region, drowsiness, convulsions, coma. Lassitude and amnesia have been reported with therapeutic doses.
Eye disorders	Blurred vision, diplopia, transient amaurosis, bilateral amaurosis
Ear and labyrinth disorders	Tinnitus, hyperacusis
Cardiac disorders	Pallor, sweating, hypotension, bradycardia, myocardial depression, cardiac dysrhythmias and possibly cardiac arrest or circulatory collapse.
Vascular disorders	Hypotension
Respiratory, thoracic or mediastinal disorders	Dyspnoea, bronchospasm, respiratory depression, respiratory arrest
Gastrointestinal disorders	Nausea, vomiting
Skin and subcutaneous tissue disorders	Rash, urticaria, oedema (including angioedema, face oedema)

Description of selected adverse reactions

Infections and infestations

Reports of diarrhoea following the use of CEFTRIAXONE iPHARMA may be associated with Clostridium difficile. Appropriate fluid and electrolyte management should be instituted (see section 4.4).

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, as contained in CEFTRIAXONE iPHARMA compared with adults (see sections 4.3, 4.4, and 5.2).

Cases of ceftriaxone precipitation in the urinary tract have been reported. 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, as contained in CEFTRIAXONE iPHARMA (see section 4.4).

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 iPHARMA (see section 4.4).

Nervous system disorders reported with lidocaine (lignocaine) use

Nervous system reactions may be excitatory and/or depressant. Signs of CNS stimulation may be brief, or may not occur at all, so that the first signs of toxicity may be confusion and drowsiness, followed by coma and respiratory failure.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

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

Lidocaine (lignocaine) used as solvent for intramuscular injection

Symptoms of acute systemic toxicity:

Central nervous system toxicity presents with symptoms of increasing severity. Patients may present initially with circumoral paraesthesia, numbness of the tongue, light-headedness followed by sedation, hyperacusis and tinnitus. Visual disturbance and muscular tremors or muscle twitching are more serious and precede the onset of generalised convulsions. These signs must not be mistaken for neurotic behaviour. Unconsciousness and grand mal convulsions may follow, which may last from a few seconds to several minutes. Hypoxia and hypercapnia occur rapidly following convulsions due to increased muscular activity, together with the interference with normal respiration and loss of the airway. In severe cases, apnoea may occur. Acidosis increases the toxic effects of local anaesthetics. Effects on the cardiovascular system may be seen in severe cases. Hypotension, bradycardia, dysrhythmia and cardiac arrest may occur as a result of high systemic concentrations, with potentially fatal outcome.

Recovery occurs as a consequence of redistribution of the local anaesthetic medicine from the central nervous system, and of metabolism and may be rapid unless large amounts of lignocaine (lidocaine) have been injected.

Treatment of acute toxicity:

If signs of acute systemic toxicity appear, the injection should be stopped immediately. Treatment will be required if convulsions and CNS depression occurs. The objectives of treatment are to maintain oxygenation,

stop the convulsions and support the circulation. A patent airway should be established and oxygen should be administered, together with assisted ventilation (mask and bag) if necessary. The circulation should be maintained with infusions of plasma or intravenous fluids. Where further supportive treatment of circulatory depression is required, use of a vasopressor type of medicine may be considered although this involves a risk of central nervous system excitation. If the convulsions do not stop spontaneously in 15 – 20 seconds, they may be controlled by the intravenous administration of diazepam or thiopentone sodium, bearing in mind that anticonvulsant medicines may also depress respiration and the circulation. Prolonged convulsions may jeopardise the patient's ventilation and oxygenation and early endotracheal intubation should be considered. If cardiac arrest should occur, standard cardiopulmonary resuscitation procedures should be instituted. Continual optimal oxygenation and ventilation and circulatory support as well as treatment of acidosis are of vital importance.

Dialysis is of negligible value in the treatment of acute overdosage with lidocaine (lignocaine).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 20.1.1 Broad and medium spectrum antibiotics.

ATC code: J01DD04.

The bactericidal activity of ceftriaxone results from inhibition of bacterial cell wall synthesis. Ceftriaxone exerts *in-vitro* activity against a wide range of gram-negative and gram-positive microorganisms. Ceftriaxone is stable to most β-lactamases, both penicillinases and cephalosporinases, of gram-positive and gram-negative bacteria.

Resistance

Gram-positive aerobes

Methicillin-resistant *Staphylococcus* spp. is resistant to ceftriaxone. *Enterococcus faecalis*, *Enterococcus faecium* and *Listeria monocytogenes* are resistant.

Gram-negative aerobes

Some isolates of the following species are resistant to ceftriaxone, mainly due to the production of the chromosomally encoded ß-lactamase:

Acinetobacter anitratus (mostly *A. baumanii*), *Citrobacter freundii*, *Enterobacter aerogenes*, *Enterobacter cloacae*, *Enterobacter* spp. (other), *Proteus penneri*, *Proteus vulgaris, Pseudomonas fluorescens, Pseudomonas* spp. (other), *Providentia rettgeri*, *Serratia marcescens*, *Serratia* spp. (Other), *Stenotrophomonas maltophilia.*

Some isolates of *Klebsiella pneumoniae* species are resistant due to production of extended spectrum, plasmid-mediated ß-lactamase.

With a few exceptions clinical *P. aeruginosa* isolates are resistant to ceftriaxone.

Ureaplasma urealyticum, Mycoplasma sp.*, Mycobacterium* sp. and fungi are resistant to ceftriaxone.

Anaerobic organisms

Some isolates of *Bacteroides* spp. (bile-sensitive) are resistant to ceftriaxone due to ß-lactamase-production.

Many strains of ß-lactamase-producing *Bacteroides* spp. (notably *B. fragilis*) are resistant. *Clostridium difficile* is resistant.

The following organisms are also resistant:

Chlamydia spp.

Chlamydophila spp.

Mycoplasma spp.

Legionella spp.

Ureaplasma urealyticum

Use of lidocaine (lignocaine) as solvent

Lidocaine (lignocaine) has a local anaesthetic action.

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 under the plasma concentration-time curve after intramuscular administration is equivalent to that after intravenous administration of an equivalent dose.

Lidocaine (lignocaine), used as solvent for intramuscular injection, is absorbed from muscle and its rate of absorption is determined by factors such as the site of administration and the tissue vascularity.

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).

Lidocaine (lignocaine), used as solvent for intramuscular injection, crosses the blood-brain and placental barriers.

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).

Lidocaine (lignocaine), used as solvent for intramuscular injection, is bound to plasma proteins, including alpha-1-acid-glycoprotein.

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.

Lidocaine (lignocaine), used as solvent for intramuscular injection, is metabolised in the liver and about 90 % of a given dose undergoes N-dealkylation to form monoethylglycinexylidide and glycinexylidide, both of which may contribute to the therapeutic and toxic effects of lidocaine (lignocaine). Further metabolism occurs and metabolites are excreted in the urine with less than 10 % of unchanged lidocaine (lignocaine). The elimination half-life of lidocaine (lignocaine) may be prolonged in patients with hepatic dysfunction.

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.

Elderly

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:

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).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

CEFTRIAXONE iPHARMA IM solvent (Lidocaine (lignocaine)):

Sodium chloride

Sodium hydroxide (pH adjustment)

6.2 Incompatibilities

Ceftriaxone is incompatible with amsacrine, vancomycin, fluconazole and aminoglycosides.

CEFTRIAXONE iPHARMA should not be added to solutions containing calcium, such as Hartmann's solution and Ringer's solution because a precipitate can form.

CEFTRIAXONE iPHARMA must not be mixed or administered simultaneously with calcium containing solutions including total parenteral nutrition.

If treatment with a combination of another antibiotic with CEFTRIAXONE iPHARMA is intended, administration should not occur in the same syringe or in the same infusion solution.

CEFTRIAXONE iPHARMA must not be mixed with other medicines except those mentioned in section 6.6.

6.3 Shelf life

Unopened vials: 3 years

Unopened ampoules containing lidocaine (lignocaine) solvent: 4 years

Chemical and physical in-use stability of the reconstituted product has been demonstrated for at least 6 hours at or below 25 °C or 24 hours at 2-8 °C

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would not be longer than the times stated above for the chemical and physical in-use stability.

6.4 Special precautions for storage

Store at or below 30 °C, keep vial, bottle and ampoules in the outer carton in order to protect from light.

For storage conditions of the reconstituted medicine, see section 6.3.

6.5 Nature and contents of container

CEFTRIAXONE 500 and 1 000 IV iPHARMA are packed into Ph Eur Type II colourless glass vials with pre-sterilised grey rubber stoppers and capsulated with aluminium caps.

Solvent: sterile water for injection is filled in 5 ml type I glass ampoule.

CEFTRIAXONE 500 IM iPHARMA is packed into Ph Eur Type II colourless glass vials with pre-sterilised grey rubber stoppers and capsulated with aluminium caps.

Solvent: Type (I) amber coloured glass ampoule with 2 ml lidocaine (lignocaine) HCl 1 %.

CEFTRIAXONE 1 000 IM iPHARMA is packed into Ph Eur Type II colourless glass vials with pre-sterilised grey rubber stoppers and capsulated with aluminium caps.

Solvent: Type (I) amber coloured glass ampoule with 3,5 ml lidocaine (lignocaine) HCl 1 %.

Pack sizes:

CEFTRIAXONE 500 IV iPHARMA: Outer carton containing 1 powder vial and 1 solvent ampoule of 5 ml sterile water for injection.

CEFTRIAXONE 1 000 IV iPHARMA: Outer carton containing 1 powder vial and 2 solvent ampoules of 5 ml sterile water for injection.

CEFTRIAXONE 500 IM iPHARMA: Outer carton containing 1 powder vial and 1 solvent ampoule of 2 ml lidocaine (lignocaine) HCl 1 %.

CEFTRIAXONE 1 000 IM iPHARMA: Outer carton containing 1 powder vial and 1 solvent ampoule of 3,5 ml lidocaine (lignocaine) HCl 1 %.

6.6 Special precautions for disposal and other handling

Preparation of solutions for injection and infusion

The use of freshly prepared solutions is recommended. For storage conditions of the reconstituted medicine, see section 6.3.

CEFTRIAXONE iPHARMA should not be mixed in the same syringe with any medicine other than 1 % Lidocaine (lignocaine) Hydrochloride solution (for intramuscular injection only).

The infusion line should be flushed after each administration.

In neonates, intravenous doses should be given over 60 minutes to reduce the potential risk of bilirubin encephalopathy.

Intramuscular injection

For IM injection, CEFTRIAXONE iPHARMA 500 mg is dissolved in 2 ml and CEFTRIAXONE iPHARMA 1000 mg in 3,5 ml of water for injection. CEFTRIAXONE iPHARMA dissolved in a 1 % lidocaine (lignocaine) solution instead of water for injection can reduce pain at the site of injection. CEFTRIAXONE iPHARMA must be injected well within the body of a relatively large muscle. It is recommended that not more than 1 g be injected at one site

Reconstitution with 1 % lidocaine (without adrenaline) has no effect on the absorption or the elimination of CEFTRIAXONE iPHARMA. The lidocaine (lignocaine) solution must never be administered intravenously.

Intravenous injection

For IV injection, CEFTRIAXONE iPHARMA 500 mg is dissolved in 5 ml, and CEFTRIAXONE iPHARMA 1000 mg in 10 ml sterile water for injection. The intravenous administration should be given over 2 - 4 minutes.

Intravenous infusion

The infusion should be given over a period of at least 30 minutes.

CEFTRIAXONE iPHARMA solutions should not be mixed with or piggybacked into solutions containing other antimicrobial medicines or into diluent solutions other than those listed above, owing to possible incompatibility.

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

7 HOLDER OF CERTIFICATE OF REGISTRATION

iPharma (Pty) Ltd

124 Elevation Avenue, Randjesfontein

Midrand, 1683, South Africa

8 REGISTRATION NUMBER

CEFTRIAXONE 500 IV iPHARMA: 50/20.1.1/0656

CEFTRIAXONE 1 000 IV iPHARMA: 50/20.1.1/0657

CEFTRIAXONE 500 IM iPHARMA: 50/20.1.1/0673

CEFTRIAXONE 1 000 IM iPHARMA: 50/20.1.1/0674

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15 March 2022.

10 DATE OF REVISION OF THE TEXT

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