PROFESSIONAL INFORMATION

SCHEDULING STATUS: **S4**

1 NAME OF THE MEDICINE

ADCO CEFTRIAXONE 500 mg powder for injection

ADCO CEFTRIAXONE 1 g powder for injection

ADCO CEFTRIAXONE 2 g parenteral infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

ADCO CEFTRIAXONE 500 mg: Each vial contains 500 mg sterile ceftriaxone as ceftriaxone sodium.

ADCO CEFTRIAXONE 1 g: Each vial contains 1 g sterile ceftriaxone as ceftriaxone sodium.

ADCO CEFTRIAXONE 2 g: Each vial contains 2 g sterile ceftriaxone as ceftriaxone sodium.

Sugar content: Sugar free

For list of full excipients, see section 6.1

3 PHARMACEUTICAL FORM

Powder for injection

ADCO CEFTRIAXONE 500 mg:

10 mL clear, colourless glass vial containing an almost white or yellowish sterile crystalline powder with an aluminium cap.

ADCO CEFTRIAXONE 1 g:

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10 mL clear, colourless glass vial containing an almost white or yellowish sterile crystalline powder with an aluminium cap.

Parenteral infusion

ADCO CEFTRIAXONE 2 g:

50 mL clear, colourless glass vial containing an almost white or yellowish sterile crystalline powder with an aluminium cap.

Reconstituted solutions may vary in colour from pale yellow to amber, depending on the concentration and length of storage.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

ADCO CEFTRIAXONE is indicated for the treatment of the following infections:

BACTERIAL SEPTICAEMIA caused by:

Methicillin-sensitive *Staphylococcus aureus* (MSSA), *Streptococcus pneumoniae, Haemophilus influenzae, Escherichia coli,* or *Klebsiella pneumoniae.*

MENINGITIS caused by:

Haemophilus influenzae, Neisseria meningitidIs or *Streptococcus pneumonia.*

INTRA-ABDOMINAL INFECTIONS caused by:

Escherichia coli, Klebsiella pneumoniae or *Peptostreptococcus* species.

SKIN AND SKIN STRUCTURE INFECTIONS caused by:

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Methicillin sensitive *Staphylococcus aureus* (MSSA), *Streptococcus pyogenes, Streptococcus viridans* group*, Escherichia coli, Enterobacter cloacae, Klebsiella oxytoca, Klebsiella pneumoniae, Proteus mirabilis, Morganella morganii, 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, Morganella morganii or *Klebsiella pneumoniae.*

RESPIRATORY TRACT INFECTIONS caused by:

Streptococcus pneumoniae, Methicillin-sensitive *Staphylococcus aureus* (MSSA)*, Haemophilus influenzae, Haemophilus parainfluenzae, 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 influenzae (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 beta-lactamase-, and non-beta-lactamase-producing strains, and pharyngeal gonorrhoea caused by non-beta-lactamase-producing strains of *Neisseria gonorrhoeae.*

PERIOPERATIVE INFECTION PROPHYLAXIS

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4.2 Posology and method of administration

Posology

Standard dosage

Adults and children over 12 years:

The usual dosage is 1 – 2 g ADCO CEFTRIAXONE 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.

Refer below to **Special dosage instructions** for other patient populations.

Duration of therapy

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

Combination treatment

Synergy between ADCO CEFTRIAXONE and aminoglycosides has been demonstrated with many gram-negative bacteria under experimental conditions. Although enhanced activity of such combinations is not always predictable, it should be considered in severe, life-threatening infections due to microorganisms such as *Pseudomonas aeruginosa*. Due to chemical incompatibility between ADCO CEFTRIAXONE and aminoglycosides, the two medicines must be administered separately at the recommended dosages. Chemical incompatibility with ADCO CEFTRIAXONE has also been observed with IV administration of amsacrine, vancomycin and fluconazole.

Special dosage instructions

Meningitis

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

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For meningitis in infants and children see **Paediatric population** below.

Gonorrhoea

For the treatment of uncomplicated gonorrhoea, (penicillinase-producing and non-penicillinase-producing strains) a single intramuscular (IM) dose of 250 mg ADCO CEFTRIAXONE is recommended.

Peri-operative infection prophylaxis

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

Lyme borreliosis

50 mg/kg to a maximum of 2 g in children and adults, once daily for 14 days.

Special populations

Geriatric use

No dose adjustment of ADCO CEFTRIAXONE is required in patients ≥ 65 years of age provided there is no severe renal and hepatic impairment.

Renal impairment

In patients with impaired renal function there is no need to reduce the dosage of ADCO CEFTRIAXONE. No dose adjustment of ADCO CEFTRIAXONE is required, provided hepatic function is not impaired. In cases of severe renal failure (creatinine clearance < 10 mL/min) the ADCO CEFTRIAXONE dosage should not exceed 2 g daily.

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In patients with both severe renal and hepatic dysfunction, the plasma concentrations of ceftriaxone should be determined at regular intervals and if necessary, the dose should be adjusted.

Dialysis

ADCO CEFTRIAXONE is not removed by peritoneal- or haemodialysis. In patients undergoing dialysis, no additional supplementary dosing is required following the dialysis. Plasma concentrations should however be monitored, to determine whether dosage adjustments are necessary, since the elimination rate in these patients may be altered.

Hepatic impairment

No dose adjustment is required, provided renal function is not impaired.

Severe renal and hepatic impairment

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

Paediatric population

Neonates, infants and children up to 12 years:

The following dosage schedules are recommended for once daily administration:

Neonates (up to 14 days)

20 – 50 mg/kg bodyweight once daily. The daily dose should not exceed 50 mg/kg. ADCO CEFTRIAXONE is contraindicated in premature neonates up to a postmenstrual age of 41 weeks (gestational age + chronological age) (see section 4.3). ADCO CEFTRIAXONE is contraindicated in neonates (≤ 28 days) if they require (or are expected to require) treatment with calcium-containing IV

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solutions, including continuous calcium-containing infusions such as parenteral nutrition because of the risk of precipitation of ceftriaxone-calcium (see sections 4.3, 4.4 and 4.8).

Neonates, 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, in infants and children up to 12 years of age should be given by infusion over at least 30 minutes.

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

Meningitis

In bacterial meningitis in infants and children, treatment begins with doses of 100 mg/kg (up to a maximum of 4 g) once daily. As soon as the causative organism has been identified and its sensitivity determined, the dosage can be reduced accordingly.

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

Method of administration

Ceftriaxone must be reconstituted prior to use. 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 injection

For IM injection, ADCO CEFTRIAXONE 500 mg is dissolved in 2 mL and ADCO CEFTRIAXONE 1 g in 3,5 mL, of water for injection. In adults, intramuscular administrations of some cephalosporins, including ADCO CEFTRIAXONE, cause pain at the injection site. This can be reduced greatly by administering in combination with a local anaesthetic.

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ADCO CEFTRIAXONE dissolved in 3,5 mL of a 1 % lidocaine (lignocaine) solution instead of water for injection can reduce pain at the site of injection, in adults. It is recommended that not more than 1 g be injected at one site. Safe dose of 1 % lidocaine (lignocaine) has not been established.

Reconstitution with 1 % lidocaine (lignocaine) (without adrenaline) has no effect on the absorption or the elimination of ADCO CEFTRIAXONE.

Intravenous injection

The lidocaine (lignocaine) solution must never be administered intravenously (see section 4.3).

For IV injection, ADCO CEFTRIAXONE 500 mg is dissolved in 5 mL, and ADCO CEFTRIAXONE 1 g in 10 mL sterile water for injection. The intravenous administration should be given over 2 to 4 minutes.

Intravenous infusion

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

Incompatibilities: See section 6.2

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

4.3 Contraindications

- Hypersensitivity to ceftriaxone, other cephalosporins, or to any of the excipients listed in section 6.1 (see section 4.4.);
- Intravenous administration of ADCO CEFTRIAXONE solutions containing lidocaine (lignocaine) (see section 4.4);
- Premature neonates up to postmenstrual age of 41 weeks (gestational age + chronological age) (see section 4.4)
- Hyperbilirubinaemic newborns (see section 4.4);

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- Neonates (≤ 28 days) if they require (or are expected to require) treatment with calcium-containing IV solutions (see sections 4.2, 4.4 and 4.8).

4.4 Special warnings and precautions for use

ADCO CEFTRIAXONE is contraindicated in neonates (≤ 28 days) 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.

ADCO CEFTRIAXONE must not be mixed or administered simultaneously with calcium-containing solutions or products, even via different infusion lines. ADCO CEFTRIAXONE and IV calcium-containing solutions or products must not be administered within 48 hours of each other.

Precipitation of ceftriaxone-calcium may occur when ADCO CEFTRIAXONE is mixed with calcium-containing solutions in the same IV administration line. ADCO CEFTRIAXONE must not be administered simultaneously with calcium-containing IV solutions, including continuous calcium-containing infusions such as parenteral nutrition via a Y-site. Fatal outcomes 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. In some cases, times of administration of ceftriaxone and calcium-containing solutions differed (see sections 4.2, 4.3, 4,5 and 4.8).

Do not use diluents containing calcium, such as Ringer's lactate solution or Hartmann's solution to reconstitute ADCO CEFTRIAXONE. Precipitate formation can result.

There are no reports to date of intravascular or pulmonary precipitations in patients, other than neonates, treated with ceftriaxone and calcium-containing IV solutions. However, the theoretical possibility exists for an interaction between ceftriaxone and IV calcium-containing solutions in patients other than neonates. Therefore, ADCO CEFTRIAXONE and calcium-containing solutions, including continuous calcium-containing infusions such as parenteral nutrition, should not be mixed or co-administered to any patients irrespective of age even via different infusion lines at different sites. As a further theoretical consideration and based on 5 half-lives of ceftriaxone, ADCO CEFTRIAXONE and IV calcium-containing solutions should not be administered within 48 hours of each other in any patient (see sections 4.2, 4.3, 4.5 and 4.8).

Calcium-ceftriaxone precipitates in the gallbladder have been observed on ultrasound scan in patients receiving ADCO CEFTRIAXONE, particularly at doses of 1 g per day and above. The probability of such precipitates appears to be greatest in paediatric patients. Precipitates disappear after discontinuation of ADCO CEFTRIAXONE therapy and are rarely symptomatic. In symptomatic cases, conservative nonsurgical management is recommended, and discontinuation of ADCO CEFTRIAXONE treatment should be considered by the medical practitioner based on an individual benefit-risk assessment.

No data are available on potential interaction between ADCO CEFTRIAXONE and oral calcium-containing products or interaction between intramuscular ADCO CEFTRIAXONE and calcium-containing products (IV or oral).

Pseudomembranous enterocolitis and coagulation disorders have been reported with ADCO CEFTRIAXONE. It is important to consider pseudomembranous enterocolitis in patients who present with diarrhoea subsequent to administration of ADCO CEFTRIAXONE.

Cases of pancreatitis, possibly of biliary obstruction aetiology, have been reported in patients treated with ADCO CEFTRIAXONE. Most patients who developed pancreatitis have had risk factors associated with biliary stasis and biliary sludge e.g. severe illness and total parenteral nutrition.

Ceftriaxone displaces bilirubin from serum albumin.

ADCO CEFTRIAXONE is not recommended for use in neonates (especially premature) at risk of developing bilirubin encephalopathy.

Hypersensitivity

Serious and occasionally fatal hypersensitivity reactions have been reported (see section 4.8). In case of severe hypersensitivity reactions, treatment with ADCO CEFTRIAXONE 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 hypersensitivity reactions to ceftriaxone, to other cephalosporins, or to any other type of beta-lactam medicine. Caution should be used if ADCO CEFTRIAXONE is given to patients with a history of hypersensitivity to penicillin or other beta-lactam medicines as they may be at greater risk of hypersensitivity to ceftriaxone.

Severe cutaneous adverse reactions (SCAR) such as Stevens-Johnson syndrome, Lyell's syndrome/toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms (DRESS) and generalised exanthematous pustulosis (AGEP) which can be life-threatening or fatal have been reported in association with beta-lactam antibiotics such as ADCO CEFTRIAXONE treatment; however, the frequency of these events is not known (see section 4.8). When SCAR is suspected, ADCO CEFTRIAXONE should be discontinued.

Haemolytic anaemia

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 ADCO CEFTRIAXONE, the diagnosis of cephalosporin associated anaemia should be considered and ADCO CEFTRIAXONE discontinued until the aetiology is determined.

***Clostridium difficile* associated diarrhoea**

Clostridium difficile associated diarrhoea (CDAD) has been reported with the use of ceftriaxone and may range in severity from mild diarrhoea to fatal colitis. Treatment with ADCO CEFTRIAXONE 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. Toxin hyperproducing 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 diarrhoea following ADCO CEFTRIAXONE use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial medicines, such as ADCO CEFTRIAXONE.

If CDAD is suspected or confirmed, on-going 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.

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Superinfections

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

Use of lidocaine (lignocaine)

In case a lidocaine (lignocaine) solution is used as a solvent, ceftriaxone as in ADCO CEFTRIAXONE solutions must only be used for intramuscular injection. Contraindications to lidocaine (lignocaine), warnings and other relevant information as detailed in the product information of lidocaine (lignocaine) should be considered before use. **The lidocaine (lignocaine) solution should never be administered intravenously.** (see section 4.3).

Paediatrics

Safety and efficacy of ADCO CEFTRIAXONE in neonates, infants and children have been established for the dosages described under section 4.2. Studies have shown that ceftriaxone can displace bilirubin from serum albumin. ADCO CEFTRIAXONE should not be used in neonates (especially prematures) at risk of developing bilirubin encephalopathy (see section 4.3).

Blood monitoring

During prolonged treatment a complete blood count should be carried out at regular intervals.

Influence on diagnostic tests

In patients treated with ceftriaxone the Coombs' test may become falsely positive. ADCO CEFTRIAXONE, like other antibiotics, may result in false-positive test results for galactosaemia.

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

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.

Special groups

***Patients with reduced renal and liver function*:** Refer to section 4.2.

The elderly: Refer to section 4.2.

Children: Refer to section 4.2.

Renal lithiasis

Cases of renal lithiasis have been reported, which is reversible upon discontinuation of ceftriaxone (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 spirochaete infections may experience a JHR shortly after ceftriaxone as in ADCO CEFTRIAXONE treatment is started. JHR is usually a self - limiting condition or can be managed by symptomatic treatment. ADCO CEFTRIAXONE treatment should not be discontinued if such reaction occurs.

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Encephalopathy

Encephalopathy has been reported with the use of ceftriaxone (see section 4.8), particularly in elderly patients with severe renal impairment (see section 4.2) or central nervous system disorders. If ceftriaxone-associated encephalopathy is suspected (e.g. decreased level of consciousness, altered mental state, myoclonus, convulsions), discontinuation of ADCO CEFTRIAXONE should be considered.

4.5 Interactions with other medicines and other forms of interaction

Renal function impairment has not been observed after concurrent administration of ADCO CEFTRIAXONE and diuretics (e.g. furosemide).

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

No effect similar to that of disulfiram has been demonstrated after ingestion of alcohol subsequent to the administration of ceftriaxone. ADCO CEFTRIAXONE does not contain an N-methylthiotetrazole moiety associated with possible ethanol intolerance and bleeding problems. In an *in vitro* study, antagonistic effects have been observed with the combination of chloramphenicol and ceftriaxone.

Interaction with laboratory tests:

In patients treated with ADCO CEFTRIAXONE, the Coombs' test and tests for galactosaemia may become false-positive.

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Non-enzymatic methods for glucose determination in urine may give false-positive results. For this reason, urine-glucose determination during therapy with ADCO CEFTRIAXONE should be done enzymatically.

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.

Interaction with calcium-containing products:

ADCO CEFTRIAXONE should not be added to solutions containing calcium. Do not use diluents containing calcium such as Ringer's lactate solution or Hartmann's solution to reconstitute ADCO 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 ADCO CEFTRIAXONE is mixed with calcium-containing solutions in the same IV administration line. ADCO CEFTRIAXONE must not be administered simultaneously with calcium containing IV solutions, including continuous calcium containing infusions such as parenteral nutrition via a Y-site (see sections 4.2, 4.3, 4.4 and 4.8).

Concomitant use of ADCO CEFTRIAXONE with vitamin K antagonists may increase the risk of bleeding. Coagulation parameters should be monitored frequently, and the dose of the anticoagulant adjusted accordingly, both during and after treatment with ADCO CEFTRIAXONE (see section 4.8).

4.6 Fertility, pregnancy and lactation

Safety in pregnancy and lactation has not been established.

Ceftriaxone crosses the placental barrier and is excreted in breast-milk.

Pregnancy

ADCO CEFTRIAXONE crosses the placental barrier. Safety in human pregnancy has not been established. Reproductive studies in animals have shown no evidence of embryotoxicity, foetotoxicity,

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teratogenicity or adverse effects on male or female fertility, birth or perinatal and postnatal development. In primates, no embryotoxicity or teratogenicity has been observed.

Breastfeeding

Low concentrations of ceftriaxone are excreted in human milk. Caution should be exercised when ADCO CEFTRIAXONE is administered to a nursing woman.

4.7 Effects on ability to drive and use machines

ADCO CEFTRIAXONE may affect your mental and/or your physical abilities to perform or execute tasks or activities requiring your mental alertness, judgment and/or sound coordination and vision. Patients should be cautious when driving or operating machinery.

4.8 Undesirable effects

a*) Summary of safety profile*

The most frequently reported adverse reactions for ceftriaxone are eosinophilia, leucopenia, thrombocytopenia, diarrhoea, rash, and hepatic enzymes increased.

b*) Tabulated list of adverse reactions*

System Organ Class	Frequency	Undesirable Effect
Infections and infestations	Less frequent	Genital fungal infection
		Pseudo-membranous colitis
	Frequency unknown	Fever, superinfection
Blood and lymphatic system disorders	Frequent	Eosinophilia, leucopenia, thrombocytopenia
	Less frequent	Granulocytopenia, anaemia, coagulopathy

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	Frequency unknown	Haematoma or bleeding, lymphopenia, prolongation of prothrombin time. Isolated cases of agranulocytosis (< 500 mm^3) have been reported, most of them following total doses of 20 g or more. Coagulation disorders have been reported.
Immune system disorders	Frequency unknown	Anaphylactic shock, anaphylactic reaction, anaphylactoid reaction, Jarisch-Herxheimer reaction
Nervous system disorders	Less frequent	Headache, dizziness, encephalopathy
	Frequency unknown	Convulsion
Ear and labyrinth disorders	Frequency unknown	Vertigo
Respiratory, thoracic and mediastinal disorders	Less frequent	Bronchospasm
Gastrointestinal disorders	Frequent	Diarrhoea, loose stools
	Less frequent	Nausea, vomiting
	Frequency unknown	Stomatitis, glossitis, precipitation of ceftriaxone salts in the gallbladder, increase in liver enzymes, pseudomembranous colitis, pancreatitis.
Hepatobiliary disorders	Frequent	Hepatic enzyme increased

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	Frequency unknown	Hepatotoxicity, hepatitis, cholestatic hepatitis. Symptomatic precipitation of ceftriaxone-calcium salt in the gallbladder, kernicterus.
Skin and subcutaneous tissue disorders	Frequent	Rash
	Less frequent	Pruritus, urticaria
	Frequency unknown	Exanthema, allergic dermatitis, oedema. Isolated cases of severe cutaneous adverse reactions (erythema multiforme, Stevens-Johnson syndrome or Lyell's syndrome/ toxic epidermal necrolysis) have been reported, drug reaction with eosinophilia (DRESS). Exfoliative dermatitis, purpura, diaphoresis, flushing.
Renal and urinary disorders	Less frequent	Haematuria, dizziness, glycosuria
	Frequency unknown	Oliguria, genital mycosis
General disorders and administration site conditions	Less frequent	Phlebitis, injection site reactions, pyrexia, oedema, chills, shivering
Investigations	Less frequent	Increase in serum creatinine, Coombs test false positive, galactosaemia test false positive, non-enzymatic methods for glucose determination false positive (see section 4.5).

c. Description of selected adverse reactions

Cases of drug precipitation in the kidneys have been reported, mostly in children older than 3 years and who have been treated with either high daily doses (e.g. > 80 mg/kg/ day) or total doses exceeding 10

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g and presenting with other risk factors (e.g. fluid restrictions, confinement to bed, etc.). This event may lead to renal insufficiency and is usually reversible upon discontinuation of ADCO CEFTRIAXONE.

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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc-org) found on SAHPRA website.

For reporting of side effects directly to the Holder of the Certificate of Registration, contact +27 11 635 0134 or email Adcock.aereports@adcock.com

4.9 Overdose

In cases of overdosage, plasma concentration would not be reduced by haemodialysis or peritoneal dialysis. There is no specific antidote. Treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use, Third-generation cephalosporins

ATC code: J01DD04

Ceftriaxone is a third-generation cephalosporin. The bactericidal activity of ceftriaxone results from inhibition of bacterial cell wall synthesis.

5.2 Pharmacokinetic properties

Absorption

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The maximum plasma concentration after a single intramuscular (IM) dose of 1,0 g is about 81 mg/litre and is reached within 2 – 3 hours after administration. The area under the plasma concentration versus time curve (AUC) after intramuscular administration is equivalent to that after intravenous (IV) administration of an equivalent dose, indicating 100 % bioavailability of intramuscularly (IM) administered ceftriaxone.

Distribution

The apparent volume of distribution of ceftriaxone is 0,13 – 0,19 litres/kg. Ceftriaxone shows good tissue penetration and body-fluid distribution after a dose of 1 – 2 g; concentrations well above the minimum inhibitory concentrations of most pathogens responsible for infection are detectable for more than 24 hours in body-fluids or tissues including lung, heart, biliary tract/liver, tonsil, middle ear and nasal mucosa, bone as well as cerebrospinal, pleural, prostatic and synovial fluids.

Protein binding

Ceftriaxone is reversibly bound to albumin. There is proportionally decreased albumin binding with an increase in plasma concentration of ceftriaxone.

Penetration into particular tissues

Paediatrics:

Ceftriaxone penetrates the inflamed meninges of neonates, infants and children. Ceftriaxone concentrations exceed 1,4 mg/litre in the cerebrospinal fluid (CSF) 24 hours after (IV) injection in doses of 50 mg/kg in neonates to 100 mg/kg in infants. Peak concentration in CSF with a mean of 18 mg/litre is reached about 4 hours after intravenous injection. Mean CSF concentrations are 17 % of plasma concentrations in patients with bacterial meningitis and 4 % in patients with aseptic meningitis. The mean values of maximum plasma concentration, elimination half-life, plasma clearance and volume of

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distribution after a 50 mg/kg (IV) dose and after a 75 mg/kg (IV) dose in paediatric patients suffering from bacterial meningitis are shown in the table below.

Mean pharmacokinetic parameters of ceftriaxone in paediatric patient with meningitis:

	50 mg/kg IV	75 mg/kg IV
Maximum plasma concentrations (mcg/mL)	216	275
Elimination half-life (hr)	4,6	4,3
Plasma clearance (mL/ hr/kg)	49	60
Volume of distribution (mL/kg)	338	373
CSF concentration – inflamed meninges (mcg/mL)	5,6	6,4
Range (mcg/mL)	1,3 – 18,5	1,3 - 44
Time after dose (hr)	3,7 (± 1,6)	3,3 (± 1,4)

Adults:

In meningitis in adults, administration of 50 mg/kg leads within 2 – 24 hours to CSF concentrations several times higher than the minimum *in vitro* inhibitory concentrations required for the most common meningitis pathogens.

Ceftriaxone crosses the placental barrier and is excreted in the breast milk in low concentrations.

In healthy, young adult volunteers the total plasma clearance is 10 – 22 mL/min. The renal clearance is 5 – 12 mL/min. Fifty to sixty percent of ceftriaxone is excreted unchanged in the urine, while 40 – 50 % is excreted unchanged in the bile. The elimination half-life in adults is about eight hours.

Pharmacokinetics in special clinical situations

Neonates – urinary recovery accounts for about 70 % of the dose.

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Infants less than eight days old and elderly persons aged over 75 years – elimination half-life is usually 2 – 3 times that in young adults.

Patients with renal or hepatic dysfunction – the pharmacokinetics of ceftriaxone are only minimally altered and the elimination half-life is only slightly increased.

Impaired kidney function alone - biliary elimination of ceftriaxone is increased.

Impaired liver function alone – renal elimination of ceftriaxone is increased.

Micro-organisms resistant to ceftriaxone

Methicillin-resistant *Staphylococcus* species; *Enterococcus faecium; Listeria monocytogenes*; *Pseudomonas aeruginosa; Ureaplasma urealyticum; Mycoplasma* species; some isolates of *Bacteroides* species (bile-sensitive); and most strains of *Clostridium difficile.*

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None

6.2 Incompatibilities

ADCO CEFTRIAXONE should not be added to solutions mixed or co-administered with containing calcium-containing infusions. ADCO CEFTRIAXONE should not be mixed or co-administered to any patient irrespective of age even via different infusion lines at different sites as it can cause formation of intravascular precipitates. Do not use diluents containing calcium such as Hartmann's solution and Ringer's solution to reconstitute ADCO CEFTRIAXONE vials or to further dilute a reconstituted vial for IV administration because a precipitate can form. Ceftriaxone is incompatible with vancomycin, fluconazole and aminoglycosides.

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6.3 Shelf life

Before mixing: 36 months

After mixing: Store for up to 6 hours at 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 normally not be longer than 24 hours. Any unused portion must be discarded.

6.4 Special precautions for storage

Store in a dry cool place, at or below 25 °C, protected from light.

Storage directions for reconstituted product: Store for up to 6 hours at 25 °C or 24 hours at 2 – 8 °C.

Single dose unit. Discard any unused portion of solution.

6.5 Nature and contents of container

Packs for (IM) ***or*** (IV) ***injection containing:***

Single vials of dry substance equivalent to 500 mg ceftriaxone packed in 1s, 4s, 5s or 10s in an outer carton.

Packs for (IM)***or*** (IV) ***injection containing*****:**

Single vials of dry substance equivalent to 1 g ceftriaxone packed in 1s, 4s, 5s or 10s in an outer carton.

Packs for (IV) ***infusion containing*****:**

1 vial with dry substance equivalent to 2 g ceftriaxone packed in 1s, 4s, 5s or 10s in an outer carton.

6.6 Special precautions for disposal and other handling

Intramuscular injection

Lungile Simelane

For IM injection, ADCO CEFTRIAXONE 500 mg is dissolved in 2 mL and ADCO CEFTRIAXONE 1 g in 3,5 mL of water for injection. ADCO CEFTRIAXONE dissolved in a 1 % lidocaine (lignocaine) solution instead of water for injection can reduce pain at the site of injection.

Intravenous injection

For (IV) injection, ADCO CEFTRIAXONE 500 mg is dissolved in 5 mL, and ADCO CEFTRIAXONE 1 g in 10 mL sterile water for injection.

Intravenous infusion

For (IV) infusion, 2 g of ADCO CEFTRIAXONE is dissolved in approximately 40 mL of one of the following calcium-free infusion solutions: sodium chloride 0,9 %; sodium chloride 0,45 % + dextrose 2,5 %; dextrose 5 %; dextrose 10 %; dextran 6 % in dextrose 5 %; hydroxy ethyl starch 6 – 10 % infusions; sterile water for injection. ADCO CEFTRIAXONE solutions should not be mixed with or piggybacked into solutions containing other antimicrobial medication or into diluent solutions other than those listed above, owing to possible incompatibility.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Adcock Ingram Critical Care (Pty) Ltd

1 Sabax Road

Aeroton

Johannesburg

2013

Tel: +27 11 494 8000

8 REGISTRATION NUMBER(S)

Lungile Simelane

ADCO CEFTRIAXONE 500 mg: 37/20.1.1/0042

ADCO CEFTRIAXONE 1 g: 37/20.1.1/0043

ADCO CEFTRIAXONE 2 g: 37/20.1.1/0044

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 04 July 2004

10 DATE OF REVISION OF THE TEXT

14 April 2025

Namibia:

ADCO CEFTRIAXONE 500 mg: NS2 04/20.1.1/1959

ADCO CEFTRIAXONE 1 g: NS2 04/20.1.1/1957

ADCO CEFTRIAXONE 2 g: NS2 04/20.1.1/1958

Botswana:

ADCO CEFTRIAXONE 500 mg: S2 BOT0801463

ADCO CEFTRIAXONE 2 g: S2 BOT1001650

Lungile Simelane