PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

Rocephin ® 250 mg (injection)

Rocephin ® 500 mg (injection)

Rocephin ® 1 g (injection)

Rocephin ® 2 g (injection)

Water for injection (injection)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient: ceftriaxone in the form of the disodium salt

Each vial contains dry substance equivalent to 0.25 g, 0.5 g, 1 g or 2 g ceftriaxone

Rocephin (contains approximately 83 mg (3,6 mmol) of sodium per gram) of ceftriaxone.

Sugar free.

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Powder for solution for injection or infusion.

Sterile, whitish powder in clear glass vials.

4 CLINICAL PARTICULARS

4.1 Therapeutic indication

Rocephin 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 meningitides or Streptococcus pneumoniae.

Intra-abdominal infections caused by Escherichia coli, Klebsiella pneumoniae, Clostridium species (Note: 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, 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 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 Rocephin may reduce the incidence of post-operative infections.

4.2 Posology and method of administration

Posology

Standard dosage

Adults and children over 12 years:

The usual dosage is 1 - 2 g of Rocephin 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 treatment:

The duration of treatment varies according to the course of the disease. Administration of Rocephin should be continued for a minimum of 48 - 72 hours after the patient has become afebrile or evidence of bacterial eradication has been obtained.

Combination treatment

Synergy between Rocephin 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

Rocephin and aminoglycosides, the two medicines must be administered separately at the recommended dosages. Chemical incompatibility with Rocephin has also been observed with IV administration of amsacrine, vancomycin and fluconazole.

Special dosage instructions

Pediatric use

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. Rocephin is contraindicated in premature neonates up to a postmenstrual age of 41 weeks (gestational age + chronological age) (see section 4.3 contraindications). Rocephin 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 (see sections 4.3, 4.4 and 4.8).

For 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 dosage 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.

Geriatric use

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

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

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

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: Rocephin is not removed by peritoneal- or hemodialysis. 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.

Severe renal and hepatic impairment

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

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

Lyme borreliosis

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

Gonorrhoea: In the treatment of uncomplicated gonorrhoea (penicillinase-producing and non-penicillinase-producing strains) a single IM dose of 250 mg is recommended

Perioperative prophylaxis: A single dose of 1 to 2 g, depending on the risk of infection of 30 to 90 minutes prior to surgery. In colorectal surgery, administration of Rocephin with or without a 5-nitroimidazole, e.g. ornidazole (separate administration, see Method of administration below) has been proven effective.

Method of administration*:*

Rocephin must be reconstituted prior to use.

As a general rule the solutions should be used immediately after preparation.

Reconstituted solutions retain their physical and chemical stability for 6 hours at room temperature (or 24 hours in the refrigerator at 2 - 8 °C). 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, Rocephin 250 mg and 500 mg is dissolved in 2 mL; Rocephin 1 g in 3,5 mL of water for injections. In adults, intramuscular administrations of some cephalosporins, including Rocephin, cause pain at the injection site. This can be reduced greatly by administering in combination with a local anaesthetic.

Rocephin dissolved in 3,5 mL of a 1 % lignocaine (lidocaine) solution instead of water for injections can reduce pain at the site of injection, in adults. It is recommended that no more than 1 g of Rocephin be injected at one site. Safe dose of 1 % lignocaine (lidocaine) has not been established.

Reconstitution with 1 % lignocaine/lidocaine (without adrenaline) has no effect on the absorption or the elimination of Rocephin. **The lignocaine (lidocaine) solution should never be administered** intravenously (see section 4.3 contraindications).

Intravenous injection. For IV injection, Rocephin 250 mg or 500 mg is dissolved in 5 mL, and Rocephin 1 g in 10 mL water for injections. The intravenous administration should be given over 2 to 4 minutes.

Intravenous infusion. The infusion should be given over at least 30 minutes. For IV infusion, 2 g Rocephin is dissolved in 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 %, water for injections. Rocephin 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.

Incompatibilities: See section 6.2

4.3 Contraindications

Hypersensitivity

Rocephin is contraindicated in patients with known hypersensitivity to ceftriaxone, any of its excipients or to any other cephalosporin. Patients with previous hypersensitivity reactions to penicillin and other beta lactam medicines may be at greater risk of hypersensitivity to ceftriaxone (see section 4.4 Special warnings and precautions for use– Hypersensitivity).

Lidocaine/Lignocaine

Contraindications to lidocaine/lignocaine must be excluded before intramuscular injection of Rocephin when lidocaine solution is used as a solvent (see section 4.2). See the contraindications section in the professional information of lidocaine. Rocephin solutions containing lidocaine should never be administered intravenously.

Premature Neonates

Rocephin is contraindicated in premature neonates up to postmenstrual age of 41 weeks (gestational age + chronological age) .

Hyperbilirubinemic newborns

Hyperbilirubinaemic newborns, should not be treated with Rocephin. In vitro studies have shown that Rocephin can displace bilirubin from its binding to serum albumin leading to a possible risk of bilirubin encephalopathy in these patients.

Neonates and Calcium Containing IV Solutions

Rocephin 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.

A small number of cases of fatal outcomes with calcium-Rocephin precipitates in the lungs and kidneys have been reported at autopsy in both term and preterm neonates receiving Rocephin and calcium- containing fluids. In some of these cases, the same intravenous infusion line was used for both Rocephin 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 to whom Rocephin and calcium-containing fluids were administered at different time points via different intravenous lines; no crystalline material was observed at autopsy in this neonate. There have been no similar reports in patients other than neonates, (see sections 4.2, 4.4 and 4.8).

4.4 Special warnings and precautions for use

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

Precipitation of ceftriaxone-calcium may occur when Rocephin is mixed with calcium-containing solutions in the same IV administration line. Rocephin 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 Rocephin and calcium-containing fluids. In some of these cases, the same intravenous infusion line was used for both Rocephin 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 Rocephin and calcium-containing fluids were administered at different time points via different intravenous lines. 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 Rocephin. 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, Rocephin 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, Rocephin 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).

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

Hypersensitivity

Serious and occasionally fatal hypersensitivity reactions have been reported (see section 4.8 Undesirable effects). In case of severe hypersensitivity reactions, treatment with Rocephin 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 Rocephin is given to patients with a history of hypersensitivity to other beta-lactam medicines.

Haemolytic anaemia

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

Clostridium difficile associated diarrhoea

Clostridium difficile associated diarrhoea (CDAD) has been reported with the use of Rocephin, and may range in severity from mild diarrhoea to fatal colitis. Treatment with Rocephin 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 hyper-producing strains of C. difficile cause increased morbidity and mortality, as these infections can be

refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhoea following Rocephin use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents, such as Rocephin.

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.

Superinfections

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

Calcium-ceftriaxone precipitates

Calcium-ceftriaxone precipitates in the gallbladder have been observed on ultrasound scan in patients receiving Rocephin, 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 Rocephin therapy and are rarely symptomatic. In symptomatic cases, conservative nonsurgical management is recommended, and discontinuation of Rocephin treatment should be considered by the medical practitioner based on an individual benefit-risk assessment.

Pancreatitis

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

Paediatrics

Safety and efficacy of Rocephin in neonates, infants and children have been established for the dosages described under section 4.2. Studies have shown that Rocephin can displace bilirubin from serum albumin. Rocephin 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 Rocephin the Coombs' test may become falsely positive. Rocephin, like other antibiotics, may result in false-positive test results for galactosemia.

Likewise, nonenzymatic methods for the glucose determination in urine may give false positive results. For this reason, urine-glucose determination during therapy with Rocephin 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.

4.5 Interaction with other medicines and other forms of interaction

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

There is conflicting evidence regarding a potential increase in renal toxicity of aminoglycosides when used with cephalosporins including Rocephin. 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 Rocephin. Rocephin 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 Rocephin.

Influence on diagnostic tests

In patients treated with Rocephin the Coombs test may become false-positive. Treatment with Rocephin may result in false-positive test for galactosemia.
Likewise, non-enzymatic methods for the glucose determination in urine may give false-positive results. For this reason, urine-glucose determination during therapy with Rocephin should be done enzymatically.
The presence of Rocephin 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: Rocephin 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 Rocephin vials, or to further dilute a reconstituted vial for IV administration because a precipitate can form. Precipitation of ceftriaxone-calcium can also occur when Rocephin is mixed with calcium-containing solutions in the same IV administration

line. Rocephin 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 Rocephin 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 Rocephin (see section 4.8 Undesirable Effects).

4.6 Fertility, pregnancy and lactation

Safety in human pregnancy has not been established. Rocephin crosses the placental barrier. Rocephin is excreted in the breast-milk. Safety in lactation has not been established

Pregnancy

Rocephin crosses the placental barrier. Safety in human pregnancy has not been established. Reproductive studies in animals have shown no evidence of embryotoxicity, fetotoxicity, teratogenicity or adverse effects on male or female fertility, birth or perinatal and postnatal development. In primates, no embryotoxicity or teratogenicity has been observed.

Lactation

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

Pediatric Use

See section 4.2

Geriatric use

See section 4.2

Renal Impairment

See section 4.2

Hepatic Impairment

See section 4.2 Special dose instructions

4.7 Effects on ability to drive and use machines.

During treatment with Rocephin, 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

a. Summary of the safety profile:

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

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

Tabulated summary of adverse drug reactions from clinical trials

Adverse drug reactions from clinical trials (Table 1) are listed by MedDRA system organ class. The corresponding frequency category for each adverse drug reaction is based on the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1000).

Table 1 Summary of adverse reactions occurring in patients treated with Rocephin in clinical trials

Adverse reactions	Frequency category
Blood and lymphatic system disorders	
Eosinophilia	Common
Leucopenia	Common
Thrombocytopenia	Common
Granulocytopenia	Uncommon
Anaemia	Uncommon
Coagulopathy	Uncommon
Gastrointestinal disorders	
Diarrhoea	Common
Loose stools	Common
Nausea	Uncommon
Vomiting	Uncommon
General disorders and administration site conditions	
Phlebitis	Uncommon
Injection site reactions	Uncommon
Pyrexia	Uncommon
Oedema	Rare
Chills	Rare
Hepatobiliary disorders	
Hepatic enzyme increased	Common
Infections and infestations	
Genital fungal infection	Uncommon
Pseudo-membranous colitis	Rare
Investigations	
Blood creatinine increased	Uncommon
Nervous system disorders	
Headache	Uncommon
Dizziness	Uncommon
Renal and urinary disorders	
Haematuria	Rare
Glycosuria	Rare

Respiratory, thoracic and mediastinal disorders	
Bronchospasm	Uncommon
Skin and subcutaneous tissue disorders	
Rash	Common
Pruritus	Uncommon
Urticaria	Rare

Post Marketing Experience

The following adverse drug reactions have been identified from post marketing experience with Rocephin.

Infections and infestations: Superinfection

Blood and lymphatic system disorders: Isolated cases of agranulocytosis (< 500/mm3) have been reported, most of them after 10 days of treatment and following total doses of 20 g or more. Coagulation disorders have been reported. Immune system disorders: Anaphylactic or anaphylactoid reactions.

Nervous system disorders: Convulsion

encephalopathy

Reversible encephalopathy has been reported with the use of cephalosporins, including ceftriaxone, particularly when high doses are administered in patients with renal impairment and additional predisposing factors such as older age, pre-existing central nervous system disorders.

Gastrointestinal disorders: Pancreatitis, stomatitis, glossitis. Pseudomembranous enterocolitis has been reported.

Hepato-biliary disorders: Symptomatic precipitation of ceftriaxone-calcium salt in the gallbladder, kernicterus

Skin and subcutaneous tissue disorders: Acute generalised exanthematous pustulosis (AGEP), and 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: Oliguria. Renal precipitation have been reported, mostly in children older than 3 years 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). This event may be symptomatic or asymptomatic, may lead to renal insufficiency, and is reversible upon discontinuation of Rocephin.

General disorders and administration site conditions: Phlebitis reactions occurred after IV administration, these may be minimised by slow (2 - 4 minutes) injection.

Investigations: Coombs test false positive, galactosemia test false positive, non-enzymatic methods for glucose determination false positive (see section 4.5).

c. Description of selected adverse reactions from clinical trials

Interaction with calcium: Cases of ceftriaxone precipitation in the urinary tract have been reported, mostly in children treated with high doses (e.g. 80 mg/kg/day) or total doses exceeding 10 grams) and who have other risk factors (e.g. dehydration, confinement to bed). 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 Rocephin.

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 professionals are asked to report any suspected adverse reactions to SAHPRA via he 6.04 Adverse Drug Reaction Report Form , found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

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 of overdosage should be symptomatic.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use. Third generation cephalosporins. ATC code: J01DD04.

Mechanism of action

The following organisms have been found to be resistant to ceftriaxone:

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

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 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) are resistant to ceftriaxone, mainly due to the production of the chromosomally encoded ß-lactamase.

Some isolates of Klebsiella pneumoniae are resistant due to production of extended spectrum, plasmid-mediated ß-lactamase. 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 WHO Antimicrobial Resistance, Global Report on Surveillance, 2014, lists the following bacteria-antibacterial medicine resistant combinations ranging between 56 % - 90 % for 3rd generation cephalosporins including ceftriaxone as: E. coli and K. pneumoniae mainly conferred by extended spectrum beta-lactamases (ESBLs), and N. gonorrhoeae.

5.2 Pharmacokinetic properties

The pharmacokinetics of ceftriaxone are non-linear and all basic pharmacokinetic parameters, except the elimination half-life, are dose dependent if based on total medicine 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.

Absorption:

Rocephin is administered as an intramuscular injection or as an IV injection or infusion.

The maximum plasma concentration after a single IM dose of 1,0 g is about 81 mg/L and is reached within 2 - 3 hours after administration. The area under the plasma concentration-time curve after

IM administration is equivalent to that after IV administration of an equivalent dose, indicating 100 % bio-availability of intramuscularly administered ceftriaxone.

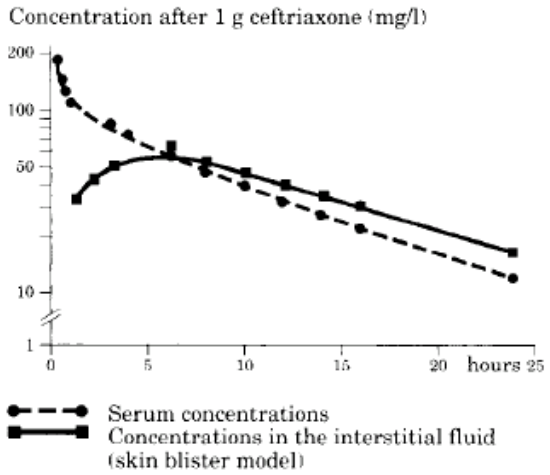
After intravenous bolus administration of ceftriaxone 500 mg and 1 g, mean peak plasma ceftriaxone levels are approximately 120 and 200 mg/L respectively. After intravenous infusion of ceftriaxone 500 mg, 1 g and 2 g, the plasma ceftriaxone levels are approximately 80, 150 and 250 mg/l respectively. Following intramuscular injection, mean peak plasma ceftriaxone levels are approximately half those observed after intravenous administration of an equivalent dose.

Distribution:

The volume of distribution of ceftriaxone is 7 - 12 L. Ceftriaxone has shown excellent tissue and body fluid penetration after a dose of 1 - 2 g; concentrations well above the minimal inhibitory concentrations of most pathogens responsible for infection, are detectable for more than 24 hours in over 60 tissues or body fluids including lung, heart, biliary tract/liver, tonsils, middle ear and nasal mucosa, bone as well as cerebrospinal, pleural, prostatic and synovial fluids.

On intravenous administration, ceftriaxone diffuses into the interstitial fluid, where if it is given in the recommended dosage range, bactericidal concentrations lasting 24 hours may be maintained.

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).



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.

Metabolism:

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

Elimination:

Total plasma clearance is 10 - 22 mL/min. Renal clearance is 5 - 12 mL/min. 50 - 60 % 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 8 hours.

Pharmacokinetics in special populations

Children: Pediatric 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.

Elderly: Geriatric population

In elderly persons aged over 75 years the average elimination half-life is usually two to three times that of young adults.

Renal or hepatic impairment:

In patients with renal or hepatic dysfunction, the pharmacokinetics of ceftriaxone are only minimally altered and the elimination half-life is only slightly increased (less than two fold), even in patients with severely impaired renal function.

The 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.

Hepatic impairment:

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lidocaine hydrochloride in form of lidocaine hydrochloride monohydrate

Water for injections

6.2 Incompatibilities

Rocephin 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 as it can cause the formation of intravascular precipitates. Do not use diluents containing calcium

such as Hartmann's solution or Ringer's lactate solution to reconstitute Rocephin vials or to further dilute a reconstituted vial for *IV* administration because a precipitate can form.

6.3 Nature and contents of container

Packs for IM or IV injection containing

Rocephin 250 mg: 1 vial with dry substance equivalent to 250 mg ceftriaxone and 1 ampoule water for injection 5 mL.

Rocephin 500 mg: 1 vial with dry substance equivalent to 500 mg ceftriaxone and 1 ampoule water for injection 5 mL. Packs of 50 vials with no water for injection.

Rocephin 1 g: 1 vial with dry substance equivalent to 1 g ceftriaxone + 1 ampoule water for injection 10 mL. Packs of 143 vials with no water for injection.

Packs for IV infusion containing

Rocephin 2 g: 1 vial with dry substance equivalent to 2 g ceftriaxone. Packs of 50 vials with no water for injection.

Not all strengths and/or pack sizes may be marketed.

6.4 Special precautions for disposal and other handling

Instructions for reconstitution: see section 4.2

Disposal of unused/expired medicines

The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via wastewater, and disposal through household waste should be avoided.

Use established 'collection systems' if available in your location

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

Roche Products (Pty) Ltd

90 Bekker Road, Hertford Office Park,

Building E, Vorna Valley, Midrand,

Johannesburg, 1686

South Africa

Roche Ethical Assistance Line (REAL) toll-free: 0800 21 21 25

8. REGISTRATION NUMBER(S)

Rocephin 250 mg: R/20.1.1/44

Rocephin 500 mg: R/20.1.1/45

Rocephin 1 g: R/20.1.1/46

Rocephin 2 g: R/20.1.1/47

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Registration: 16 January 1987

10. DATE OF REVISION OF THE TEXT

Last revision: 31 October 2022

Namibia: NS2 90/20.1.1/001425/6
Botswana NS2 B9308260/5
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Approved Manufacturer(s):

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