PROFESSIONAL INFORMATION

SCHEDULING STATUS S4

1. NAME OF THE MEDICINE

ROCIJECT 0,5 g INJECTION (Powder for injection)

ROCIJECT 1,0 g INJECTION (Powder for injection)

ROCIJECT 2,0 g INJECTION (Powder for injection)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Rociject is available in single dose vials each containing dry sterile ceftriaxone sodium equivalent to 0,5 g ceftriaxone, 1,0 g ceftriaxone, or 2,0 g ceftriaxone (I.M., I.V., or for I.V. infusion).

Rociject does not contain any inactive ingredients.

3. PHARMACEUTICAL FORM

Powder for injection.

Sterile, almost white or yellowish, crystalline powder in clear glass vials.

Reconstituted solution: Clear, pale yellow to amber solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ROCIJECT 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, Haemophilus influenzae, Escherichia coli,* or *Klebsiella pneumoniae.*

- **Meningitis** caused by:

  Haemophilus influenzae, Neisseria meningitides, or *Streptococcus pneumoniae.*

- ***Intra-abdominal infections*** caused by:

  Escherichia coli, Klebsiella pneumoniae, 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, 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.*

- **Surgical prophylaxis**

4.2 Posology and method of administration

Posology

Standard dosage:

Adults and children over 12 years: The usual dosage is 1 to 2 g ROCIJECT 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 to 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 to 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.

Duration of therapy:

The duration of therapy varies according to the course of the disease. Administration of ROCIJECT 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 I.M. dose of 250 mg ROCIJECT is recommended.

Peri-operative prophylaxis: A single dose of 1 to 2 g ROCIJECT administered 30 to 90 minutes prior to surgery.

In colorectal surgery, administration of ROCIJECT with or without a 5-nitroimidazole, e.g. ornidazole, has been proven effective, (separate administration: see '*Method of administration*')

Special populations

Impaired renal and hepatic function:

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

In cases of severe renal failure (creatinine clearance < 10 ml/min) the ROCIJECT 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.

Elderly patients:

The dose recommended for adults requires no modification in the case of geriatric patients.

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 medicine.

Intramuscular injection*:*

For I.M. injection, ROCIJECT 0,5 g is dissolved in 2 ml and ROCIJECT 1 g in 3,5 ml, of water for injection. ROCIJECT 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 ROCIJECT be injected at one site.

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

Intravenous injection:

The lignocaine solution must never be administered intravenously.

For I.V. injection, ROCIJECT 0,5 g is dissolved in 5 ml, and ROCIJECT 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 ROCIJECT 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 %
- Hydroxyethyl starch 6 - 10 % infusions
- Sterile water for injection

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

4.3 Contraindications

- Hypersensitivity to ceftriaxone or cephalosporins.
- Hypersensitivity to penicillins, due to the possibility of allergic cross-reactivity.

- Hyperbilirubinaemic neonates and premature babies, should not be treated with ROCIJECT. Ceftriaxone can displace bilirubin from its binding to serum albumin and bilirubin encephalopathy can possibly develop in these patients.
- ROCIJECT should not be administered concurrently with calcium-containing solutions or products in newborns because of the risk of precipitation of ceftriaxone-calcium salt (see section 4.4).

The contra-indications of lidocaine (lignocaine) must be excluded before injecting ROCIJECT intramuscularly, when lignocaine is used as a solvent (see section 4.2).

4.4 Special warnings and precautions for use

Calcium containing solutions, diluents or products

ROCIJECT must not be mixed or administered simultaneously with calcium-containing solutions or products, even via different infusion lines. Calcium-containing solutions or products must not be administered within 48 hours of last administration of ROCIJECT.

Cases of fatal reactions with calcium-ceftriaxone precipitates in lungs and kidneys in both term and premature neonates have been described. In some cases the infusion lines and times of administration of ceftriaxone and calcium-containing solutions differed (see section 4.3, section 4.5 and section 4.8).

Hypersensitivity

Anaphylactic reactions with fatal outcome have been reported (see section 4.8), even if a patient is not known to be allergic or previously exposed.

Before therapy with ROCIJECT is instituted, careful inquiry should be made to determine whether the patient has had any previous hypersensitivity reactions to ceftriaxone, any other cephalosporin, or to any penicillin or other beta-lactam medicine. ROCIJECT is contra-indicated in patients who have had a previous hypersensitivity reaction to any cephalosporin; see section 4.3.

ROCIJECT should only be given with caution to patients prone to allergies.

***Clostridium difficile* associated diarrhoea (CDAD)**

CDAD has been reported with ROCIJECT and may vary from mild diarrhoea to fatal colitis (see section 4.8).

Treatment with antibacterial medicines alters the normal flora of the colon leading to overgrowth of *C. difficile,* which produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy.

CDAD should be considered in all patients who present with diarrhoea after antibiotic use. Careful medical history is required, since CDAD has been reported to occur over two months after the administration of antibacterial medicines. If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile* and surgical evaluation should be instituted as clinically indicated.

Superinfections with non-susceptible micro-organisms may occur (see section 4.8). Prolonged use of ROCIJECT may result in overgrowth of non-susceptible organisms, such as enterococci and *Candida* spp.

Haematological changes

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

Gastro-intestinal disease

ROCIJECT should be used with caution in patients with a history of gastro-intestinal disease, particularly colitis.

Pseudomembranous enterocolitis and coagulation disorders have been reported with ROCIJECT; see section 4.8. It is important to consider pseudomembranous enterocolitis in patients who present with diarrhoea subsequent to the administration of ROCIJECT. ROCIJECT should be discontinued if severe and/or bloody diarrhoea occurs during treatment and appropriate therapy instituted.

Hepato-biliary

Shadows, which have been mistaken for gallstones, have been detected on 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 ROCIJECT 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 ROCIJECT. 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 (as contained in ROCIJECT) displaces bilirubin from serum albumin.

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

Sodium

Each gram of ROCIJECT contains about 3,6 mmol sodium, which should be taken into account when patients are on sodium restricted diets.

4.5 Interaction with other medicines and other forms of interaction

Calcium-containing products:

Do not use diluents containing calcium, such as Ringer's solution or Hartman's solution to reconstitute ROCIJECT. Particulate formation can result.

Precipitation of ceftriaxone-calcium can also occur when ROCIJECT is mixed with calcium-containing solutions in the same IV administration line. ROCIJECT must not be administered simultaneously with calcium-containing IV solutions, including continuous calcium-containing infusions such as parenteral nutrition via a Y-site.

There are no reports to date of intravascular or pulmonary precipitations in patients, other than neonates, treated with ceftriaxone and calcium-containing I.V. solutions. However, the theoretical possibility exists for an interaction between ceftriaxone and I.V. calcium-containing solutions in patients other than neonates. See section 4.4. Therefore, ROCIJECT and calcium-containing solutions, including continuous calcium-containing infusions such as parenteral nutrition, should not be mixed or co-administered to any patient irrespective of age even via different infusion lines at different sites.

ROCIJECT and I.V. calcium-containing solutions should not be administered within 48 hours of each other in any patient (see section 4.3 and section 4.2).

No data is available on a potential interaction between ceftriaxone and oral calcium-containing medicines or an interaction between intramuscular ceftriaxone and calcium-containing medicines (I.V. or oral).

Chloramphenicol

In an *in vitro* study, antagonistic effects have been observed with the combination of chloramphenicol and ceftriaxone (as contained in ROCIJECT).

Oral contraceptives

ROCIJECT may reduce the efficacy of oral hormonal contraceptives. Additional contraceptive measures should be advised during ROCIJECT treatment and one month thereafter.

Incompatibilities

Apart from calcium salts, ceftriaxone medicines (such as ROCIJECT) are incompatible with amsacrine, vancomycin, fluconazole and aminoglycosides.

Laboratory tests

In patients treated with ROCIJECT 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

ROCIJECT should not be used in pregnancy and lactation as safety has not been established.

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

4.7 Effects on ability to drive and use machines

ROCIJECT may cause dizziness (see section 4.8). Patients should be cautioned against driving or operating machinery until it is established that they do not become drowsy.

4.8 Undesirable effects

Infections and infestations:

Less frequent: Mycosis of the genital tract.

Superinfections of various sites with yeasts, fungi or other resistant organisms such as *Pseudomonas aeruginosa, Enterobacter* spp., *Candida* and enterococci.

Blood and the lymphatic system disorders:

Less frequent: Neutropenia, eosinophilia, haematoma or bleeding, thrombocytopenia, leukopenia, lymphopenia, granulocytopenia, anaemia and haemolytic anaemia. Prolongation of prothrombin time. Fatal haemolysis, positive antiglobulin Coombs' test and isolated cases of agranulocytosis (< 500/mm^3) have been reported, most of them following total doses of 20 g or more.

Frequency not known: Hypoprothrombinaemia.

Immune system disorders:

Less frequent: Anaphylactic shock and anaphylactoid reactions, acute interstitial nephritis as manifestation of hypersensitivity.

Nervous system disorders:

Less frequent: Headache and dizziness.

Frequency not known: Convulsions at high doses.

Gastro-intestinal disorders:

Frequent: Loose stools/diarrhoea, nausea, vomiting.

Less frequent: Stomatitis, glossitis, pseudomembranous colitis (mostly caused by *Clostridium difficile)*, pancreatitis (possibly caused by obstruction of bile ducts).

Hepato-biliary disorders:

Less frequent: Precipitation of ceftriaxone calcium salts in the gallbladder (see section 4.4), increase in liver enzymes (AST, ALT, alkaline phosphatase), hyperbilirubinaemia, hepatitis and cholestatic jaundice.

Frequency unknown: Hepatotoxicity

Skin and subcutaneous tissue disorders:

Less frequent: Exanthema, allergic dermatitis, maculopapular rash, pruritus, urticaria, oedema. Isolated cases of severe cutaneous adverse reactions (erythema multiforme, Stevens-Johnson syndrome or Lyell's syndrome/toxic epidermal necrolysis) have been reported.

Renal and urinary disorders:

Less frequent: Oliguria, glycosuria, haematuria, increase in serum creatinine.

Renal precipitation 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 per 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 anuria and renal insufficiency and is usually reversible upon discontinuation of ROCIJECT.

General disorders and administrative site conditions:

Less frequent: Injection site pain and phlebitis may occur after I.V. administration. These may be minimised by slow (2 to 4 minutes) injection of the medicine. Intramuscular injection ***without*** lignocaine solution is painful, (see section 4.2**)**.

Fever and shivering.

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 requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

Health care providers are asked to report any suspected adverse reactions to Acino Pharma (Pty) Ltd: E-mail: drugsafety_ZA@arceralifesciences.com.

4.9 Overdose

In the case 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

A 20.1.1 Broad and medium spectrum antibiotics

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 I.M. dose of 1,0 g is about 81 mg/l and is reached within 2 to 3 hours after administration. The area under the plasma concentration (AUC) versus time curve after I.M. administration is equivalent to that after I.V. administration of an equivalent dose, indicating 100 % bioavailability of intramuscularly administered ceftriaxone.

Distribution: The volume of distribution of ceftriaxone is 0,13 to 0,19 l/kg. Ceftriaxone shows good tissue penetration and body-fluid distribution after a dose of 1 to 2 g; concentrations 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, and the ratio of the bound to the unbound ceftriaxone decreases with the increase in concentration, e.g. from 95 % binding at plasma concentrations of less than 100 mg/l, to 85 % binding at 300 mg/l.

Penetration into particular tissues: Ceftriaxone penetrates the inflamed meninges of neonates, infants and children.

Ceftriaxone concentrations exceed 1,4 mg/l 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 of

a mean of 18 mg/l 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 patients with meningitis:

	50 mg/kg I.V.	75 mg/kg I.V.
Maximum Plasma Concentrations (µg/ml)	216	275
Elimination Half-life (h)	4,6	4,3
Plasma Clearance (ml/h/kg)	49	60
Volume of Distribution (ml/kg)	338	373
CSF Concentration – inflamed meninges (µg/ml)	5,6	6,4
Range (µg/ml)	1,3 to 18,5	1,3 to 44
Time after dose, in hours (± SD)	3,7 (±1,6)	3,3 (±1,4)

In adults with meningitis, administration of 50 mg/kg leads within 2 to 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.

Biotransformation: Ceftriaxone is not metabolised systemically, but is converted to inactive metabolites by the gut flora.

Elimination: In healthy, young adult volunteers the total plasma clearance is 10 to 22 ml/min. The renal clearance is 5 to 12 ml/min. Fifty to sixty percent of ceftriaxone is excreted unchanged in the urine, while 40 to 50 % is excreted unchanged in the bile. The elimination half-life in adults is about 8 hours.

Special populations

Neonates: Urinary recovery accounts for about 70 % of the dose.

Infants less than 8 days old and elderly persons aged over 75 years: Elimination half-life is usually 2 to 3 times that in young adults.

Patients with renal or hepatic dysfunction: The pharmacokinetics of ceftriaxone are minimally altered and the elimination half-life is 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; *Mycobacterium* species; some isolates of *Bacteriodes* species (bile-sensitive); and most strains of *Clostridium difficile*.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Rociject does not contain any inactive ingredients.

6.2 Incompatibilities:

Calcium-containing solutions are not among the appropriate solutions described for reconstitution, due to possible incompatibility. Do not use diluents containing calcium, such as Ringer's solution or Hartman's solution to reconstitute ROCIJECT. Particulate formation can result. ROCIJECT and calcium-containing infusions such as parenteral nutrition, should not be mixed or co-administered to any patient irrespective of age even via different infusion lines at different sites (see section 4.3 and section 4.4).

In the past few years, isolated neonatal deaths associated with calcium-ceftriaxone precipitates in the lungs and kidneys have been described worldwide. In some of these cases ceftriaxone and the calcium-containing solutions or medications were administered by different routes and at different times.

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

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25 ºC and protect from light. Keep vials in carton until required for use.

Reconstituted product: Store for up to 6 hours below 25 ºC or up to 24 hours in a refrigerator (2 to 8 ºC).

6.5 Nature and contents of container

Packs for I.M.or for I.V. infusion containing:

Single dose clear, colourless, Type 1 borosilicate, 10 ml glass vial with dry substance equivalent to 0,5 g ceftriaxone in packs with 1 or 10 vials.

Single dose clear, colourless, Type 1 borosilicate, 10 ml glass vial with dry substance equivalent to 1 g ceftriaxone in packs with 1 or 10 vials.

Single dose clear, colourless, Type 1 borosilicate, 10 ml glass vial with dry substance equivalent to 2 g ceftriaxone in packs with 1 or 10 vials.

6.6 Special precautions for disposal and other handling

No special requirements

7.HOLDER OF CERTIFICATE OF REGISTRATION

Acino Pharma (Pty) Ltd

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Tel: 011 516 1700

8. REGISTRATION NUMBERS

ROCIJECT 0,5 g:	37/20.1.1/0368
ROCIJECT 1 g:	35/20.1.1/0345
ROCIJECT 2 g:	37/20.1.1/0352

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

- ROCIJECT 0,5 g: 24 October 2003
- ROCIJECT 1 g: 26 March 2002
- ROCIJECT 2 g: 24 October 2003

10. DATE OF REVISION OF THE TEXT

16 July 2026