1.5.5 CLEAN PROPOSED PROFESIONAL 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

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:

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:

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

MENINGITIS caused by:

Haemophilus influenzae, Neisseria meningitides or Streptococcus pneumonia.

INTRA-ABDOMINAL INFECTIONS caused by:

Escherichia coli, Klebsiella pneumoniae or Peptostreptococcus species.

SKIN AND SKIN STRUCTURE INFECTIONS caused by:

Methicilin-sensitive *Staphylococcus aureus* (MSSA), *Streptococcus pyogenes, Streptococcus viridans* group*, Escherichia coli, Enterobacter cloacae, Klebsiella oxytoca, Klebsiella pneumoniae, Proteus miribalis, Morganella morganii, Serratia marcescans* or *Peptostreptococcus* species.

BONE AND JOINT INFECTIONS caused by:

Methicilin-sensitive *Staphylococcus aureus* (MSSA)*, Streptococcus pneumonia, Escherichia coli, Proteus miribalis, Klebsiella pneumoniae* or *Enterobacter* species.

RENAL AND URINARY TRACT INFECTIONS (complicated and uncomplicated) caused by: *Escherichia coli, Proteus miribalis, Proteus vulgaris, Morganella morganii* or *Klebsiella pneumoniae.*

RESPIRATORY TRACT INFECTIONS caused by:
Streptococcus pneumonia, Methicilin-sensitive *Staphylococcus aureus* (MSSA)*, Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella pneumoniae, Escherichia coli, Enterobacter aerogenes, Proteus miribalis* or *Serratia marcescens.*

EAR NOSE AND THROAT INFECTIONS (Acute Bacterial Otitis Media) caused by: *Streptococcus pneumonia, 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

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. 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:

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. 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:

No dose modification is needed in the elderly.

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.

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 dose can be adapted accordingly.

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

Gonorrhoea:

For the treatment of uncomplicated gonorrhoea (both beta-lactamase-producing and non-beta-lactamase-producing strains), a single intramuscular (i.m.) dose of 125 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-nitroimidozole, e.g. metronidazole, has been proven effective, (separate administration: see **'Method of administration'**)

Impaired renal and hepatic function:

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

In cases of severe renal failure (creatinine clearance < 10 ml/ min) the ADCO-CEFTRIAXONE dosage should not exceed 2 g daily.

In patients with liver damage, there is no need for the dosage to be reduced, provided that renal function is intact.

Method of administration

Ceftriaxone 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 +5 °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 drug.

Intramuscular injection

For i.m. injection, ADCO-CEFTRIAXONE 250 mg or 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 % lignocaine solution instead of water for injection can reduce pain at the site of injection. It is recommended that not more than 1 g be injected at one site.

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

Intravenous injection

The lignocaine solution must never be administered intravenously.

For i.v. injection, ADCO-CEFTRIAXONE 250 mg or 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.

For i.v. 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.

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

4.3 Contraindications

Hypersensitivity to cephalosporins or any other ingredients.

Hypersensitivity to penicillins, due to the possibility of cross-reactivity.

4.4 Special warnings and precautions for use

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. Superinfections with non-susceptible micro-organisms may occur. Shadows, which have been mistaken for gallstones have been detected in sonograms of the gallbladder, usually following doses higher than the standard recommended dose. These shadows are, however, precipitates of calcium ceftriaxone, which disappear on completion or discontinuation of ADCO-CEFTRIAXONE therapy. In symptomatic cases, conservative non-surgical management is recommended.

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.

Caution should be exercised when considering ADCO-CEFTRIAXONE treatment in hyperbilirubinaemic neonates. ADCO-CEFTRIAXONE is not recommended for use in neonates (especially premature) at risk of developing bilirubin encephalopathy.

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 no evidence that ADCO-CEFTRIAXONE increases renal toxicity of aminoglycosides.

The elimination of ADCO-CEFTRIAXONE is not altered by probenecid.

Interaction with Laboratory Tests:

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

Non-enzymatic methods for glucose determination in urine may give false-positive results.

4.6 Fertility, pregnancy and lactation

Pregnancy and lactation

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

Safety in pregnancy and lactation has not been established.

4.7 Effects on ability to drive and use machines

N/A

4.8 Undesirable effects

a. Summary of the safety profile

Not Applicable

b. Tabulated summary of adverse reactions

Gastro-intestinal system: Loose stools/ diarrhoea, nausea, vomiting, stomatitis, glositis, precipitation of ceftriaxone salts in the gallbladder, increase in liver enzymes, pseudomembranous colitis.

Haematological system: Eosinophilia, haematoma or bleeding, thrombocytopenia, leukopenia, lymphopenia, granulocytopenia and haemolytic anaemia. 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.

Skin and appendages: Exanthema, allergic dermatitis, pruritis, urticaria, oedema. Isolated cases of severe cutaneous adverse reactions (erthema mutiforme, Stevens-Johnson syndrome or Lyell's syndrome/ toxic epidermal necrolysis) have been reported.

Central Nervous system: Headache and dizziness.

Urogenital system: Oliguria, genital mycosis. 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 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.

Hypersensitivity reactions: Anaphylactic shock and anaphylactoid reactions.

Local reactions: Phlebitic reactions may occur after i.v. administration. These may be minimized by slow (2 – 4 minutes) injection of the medicine.
Intramuscular injection *without* lignocaine solution is painful, (see **section 4.2**)

Other: Increase in serum creatinine, fever, shivering.

c. Description of selected adverse reactions

N/A

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 the "6.04

Adverse Drug Reaction Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

In cases of over-dosage, 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

The maximum plasma concentration after a single intramuscular (i.m.) dose of 1,0 g is about 81mg/ 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 (i.v.) administration of an equivalent dose, indicating 100 % bioavailability of intramuscularly (i.m.) 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 i.v. 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 distribution after a 50 mg/ kg i.v. dose and after a 75 mg/ kg i.v. 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.

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 faecum; 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 containing calcium, such as Hartmann's solution and Ringer's solution. Ceftriaxone is incompatible with vancomycin, fluconazole and aminoglycosides.

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 ºC, 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.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

Packs for i.m. or i.v. injection containing:

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

***Packs for i.m. or i.v. injection containing*:**

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

***Packs for i.v. infusion containing*:**

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

6.6 Special precautions for disposal and other handling

Intramuscular injection

For i.m. injection, ADCO-CEFTRIAXONE 250 mg or 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 % lignocaine solution instead of water for injection can reduce pain at the site of injection.

Intravenous injection

For i.v. injection, ADCO-CEFTRIAXONE 250 mg or 500 mg is dissolved in 5 ml, and ADCO-CEFTRIAXONE 1 g in 10 ml sterile water for injection.

Intravenous infusion:

For i.v. 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)

ADCO-CEFTRIAXONE 500 mg: 37/20.1.1/0042

NA: NS2 04/20.1.1/1959
BW: S2 BOT0801463

ADCO-CEFTRIAXONE 1 g: 37/20.1.1/0043

NA: NS2 04/20.1.1/1957

ADCO-CEFTRIAXONE 2 g: 37/20.1.1/0044

NA: NS2 04/20.1.1/1958
BW: S2 BOT1001650

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of Registration: 04 July 2004

10. DATE OF REVISION OF THE TEXT

Date amended: 28 April 2022