Rocephin®

Ceftriaxone

Composition

Active ingredient
Ceftriaxone (as the disodium salt).
Rocephin contains approximately 83 mg (3.6 mEq) of sodium per gram of ceftriaxone.

Pharmaceutical form and active substance quantity per unit

250 mg i.v.
Dry substance: ceftriaxone 250 mg as disodium ceftriaxone per vial.
Solvent: water for injection 5 ml.

250 mg i.m.
Dry substance: ceftriaxone 250 mg as disodium ceftriaxone per vial.
Solvent: lidocaine hydrochloride 20 mg, water q.s. 2 ml of solution.

500 mg i.v.
Dry substance: ceftriaxone 500 mg as disodium ceftriaxone per vial.
Solvent: water for injection 5 ml.

500 mg i.m.
Dry substance: ceftriaxone 500 mg as disodium ceftriaxone per vial.
Solvent: lidocaine hydrochloride 20 mg, water q.s. 2 ml of solution.

1 g i.v.
Dry substance: ceftriaxone 1 g as disodium ceftriaxone per vial.
Solvent: water for injection 10 ml.

1 g i.m.
Dry substance: ceftriaxone 1 g as disodium ceftriaxone per vial.
Solvent: lidocaine hydrochloride 35 mg, water q.s. 3.5 ml of solution.

2 g i.v.
Dry substance: ceftriaxone 2 g as disodium ceftriaxone per vial.

Indications/uses

Infections caused by pathogens sensitive to ceftriaxone, e.g.:
- Respiratory tract infections, particularly pneumonia, and ear, nose and throat infections;
- Abdominal infections (peritonitis, infections of the biliary and gastrointestinal tracts);
- Renal and urinary tract infections;
- Genital infections, including gonorrhoea;

- Sepsis;
- Infections of the bones, joints, soft tissue, skin and of wounds;
- Infections in patients with impaired immunity;
- Meningitis;
- Disseminated Lyme Borreliosis (stages II and III).

Perioperative prophylaxis of infections associated with gastrointestinal, biliary, urogenital, gynaecological surgery, but only in cases of potential or definite contamination.

Official recommendations on the appropriate use of antibiotics should be followed, especially usage recommendations to prevent the increase in antibiotic resistance.

Dosage/administration

A solvent containing lidocaine is used for intramuscular (i.m.) administration. Therefore, any contraindications to lidocaine must first be excluded before i.m. injection of ceftriaxone (see "*Contraindications"*).

(For preparation of the ready-to-use solutions [i.v., i.m. and weight-based dosing], see "*Instructions for use and handling*".)

Dosage

Adults and children over twelve years

The usual dosage is 1–2 g of Rocephin once daily (every 24 hours). In severe infections or those caused by moderately sensitive organisms, the once daily dose may be raised to 4 g.

Neonates, infants and children up to twelve years

The following dosing guidelines are recommended for once-daily administration:

Neonates (up to 14 days old)

A daily dose of 20–50 mg per kg body weight; it must not exceed 50 mg per kg. Rocephin is contraindicated in premature neonates up to a postmenstrual age of 41 weeks (gestational age + postnatal age) (see *Contraindications)*.
Rocephin is contraindicated in neonates (≤ 28 days) if they require (or are expected to require) treatment with calcium-containing intravenous solutions, including continuous calcium-containing infusions such as in parenteral nutrition, because of the risk of calcium ceftriaxone precipitation (see *Contraindications*).

Infants and children (15 days to twelve years)

A daily dose of 20–80 mg per kg.

For children with body weights of 50 kg or more, the usual adult dosage must be used.

Intravenous doses of 50 mg or more per kg body weight in infants and children up to 12 years of age should be given by slow infusion over at least 30 minutes. In neonates, intravenous doses should be given over 60 minutes to reduce the potential risk of bilirubin encephalopathy.

Elderly patients

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

Duration of treatment

The duration of therapy varies with indication and the course of the disease.

Combination therapy

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, they should be considered in severe, life-threatening infections due to microorganisms such as *Pseudomonas aeruginosa*. Because of the 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 intravenous administration of amsacrine, vancomycin and fluconazole (see *"Other information, Incompatibilities*).

Special dosage instructions

Meningitis

In bacterial meningitis in infants and children, treatment begins with doses of 100 mg/kg (no more than 4 g) once daily. As soon as the causative organism has been identified and its sensitivity determined, the dosage can be reduced accordingly. The best results have been achieved with the following durations of therapy:

Neisseria meningitidis	4 days
Haemophilus influenzae	6 days
Streptococcus pneumoniae	7 days

Lyme borreliosis

The dosage for Lyme borreliosis in children and adults is 50 mg/kg up to a maximum of 2 g, administered once daily for 14 days.

Gonorrhoea

For the treatment of gonorrhoea (penicillinase-producing and non-penicillinase-producing strains), a single i.m. dose of 0.25 g Rocephin is recommended.

Perioperative prophylaxis

To prevent postoperative infection in contaminated or potentially contaminated operations, a single dose of 1–2 g Rocephin – depending on the risk of infection – is recommended for administration 30–90 minutes prior to surgery. In colorectal surgery, coadministration of Rocephin with a 5-nitroimidazole, e.g. ornidazole, has proved effective.

Patients with renal impairment

No dose adjustment is required, provided hepatic function is not impaired. However, in cases of preterminal renal failure (creatinine clearance < 10 ml/min), the Rocephin dosage must not exceed 2 g daily.

Ceftriaxone is not eliminated by peritoneal or haemodialysis. Dialysis patients therefore require no supplementary dosing following dialysis. A daily dose of 2 g should not be exceeded in dialysis patients.

Patients with hepatic impairment

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

Patients with severe renal and hepatic impairment

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

Instructions for administration: see *Other information / Instructions for handling*.

Contraindications

Hypersensitivity

Rocephin is contraindicated in patients with known hypersensitivity to ceftriaxone, any of the excipients or any other cephalosporin. Patients with previous hypersensitivity reactions to penicillin or other beta-lactams may be at greater risk of hypersensitivity to ceftriaxone (see *Warnings and precautions, Hypersensitivity).*

For i.m. injection of Rocephin, for which lidocaine-containing solvent is used, any contraindications to lidocaine must first be excluded before i.m. injection of Rocephin (see *Dosage / Administration*).

Known hypersensitivity to the active substance lidocaine or other anilide-type local anaesthetics.

Ceftriaxone solutions containing lidocaine should never be administered intravenously.

Cardiac conduction disturbances.

Acute decompensated heart failure.

Premature infants

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

Neonates with hyperbilirubinaemia

Neonates with hyperbilirubinaemia should not be treated with Rocephin because of the risk of bilirubin encephalopathy due to displacement of bilirubin from its binding to serum albumin by ceftriaxone.

Neonates and calcium-containing intravenous solutions

Rocephin is contraindicated in neonates (≤ 28 days) who require (or are expected to require) treatment with calcium-containing preparations, including continuous calcium-containing infusions such as parenteral nutrition, because of the risk of fatal organ damage to kidneys and lungs due to precipitation of ceftriaxone calcium salts.

A small number of cases with fatal outcome in which a crystalline material was observed in the lungs and kidneys at autopsy have been reported in neonates receiving Rocephin and calcium-containing solutions. In some of these cases the same infusion line was used for Rocephin and calcium-containing solutions, and in some a precipitate was found in the

infusion line. At least one fatality has been reported in a neonate to whom Rocephin and calcium-containing solutions were administered at different time points and via different infusion lines; no crystalline material was observed at autopsy in this neonate. There have been no similar reports in patients other than neonates (see *Undesirable effects*).

Warnings and precautions

Lidocaine
All information on lidocaine in this prescribing information is of a general nature and not specifically related to i.m. administration of Rocephin.

The solvent for i.m. injection of ceftriaxone contains a local anaesthetic (lidocaine). Physicians administering local anaesthetics must have sufficient experience and be familiar with the diagnosis and treatment of possible undesirable effects (including systemic toxicity) and/or complications. The necessary equipment and drugs required for resuscitation should be immediately available in direct proximity.

Hypersensitivity
As with all beta-lactam antibiotics, there have been reports of serious and occasionally fatal hypersensitivity reactions (see Undesirable effects – After market launch). In case of severe hypersensitivity reactions, treatment with ceftriaxone must be discontinued immediately and adequate emergency measures must be initiated. Before starting treatment, it should be established whether the patient has ever had hypersensitivity reactions to ceftriaxone, to other cephalosporins or to any other beta-lactam agent. Caution is required when administering ceftriaxone to patients with a history of hypersensitivity to other beta-lactam agents.

Hypersensitivity reactions (including anaphylactic shock) may be caused by lidocaine (contained in the solvent for i.m. injection).

Severe cutaneous adverse reactions (SCARs) such as Stevens-Johnson syndrome, toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms (DRESS), erythema multiforme and acute generalised exanthematous pustulosis (AGEP) have been reported in patients receiving treatment with beta-lactam antibiotics including Rocephin or ceftriaxone. Hypersensitivity reactions can also lead to Kounis syndrome, a severe allergic reaction that can result in myocardial infarction. The first symptoms of such reactions may include chest pain associated with an allergic reaction to beta-lactam antibiotics (see *Undesirable effects*). In the event of such reactions, Rocephin should be immediately discontinued and alternative therapy considered.

Prolongation of prothrombin time
Ceftriaxone may prolong prothrombin time, which should therefore be checked in suspected vitamin K deficiency.

Haemolytic anaemia
An immune-mediated haemolytic anaemia has been observed in patients receiving cephalosporin-class antibiotics 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 ceftriaxone, the diagnosis of cephalosporin-associated

anaemia should be considered and ceftriaxone discontinued until the aetiology is determined.

Clostridium difficile-associated diarrhoea (CDAD)

Clostridium difficile-associated diarrhoea (CDAD) has been reported with use of nearly all antibacterial agents, including Rocephin, and may range in severity from mild diarrhoea to fatal colitis. Treatment with antibacterial agents 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. 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 must be considered in all patients who present with diarrhoea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur up to two months after the administration of antibacterial agents.

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.

Antiperistaltic drugs are contraindicated in this case.

Superinfections

On long-term use of Rocephin, non-susceptible microorganisms may become difficult to control. Close patient supervision is therefore essential. If superinfection occurs during treatment, appropriate measures should be taken.

Calcium ceftriaxone precipitates

Calcium ceftriaxone precipitates have been identified on ultrasound examination of the gallbladder in patients treated with ceftriaxone, particularly at daily doses of 1 g and above. The likelihood of such precipitates seems to be highest in paediatric patients. The precipitates disappear after discontinuation of ceftriaxone therapy and are rarely symptomatic. In symptomatic cases conservative, nonsurgical management is recommended. The physician should also consider discontinuation of ceftriaxone treatment, based on individual benefit-risk assessment.

Pancreatitis

Rare cases of pancreatitis possibly due to cholestasis have been reported in patients treated with Rocephin. Most patients presented with risk factors for cholestasis and biliary sludge, e.g. extensive prior therapy, severe illness and total parenteral nutrition. The possibility cannot be excluded that Rocephin-induced precipitation in the gallbladder acts as a trigger or cofactor.

Ceftriaxone can displace bilirubin from its binding to serum albumin. Treatment of hyperbilirubinaemic neonates is therefore contraindicated (see *Contraindications*).

Encephalopathy

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

Monitoring of blood counts

Full blood counts should be performed at regular intervals during prolonged treatment.

Investigations

False-positive Coombs test, false-positive galactosaemia test, false-positive result with non-enzymatic methods for glucose determination.

Renal impairment

Caution is advised in patients with impaired renal function receiving concomitant treatment with aminoglycosides and diuretics.

Neonates, children and adolescents

Ceftriaxone must not be mixed or administered concurrently with calcium-containing solutions, even if the solutions are given via different infusion lines. Cases of fatal reactions due to calcium ceftriaxone precipitates in lungs and kidneys have been described in neonates, even when different infusion lines and times of administration were used for ceftriaxone and the calcium-containing solutions. For this reason intravenous calcium-containing solutions must not be administered to neonates for at least 48 hours after the last dose of Rocephin (see *Contraindications*).

Cases of intravascular ceftriaxone calcium precipitation after concomitant use of ceftriaxone with intravenous calcium-containing solutions have not been reported in other age groups. Nevertheless, coadministration should be avoided in all patients.

Precautions for lidocaine (contained in the solvent for i.m. injection)

The risk of serious adverse reactions to local anaesthetics such as lidocaine is increased in the following situations:

– Elderly patients
– Patients in poor general health
– Atrioventricular (AV) block (because local anaesthetics can delay impulse conduction)
– Severe liver disease
– Severe renal failure

In these cases, i.m. injection of Rocephin (with lidocaine solvent) should be undertaken with particular caution.

Patients treated with class III antiarrhythmics (e.g. amiodarone) should be kept under surveillance, and ECG monitoring considered, since cardiac effects may be additive.

Injections of lidocaine-containing solutions in the head and neck region, if inadvertently given by the intra-arterial route, may cause central nervous system symptoms even at low dosage.

This medicinal product contains 83 mg of sodium per gram of ceftriaxone, corresponding to 4.2% of the WHO-recommended maximum daily dietary sodium intake of 2 g for an adult.

Interactions

No impairment of renal function has been observed after concurrent administration of large doses of Rocephin and potent diuretics such as furosemide. There are conflicting data regarding a potential increase in renal toxicity of aminoglycosides when used with

cephalosporins. The recommendations on monitoring of aminoglycoside levels and renal function in clinical practice should be closely adhered to in such cases. Nevertheless, the two products must be administered separately (see Incompatibilities).

No disulfiram-like effect has been demonstrated after Rocephin administration alcohol ingestion. Ceftriaxone does not contain the N-methylthiotetrazole moiety that could lead to ethanol intolerance and bleeding problems as is the case with other cephalosporins.

Probenecid has no effect on the elimination of ceftriaxone.

Bacteriostatics may adversely interfere with the bactericidal effect of cephalosporins. Antagonistic effects were observed in an *in vitro* study of ceftriaxone in combination with chloramphenicol.

Diluents containing calcium (e.g. Ringer's solution or Hartmann's solution) must not be used to reconstitute Rocephin vials or to further dilute a reconstituted vial for intravenous administration because precipitates may form. Calcium ceftriaxone precipitates may also form when Rocephin is mixed with calcium-containing solutions in the same infusion line. Rocephin must not be administered simultaneously with calcium-containing infusion solutions, including continuous calcium-containing infusions such as in parenteral nutrition via a Y-site. However, in patients other than neonates, Rocephin and calcium-containing solutions may be administered consecutively if the infusion lines are thoroughly flushed between infusions with a compatible solution. *In vitro* studies using plasma from adults and neonatal cord blood demonstrated that neonates have an increased risk of calcium ceftriaxone precipitation (see *Dosage / Administration* and *Contraindications*).

There are no reports of interactions between ceftriaxone and oral calcium-containing products or between intramuscular ceftriaxone and calcium-containing products (intravenous or oral).

Concomitant use of ceftriaxone with vitamin K antagonists may increase the risk of bleeding.

Coagulation parameters should be regularly monitored and the dose of anticoagulant adjusted accordingly both during and after treatment with ceftriaxone (see *Undesirable effects*).

Interactions with lidocaine (contained in the solvent for i.m. injection)

Pharmacokinetic interactions: Lidocaine is a substrate of the CYP450 enzymes CYP1A2 and CYP3A4. The metabolism of lidocaine may therefore be inhibited by coadministration of CYP inhibitors (e.g. itraconazole, voriconazole, fluconazole, clarithromycin, erythromycin, cimetidine) and increased by coadministration of enzyme inducers (e.g. barbiturates, carbamazepine, phenytoin, primidone, rifampicin).

Pharmacodynamic interactions: Coadministration of drugs structurally related to amide-type local anaesthetics (e.g. antiarrhythmics such as mexiletine or tocainide) may be associated with additive systemic toxic effects. I.m. injection of Rocephin (with lidocaine-containing solvent) should therefore be administered with particular caution in patients treated with such medicinal products.

Lidocaine may enhance the effect of muscle relaxants.

It is recommended to also consult the prescribing information of the coadministered medicinal products.

Pregnancy and lactation

Pregnancy

Ceftriaxone crosses the placental barrier (see *Pharmacokinetics: Distribution*). No controlled clinical studies are available. Although no evidence of teratogenicity was detected in the relevant preclinical studies, Rocephin should only be used in pregnancy, particularly in the first three months, if there is a compelling indication for its use.

Lidocaine (contained in the solvent for i.m. injection) crosses the placental barrier. Therefore, i.m. injection of ceftriaxone should not be administered during pregnancy (particularly in the first three months). If Rocephin use is essential, a dosage form without lidocaine should be selected.

The use of local anaesthetics such as lidocaine during childbirth may cause adverse reactions in the mother and/or unborn child (e.g. bradycardia).

Lactation

As ceftriaxone – albeit in low concentrations – and also lidocaine (contained in the solvent of i.m. injection) are excreted in breast milk, the product should not be used by nursing mothers. Where treatment is absolutely essential, breastfeeding should be stopped.

Effects on ability to drive and use machines

No relevant studies have been performed.

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

Undesirable effects

The undesirable effects that are typical of systemic ceftriaxone administration and may also occur with ceftriaxone after i.m. administration (with lidocaine) are listed first below. The subsequent section then describes the undesirable effects observed when using lidocaine. There are no specific data on combined use of ceftriaxone and lidocaine.

The data used to determine the frequency of adverse reactions to ceftriaxone are derived from clinical trials. Frequency is classified using the following categories: Very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1000 to < 1/100), rare (≥ 1/10,000 to < 1/1000), very rare (< 1/10,000) and not known (cannot be estimated from the available data).
The commonest reported adverse reactions to ceftriaxone are eosinophilia, leukopenia, thrombocytopenia, diarrhoea, loose stools, rash and increased hepatic enzymes.

Ceftriaxone without/with lidocaine (contained in the solvent for i.m. injection)

The following side effects, which subsided either spontaneously or after withdrawal of the drug, have been observed during the use of Rocephin:

Infections and infestations

Uncommon: Mycosis of the genital tract.

Rare: Pseudomembranous colitis.

Not known: Superinfection with non-susceptible organisms.

Blood and lymphatic system disorders

Common: Eosinophilia, leukopenia, thrombocytopenia, increased prothrombin time.

Uncommon: Granulocytopenia, anaemia, coagulopathy, elevation of serum creatinine.

Not known: Isolated cases of agranulocytosis (< 500/mm^3) have been observed, most of them following total doses of 20 g or more.

Blood counts should be performed at regular intervals during prolonged treatment. Slight prolongation of prothrombin time has been reported.

Nervous system disorders

Uncommon: Headache, dizziness.

Rare: Encephalopathy.

Not known: Convulsions.

Cardiac disorders

Not known: Kounis syndrome (see *Warnings and precautions*).

Respiratory, thoracic and mediastinal disorders

Rare: Bronchospasm.

Gastrointestinal disorders

Common: Diarrhoea, loose stools

Uncommon: Nausea, vomiting.

Very rare: Pseudomembranous enterocolitis.

Not known: Pancreatitis*, stomatitis, glossitis.

*Possibly due to bile duct obstruction. Most of the patients concerned had risk factors for cholestasis and biliary sludge, e.g. preceding major surgery, serious disease or total parenteral nutrition. The possibility that Rocephin may act as a trigger or cofactor in the formation of gallbladder precipitates cannot be ruled out.

Hepatobiliary disorders

Very common: Symptomatic precipitation of ceftriaxone calcium salt in the gallbladder of children, reversible cholelithiasis in children. This disorder occurs rarely in adults (see *Warnings and precautions*).

Common: Increase in serum liver enzymes (ALT, AST, alkaline phosphatase).

Rare: Kernicterus.

Skin and subcutaneous tissue disorders

Common: Rash, oedema.

Uncommon : Pruritus.

Rare : Urticaria,

Not known: Acute generalised exanthematous pustulosis (AGEP), severe skin reactions (erythema multiforme, Stevens-Johnson syndrome or Lyell's syndrome/toxic epidermal necrolysis).

Renal and urinary disorders

Rare: Oliguria, haematuria, glycosuria.

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 of 10 g) and who had other risk factors (e.g. dehydration, confinement to bed). This side effect may be asymptomatic or symptomatic, and may lead to ureteric obstruction and postrenal acute renal failure, but is usually reversible on discontinuation of Rocephin.

General disorders and administration site conditions

Uncommon: Phlebitis, injection site reactions (e.g. injection site pain, erythema, warmth, redness, phlebitis, extravasation, swelling, rash, pruritus, inflammation, induration, haematoma, infection, abscess), pyrexia.

Rare: Oedema, chills, anaphylactic or anaphylactoid reactions.

Vein wall inflammatory reactions after i.v. administration.

These may be minimised by slow injection (over two to four minutes).

Undesirable effects after market launch

Not known: Severe cutaneous adverse reactions (SCARs) (see "Warnings and precautions").

Interactions with calcium

Two *in vitro* studies, one using adult plasma and the other neonatal plasma from umbilical cord blood, have been carried out to assess interaction of ceftriaxone and calcium. Ceftriaxone concentrations up to 1 mM (in excess of concentrations achieved *in vivo* following administration of 2 grams ceftriaxone infused over 30 minutes) were used in combination with calcium concentrations up to 12 mM (48 mg/dl). Recovery of ceftriaxone from plasma was reduced with calcium concentrations of 6 mM (24 mg/dl) or higher in adult plasma or 4 mM (16 mg/dl) or higher in neonatal plasma. This may be reflective of calcium ceftriaxone precipitation.

A small number of cases with fatal outcome in which a crystalline material was observed in the lungs and kidneys at autopsy have been reported in neonates receiving Rocephin and calcium-containing solutions. In some of these cases the same infusion line was used for Rocephin and calcium-containing solutions, and in some a precipitate was found in the infusion line. At least one fatality has been reported in a neonate to whom Rocephin and calcium-containing solutions were administered at different time points and via different infusion lines; no crystalline material was observed at autopsy in this neonate. There have been no similar reports in patients other than neonates (see *Warnings and precautions*).

Lidocaine (contained in the solvent for i.m. injection)

Immune system disorders

Rare: Anaphylactic reactions.

Psychiatric disorders

Common: Nervousness, anxiety, euphoria, confusion.

Nervous system disorders

Common: Dizziness, paraesthesia, drowsiness, sensitivity to touch, tremor, dysarthria, convulsions, loss of consciousness.

Rare: Neuropathy.

Eye disorders

Common: Blurred vision, diplopia.

Ear and labyrinth disorders

Common: Tinnitus.

Uncommon: Hyperacusis.

Cardiac disorders

Common: Bradycardia, hypotension, hypertension.

Rare: Arrhythmias, cardiovascular collapse, cardiac arrest.

Respiratory, thoracic and mediastinal disorders

Common: Respiratory depression, respiratory arrest.

Gastrointestinal disorders

Common: Nausea, vomiting.

Skin and subcutaneous tissue disorders

Not known: Cutaneous lesions, urticaria.

Musculoskeletal and connective tissue disorders

Common: Muscle twitching.

General disorders and administration site conditions

Common: Oedema, sensation of cold or heat.

Reporting of suspected adverse reactions after marketing authorisation is very important.

It allows continued monitoring of the benefit/risk balance of the medicinal product.

Healthcare professionals are asked to report any suspected new or serious adverse reaction.

Overdose

Ceftriaxone

Excessive plasma concentrations of ceftriaxone cannot be reduced by haemodialysis or peritoneal dialysis. Symptomatic measures are recommended for the treatment of patients following overdosage.

Lidocaine (*contained in the solvent for i.m. injection)*

The toxic reactions to lidocaine overdose mainly involve the central nervous system (CNS) and cardiovascular system. CNS toxicity follows a progressive course, i.e. with the symptoms increasing continuously in severity.

The symptoms listed below appear immediately (i.e. within 1-3 minutes) following accidental intravascular injection, but only with a delay of 20-30 minutes in the case of overdose.

Early symptoms of overdose are: yawning, paraesthesia (chiefly circumoral), light-headedness, restlessness, dizziness, tinnitus, hypoacusis, visual disturbances, dysarthria and ataxia, and nausea and vomiting. In moderate overdose there may also be muscle twitching or spasms with subsequent generalised convulsions, possibly followed by unconsciousness, respiratory depression and coma.

Severe cases additionally lead to effects on the cardiovascular system (usually only after the onset of CNS symptoms). Symptoms include hypotension, bradycardia and arrhythmias. Very severe overdose may result in complete AV block and cardiovascular arrest.

If there is evidence of acute systemic toxicity, the injection should be immediately stopped. There is no specific antidote, and treatment of overdose is symptomatic. In the event of cardiovascular arrest, rapid cardiopulmonary resuscitation is indicated, including treatment of acidosis.

Properties and effects

ATC code: J01DD04

Mechanism of action

The bactericidal efficacy of ceftriaxone results from inhibition of cell wall synthesis. Ceftriaxone exerts broad-spectrum activity *in vitro* against gram-negative and gram-positive microorganisms. Ceftriaxone is highly stable to most β-lactamases – both penicillinases and cephalosporinases – of gram-positive and gram-negative bacteria.

Pharmacodynamics

Ceftriaxone is usually active against the following microorganisms *in vitro* and in clinical infections (see *Indications*):

Gram-positive aerobes	Median values	
	MIC_{50}* (in mg/l)	MIC_{90}** (in mg/l)
Staphylococcus aureus (methicillin-sensitive)	4	4
Staphylococci, coagulase-negative	4	16
Streptococcus pyogenes (beta-haemolytic, group A)	0.03	0.03
Streptococcus agalactiae (beta-haemolytic, group B)	≤ 0.06	0.06
Streptococci, beta-haemolytic (non group A or B)	≤ 0.06	0.06
Streptococcus viridans	0.125	0.5
Streptococcus pneumoniae	≤ 0.06	0.06

*MIC_{50} = Minimum inhibitory concentration for 50% of tested strains

**MIC_{90} = Minimum inhibitory concentration for 90% of tested strains

Gram-negative aerobes	Median values	
	MIC_{50} (in mg/l)	MIC_{90} (in mg/l)
Acinetobacter lwoffi	2	8
Acinetobacter anitratus[1] (mostly *A. baumanii*)	8	32
Aeromonas hydrophila	0.25	4
Alcaligenes faecalis	1	8
Alcaligenes odorans	≤ 0.25	0.5
Alcaligenes-like bacteria	≤ 0.25	0.5
Borrelia burgdorferi	≤ 0.06	≤ 0.06
Burkholderia cepacia	2	16
Capnocytophaga spp.	≤ 0.06	4
Citrobacter diversus (including *C. amalonaticus*)	0.125	0.125
Citrobacter freundii[1]	0.125	16
Escherichia coli	≤ 0.06	0.125
Enterobacter aerogenes[1]	2	16
Enterobacter cloacae[1]	0.5	16
Enterobacter spp. (other)[1]	0.25	32
Haemophilus ducreyi	0.004	0.004
Haemophilus influenzae	≤ 0.008	0.06
Haemophilus parainfluenzae	0.016	0.06
Hafnia alvei	0.125	2
Klebsiella oxytoca	≤ 0.06	0.125
Klebsiella pneumoniae[2]	≤ 0.06	0.125
Moraxella catarrhalis (formerly *Branhamella catarr.*)	0.125	0.5
Moraxella osloensis	≤ 0.25	≤ 0.25
Moraxella spp. (other)	≤ 0.25	≤ 0.25
Morganella morganii	0.06	1
Neisseria gonorrhoeae	≤ 0.008	0.06
Neisseria meningitidis	≤ 0.008	0.008
Pasteurella multocida	≤ 0.06	0.06
Plesiomonas shigelloides	≤ 0.06	0.06
Proteus mirabilis	≤ 0.06	0.06
Proteus penneri[1]	1	64
Proteus vulgaris	≤ 0.06	2
Pseudomonas fluorescens[1]	16	64
Pseudomonas spp. (other)[1]	8	16
Providencia rettgeri	≤ 0.06	2
Providencia spp. (other)	≤ 0.06	0.5
Salmonella typhi	≤ 0.06	0.125
Salmonella spp. (*enteritidis* group)	≤ 0.06	0.06
Serratia marcescens	0.5	2
Serratia spp. (other)	0.25	16
Shigella spp.	0.03	0.25
Vibrio spp.	≤ 0.06	0.25
Yersinia enterocolitica	≤ 0.125	0.125
Yersinia spp. (other)	0.25	2

Anaerobes	Median values

	MIC_{50} (in mg/l)	MIC_{90} (in mg/l)
Bacteroides spp.[3] (bile-sensitive)	2	16
Clostridium spp. (excluding the *C. perfringens* group)	2	16
Fusobacterium nucleatum	1	2
Fusobacterium spp. (other)	0.125	0.25
Gaffkia anaerobica (formerly *Peptococcus*)	0.125	1
Peptostreptococci	0.125	1

Susceptibility to ceftriaxone can be determined by the disk diffusion test or by the agar or broth dilution test using standardised techniques for susceptibility testing such as those recommended by the Clinical and Laboratory Standards Institute (CLSI). The CLSI issued the following interpretative breakpoints for tests with ceftriaxone:

	Susceptible	Moderately susceptible	Resistant
Dilution test Inhibitory concentrations in mg/l	≤ 8	16–32	≥ 64
Diffusion test (disk with 30 µg ceftriaxone) Inhibition zone diameter in mm	≥ 21	20–14	≤ 13

Microorganisms should be tested with the ceftriaxone disk, since it has been shown by *in vitro* tests to be active against certain strains resistant to cephalosporin class disks.

Instead of CLSI recommendations, alternative standardised guidelines such as those issued by DIN or ICS can be used to determine resistance.

Resistances

1) Some isolates of these species are resistant to ceftriaxone due to derepression of chromosomal β-lactamase.
2) Some isolates of *Klebsiella pneumoniae* are resistant to ceftriaxone due to plasmid-dependent β-lactamase production.
3) Some isolates of *Bacteroides* spp. are resistant to ceftriaxone.

Many strains of β-lactamase-producing *Bacteroides* spp. (notably *B. fragilis*) are resistant.

Clostridium difficile is resistant.

Methicillin-resistant *Staphylococcus* spp. are resistant to cephalosporins, including ceftriaxone. In general, *Enterococcus faecalis*, *Enterococcus faecium* and *Listeria monocytogenes* are resistant.

Many strains of gram-negative aerobes that possess multiple resistance to other antibiotics, e.g. aminopenicillins and ureidopenicillins, older cephalosporins and aminoglycosides, are susceptible to ceftriaxone. *Treponema pallidum* is sensitive *in vitro* and in animal experiments. Clinical trials indicate that primary and secondary syphilis respond well to ceftriaxone therapy.

With few exceptions, clinical isolates of *Pseudomonas aeruginosa* are resistant to ceftriaxone.

Lidocaine:

Lidocaine (contained in the solvent for i.m. injection) is an anilide-type local anaesthetic with rapid onset and medium duration of action that reversibly blocks nerve conduction close to the injection site. The local anaesthetic effect appears a few minutes after intramuscular injection of Rocephin and lasts for 45 to 60 minutes.

Clinical efficacy

Not applicable.

Pharmacokinetics

The pharmacokinetics of ceftriaxone are nonlinear and all pharmacokinetic parameters except elimination half-life are dose-dependent if based to total concentration (free and protein-bound ceftriaxone), 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 intravenous injection or infusion. A maximum plasma concentration of 81 mg/l was reached after 2–3 h after i.m. injection of 1 g ceftriaxone. Single i.v. infusion of 1 g, a concentration of 168.1 ± 28.2 mg/l was reached after 30 min. After a single i.v. infusion of 2 g, a concentration of 256.9 ± 16.8 mg/l was reached after 30 min.

The areas under the plasma-concentration-time curves after i.v. and i.m. administration are identical. This means that the bioavailability of intramuscularly administered ceftriaxone is 100%.

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 distribution volume is between 7 and 12 l.

On intravenous administration ceftriaxone diffuses rapidly into interstitial body fluid, where bactericidal concentrations against susceptible organisms are maintained for 24 hours.

After a dose of 1–2 g, ceftriaxone shows good penetration into tissue and body fluids. Concentrations above the minimal inhibitory concentrations for most pathogens are maintained for more than 24 hours in over 60 tissues or body fluids, including lung, heart, biliary tract, liver, middle ear, nasal mucosa and bone as well as cerebrospinal, pleural, synovial and prostatic fluids.

Ceftriaxone is reversibly bound to albumin. Plasma protein binding is about 95% at plasma concentrations below 100 mg/l. Binding is subject to saturation kinetics and the bound portion decreases with rising concentration (up to 85% at a plasma concentration of 300 mg/l).

Penetration into particular tissues

Ceftriaxone crosses the meninges. Penetration is greatest when the meninges are inflamed. Mean peak ceftriaxone concentrations in the cerebrospinal fluid (CSF) of patients with bacterial meningitis are 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 to 6 hours after intravenous injection.

Ceftriaxone crosses the placental barrier. Ceftriaxone is excreted in breast milk at low concentrations (3–4% of maternal plasma concentrations after 4–6 hours).

Metabolism

Ceftriaxone is not metabolised systemically but is converted to inactive metabolites by gut flora after biliary excretion into the intestinal lumen.

Elimination

Plasma clearance is 10–22 ml/min.

Renal clearance is 5–12 ml/min.

50–60% of ceftriaxone is excreted unchanged via the kidneys, while 40–50% is excreted unchanged in the bile.

The plasma half-life in adults is about 8 hours.

Kinetics in specific patient groups

Children

The half-life of ceftriaxone is prolonged in neonates. Within the first 14 days after birth, the concentration 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 patients

In persons aged over 75 years, the average plasma half-life is approximately 2–3 times that in healthy young adults.

Renal impairment

In patients with mild to moderate renal impairment, the pharmacokinetics of ceftriaxone are only minimally altered. The plasma half-life is moderately increased (less than two-fold) even in patients with severely impaired renal function.

The moderate increase in half-life in patients with renal impairment is explained by a compensatory increase in non-renal clearance of the increased free fraction of ceftriaxone due to a decrease in protein binding.

Hepatic impairment

In patients with hepatic dysfunction, the pharmacokinetics of ceftriaxone are only minimally altered and the plasma half-life is only slightly increased (less than two-fold), due to a compensatory increase in renal clearance. A further factor is the increase in the plasma protein free fraction of ceftriaxone, which contributes to the observed paradoxical increase in total drug clearance. There is also an increase in volume of distribution in line with the increase in total clearance.

Patients with severe renal and hepatic impairment

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

Lidocaine (contained in the solvent for i.m. injection): description of single-agent pharmacokinetics

Absorption

Lidocaine is rapidly absorbed, the rate of absorption being dependent on the vascularisation of the injection site.

Distribution

Plasma protein binding of lidocaine is concentration-dependent, binding decreasing with increasing concentration. At concentrations of 1 to 5 µg/ml, 60 to 80% of lidocaine is protein-bound. The steady-state volume of distribution is 91 litres.

Lidocaine crosses the placental barrier. However, total concentrations in the fetus are lower than in the mother because plasma protein binding in the fetus is lower than in the mother.

Lidocaine passes into breast milk in small amounts.

Metabolism

Lidocaine is mainly metabolised in the liver with the involvement of several CYP450 enzymes (e.g. CYP3A4 and CYP1A2). The main metabolites of lidocaine are monoethylglycine xylidide, glycinexylidide, 2,6-dimethylaniline and 4-hydroxy-2,6-dimethylaniline. Monoethylglycine xylidide and glycinexylidide are pharmacologically active, but their activity is weaker than that of the parent compound.

Elimination

Lidocaine undergoes predominantly renal elimination, with about 73% of the administered dose recovered in the urine as 4-hydroxy-2,6-dimethylaniline metabolite. Only 3% of lidocaine is excreted unchanged via the kidneys.

Plasma clearance of lidocaine following administration of an intravenous bolus injection is 9 to 10 ml/min/kg.

After intravenous bolus injection of lidocaine, the elimination half-life was 1.5 to 2 hours, and that of the active metabolites up to 10 hours. Glycinexylidide may accumulate after long-term administration.

Kinetics in specific patients groups

Paediatric population: The elimination half-life in neonates (3.2 hours) is approximately twice that in adults.

Hepatic impairment: The half-life of lidocaine after intravenous administration was increased approximately 3-fold in patients with hepatic impairment.

Renal impairment: Mild to moderate renal impairment (CrCl 30 to 60 ml/min) does not affect lidocaine pharmacokinetics, but may increase accumulation of the glycinexylidide metabolite. In patients with severe renal impairment (CrCl < 30 ml/min), lidocaine clearance was reduced by about half and its half-life approximately doubled.

Lidocaine is dialysable.

Preclinical data

Ceftriaxone

Genotoxicity

Ceftriaxone was not mutagenic *in vitro* in bacterial and mammalian cell cultures, nor clastogenic in the *in vivo* mouse micronucleus assay.

Carcinogenicity

No carcinogenicity studies have been performed to determine the carcinogenic potential of Rocephin.

Impairment of fertility

No effects on male or female fertility were observed in rat studies.

Reproductive toxicity

No embryotoxic or teratogenic effects were found in studies in mice, rats and monkeys.

Lidocaine (contained in the solvent for i.m. injection)

Mutagenicity, carcinogenicity

Lidocaine showed no genotoxic potential in mutagenicity studies. There is evidence, however, that the metabolite 2,6-xylidine has mutagenic properties and tumorigenic potential (tumours chiefly in the nasal cavity). The relevance of these findings to humans is unclear. Lidocaine should therefore not be administered for a prolonged period and at high doses.

Reproductive toxicity

In a study in male and female rats, lidocaine 30 mg/kg daily was administered orally for 8 months. No evidence of reproductive toxicity had been found in the pups by the time of weaning.

Other information

Incompatibilities

Rocephin should not be added to calcium-containing solutions such as Hartmann's solution or Ringer's solution (see *Contraindications*, *Warnings and precautions* and *Interactions*).

Ceftriaxone is incompatible with amsacrine, vancomycin, fluconazole and amino-glycosides.

Rocephin may be mixed only with the medicines specified in *Instructions for use and handling*.

Influence on diagnostic methods

During treatment with Rocephin the Coombs test may become false-positive. Rocephin, like other antibiotics, may also result in false-positive tests for galactosaemia.

Likewise, non-enzymatic methods for the determination of glucose in urine may give false-positive results. For this reason, urinary glucose determination during therapy with Rocephin should be done enzymatically.

Ceftriaxone may cause erroneously low readings for estimated blood glucose values with some blood glucose monitoring systems. Please refer to the instructions for use for the specific system. Alternative testing methods should be used if necessary.

Shelf life

Do not use this medicine after the expiry date (EXP) stated on the container.

Shelf life after opening

Reconstituted solutions retain their physical and chemical stability for 6 hours at room temperature (or 24 hours in the refrigerator at 2–8°C). For microbiological reasons the reconstituted solutions must be used immediately after preparation.

Special precautions for storage

Keep out of the reach of children.

Do not store above 30°C. Keep the container in the outer carton to protect the contents from light.

Instructions for use and handling

Reconstituted solutions range in colour from pale yellow to yellow-brown, depending on the concentration. This characteristic of the active ingredient is of no significance for the efficacy or tolerability of the drug.

Intramuscular injection

For i.m. injection, Rocephin 0.25 g is dissolved in 2 ml, and Rocephin 1 g in 3.5 ml, of 1% lidocaine solution and injected well within a relatively large mass of muscle. It is recommended that not more than 1 g be injected at one site.

The lidocaine-containing solution must never be administered intravenously (see *Contraindications* and *Warnings and precautions*).

Intravenous injection

For i.v. injection, Rocephin 500 mg is dissolved in 5 ml, and Rocephin 1 g in 10 ml, water for injections and injected intravenously over a period of 2–4 minutes.

Intravenous infusion

The infusion should last at least 30 minutes. For i.v. 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% + glucose 2.5%, glucose 5%, glucose 10%, dextran 6% in glucose 5%, water for injections.

Owing to possible incompatibility, Rocephin solutions should not be mixed with or piggy-backed into solutions containing other antibiotics. Similarly, they must not be added to diluent solutions other than those listed above.

Nevertheless, 2 g ceftriaxone and 1 g ornidazole are physically and chemically compatible in 250 ml physiological sodium chloride or glucose solution.

Diluents containing calcium (e.g. Ringer’s solution or Hartmann’s solution) must not be used to reconstitute Rocephin vials or to further dilute a reconstituted vial for intravenous administration because precipitates may form. Calcium ceftriaxone precipitates may also form when Rocephin is mixed with calcium-containing solutions in the same infusion line.

Rocephin must not be administered simultaneously with calcium-containing infusion solutions, including continuous calcium-containing infusions such as in parenteral nutrition via a Y-site. However, in patients other than neonates, Rocephin and calcium-containing solutions may be administered consecutively if the infusion lines are thoroughly flushed between infusions with a compatible solution (see *Interactions* with other medicinal products and other forms of interaction).

Weight-based dosing
The displacement volume of 1 g of ceftriaxone sodium powder in water for injection and in 1% lidocaine hydrochloride solution is approximately 0.71 ml. To accommodate weight-based dosing (especially in children up to the age of 12 years), the solvent volume must be adjusted if only part of the total solution is measured and administered. Please refer to Table 1 below to prepare a final solution at a specified concentration.

Table 1: Summary of volumes required to produce the necessary reconstitution concentrations

Solutions for intramuscular injection			
Rocephin product (nominal content)	**Volume of 1% lidocaine solution to add:**	**Resulting solution for injection**	
		Approximate volume	**Concentration**
250 mg	1.9 ml	2.1 ml	125 mg/ml
500 mg	1.7 ml	2.1 ml	250 mg/ml
1 g	2.9 ml	3.6 ml	285 mg/ml
Solutions for intravenous injection			
Rocephin product (nominal content)	**Volume of water for injection to add:**	**Resulting solution for injection**	
		Approximate volume	**Concentration**
250 mg	4.9 ml	5.1 ml	50 mg/ml
500 mg	4.7 ml	5.1 ml	100 mg/ml
1 g	9.4 ml	10.1 ml	100 mg/ml
Solutions for intravenous infusion			
Rocephin product (nominal content)	**Volume of**	**Resulting solution for infusion**	

	calcium-free solution for infusion to add:	Approximate volume	Concentration
2 g	39 ml	40.4 ml	50 mg/ml

Disposal of unused or expired medicinal products
The release of pharmaceutical preparations into the environment should be reduced to a minimum. Medicinal products should not be disposed of via the wastewater system and disposal in domestic waste should be avoided. Any medicinal products unused after the end of treatment or by the expiry date should be returned in their original packaging to the place of supply (physician or pharmacist) for proper disposal.

Packs

Packs for i.m. injection containing:

1 vial with active ingredient dry substance equivalent to 0.25 g, 0.5 g or 1 g ceftriaxone, and 1 ampoule of 2 ml or 3.5 ml 1% lidocaine solution

0.25 g vials	1, 5, 50
0.5 g vials	1, 5, 50
1 g vials	1, 5, 50

Packs for i.v. injection containing:

1 vial with active ingredient dry substance equivalent to 0.25 g, 0.5 g or 1 g ceftriaxone, and 1 ampoule of 5 ml or 10 ml water for injections

0.25 g vials	1, 5, 50
0.5 g vials	1, 5, 50
1 g vials	1, 5, 50

Packs for i.v. infusion containing:

1 vial with active ingredient dry substance equivalent to 2 g ceftriaxone

2 g vials	1, 50

Not all presentations might be marketed in your country

This is a medicament

A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.

Follow strictly the doctor’s prescription, the method of use and the instructions of the pharmacist who sold the medicament.

The doctor and the pharmacist are experts in medicine, its benefits and risks.

Do not by yourself interrupt the period of treatment prescribed for you.

Do not repeat the same prescription without consulting your doctor.

Medicine: keep out of reach of children

Council of Arab Health Ministers

Union of Arab Pharmacists

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