

IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0050/062/007

Case No: 2075450

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Roche Products Ltd

6 Falcon Way, Shire Park, Welwyn Garden City, AL7 1TW, United Kingdom

an authorisation, subject to the provisions of the said Regulations, in respect of the product

ROCEPHIN, 2 g Grams

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **02/11/2008**.

Signed on behalf of the Irish Medicines Board this

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Rocephin 2 g powder for solution for injection or infusion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 2 g vial contains 2 g ceftriaxone as 2.39 g ceftriaxone sodium.

3 PHARMACEUTICAL FORM

Powder for solution for injection or infusion.

White to yellowish-orange crystalline powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Ceftriaxone is indicated for the treatment of the following infections when known or likely to be due to one or more susceptible micro-organisms (see section 5.1) and when parenteral therapy is required:

- Respiratory tract infections including pneumonia, acute and chronic bronchitis and ear, nose and throat infections.
- Renal and urinary tract infections.
- Septicaemia.
- Meningitis.
- Abdominal infections including peritonitis and infections of the biliary tract.
- Soft tissue infections including cellulitis and wound infections.
- Gonorrhoea.
- Peri-operative prophylaxis of infections associated with surgery. Infections in patients with impaired defence mechanisms.

Treatment may be started before the results of susceptibility tests are known.

Consideration should be given to official guidance on the appropriate use of anti-bacterial agents.

4.2 Posology and method of administration

Rocephin may be administered by deep intramuscular injection, slow intravenous injection, or as a slow intravenous infusion, after reconstitution of the solution according to the directions given below and also see section 6.6. Dosage and mode of administration should be determined by the severity of the infection, susceptibility of the causative organism and the patient's condition. Under most circumstances a once-daily dose - or, in the specified indications, a single dose - will give satisfactory therapeutic results.

Adults and children 12 years and over

Standard therapeutic dosage

1 g once daily.

Severe infections

2 – 4 g daily, normally as a single dose every 24 hours.

The duration of therapy varies according to the course of the disease. As with antibiotic therapy in general, administration of Rocephin 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.

Acute, uncomplicated gonorrhoea

A single dose of 250 mg intramuscularly should be administered. Simultaneous administration of probenecid is not indicated.

Peri-operative prophylaxis

Usually 1 g as a single intramuscular or slow intravenous dose 30-90 minutes prior to surgery. In colorectal surgery, 2 g should be given intramuscularly, by slow intravenous injection or by slow intravenous infusion, in conjunction with a suitable agent against anaerobic bacteria.

Elderly

These dosages do not require modification in elderly patients provided that renal and hepatic function is satisfactory (see below).

Children under 12 years

Standard therapeutic dosage

20 – 50 mg/kg body-weight once daily.

Up to 80 mg/kg body-weight daily may be given in severe infections, except in neonates where a daily dosage of 50 mg/kg should not be exceeded. For children with body weights of 50 kg or more, the usual adult dosage should be used. Doses of 50 mg/kg or over should be given by slow intravenous infusion over at least 30 minutes.

Renal and hepatic impairment

In patients with impaired renal function, there is no need to reduce the dosage of Rocephin provided liver function is intact. Only in cases of pre-terminal renal failure (creatinine clearance < 10ml per minute) should the daily dosage be limited to 2 g or less.

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

In severe renal impairment accompanied by hepatic insufficiency, the plasma concentration of Rocephin should be determined at regular intervals in order to ensure that the plasma level is in excess of the minimum inhibitory concentration of the causative organism(s), assuming this is sensitive, and dosage adjusted so that accumulation of Rocephin does not occur.

In patients undergoing dialysis, no additional supplementary dosing is required following the dialysis. Serum concentrations should be monitored, however, to determine whether dosage adjustments are necessary, since the elimination rate in these patients may be reduced.

4.3 Contraindications

Hypersensitivity to ceftriaxone or to any of the cephalosporins.

Previous immediate and/or severe hypersensitivity reaction to penicillin or to any other type of beta-lactam drug.

Rocephin should not be given to neonates with jaundice or to those who are hypoalbuminaemic or acidotic or have other conditions, such as prematurity, in which bilirubin binding is likely to be impaired and who are therefore at risk of developing bilirubin encephalopathy.

Treatment with other calcium containing medicinal products because of the risk of precipitation of ceftriaxone-calcium salt in term newborns.

4.4 Special warnings and precautions for use

The stated dosage should not be exceeded.

As with other cephalosporins, anaphylactic shock cannot be ruled out even if a thorough patient history is taken.

Before therapy with ceftriaxone 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 drug. Ceftriaxone is contraindicated in patients who have had a previous hypersensitivity reaction to any cephalosporin. It is also contraindicated in patients who have had a previous immediate and/or any severe hypersensitivity reaction to any penicillin and to any other beta-lactam drug. Ceftriaxone should be given with caution to patients who have had any other type of hypersensitivity reaction to penicillin or any other beta-lactam drug.

Ceftriaxone should be given with caution to patients who have other allergic diatheses.

In severe renal impairment accompanied by hepatic insufficiency, dosage reduction is required as outlined under section 4.2

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including ceftriaxone. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea subsequent to administration of antibacterial agents.

As with other cephalosporins, prolonged use of ceftriaxone may result in the overgrowth of non-susceptible organisms, such as *enterococci* and *Candida* spp.

Ceftriaxone 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 hrs of the last administration of ceftriaxone (see sections 4.3, 4.8 and 6.2).

Shadows which have been mistaken for gallstones have been detected by 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 Rocephin therapy. Rarely, have these findings been associated with symptoms. In symptomatic cases, conservative non-surgical management is recommended. Discontinuation of Rocephin treatment in symptomatic cases should be at the discretion of the clinician.

Cases of pancreatitis, possibly 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.

Safety and effectiveness of Rocephin in neonates, infants and children have been established for the dosages in the section 4.2 *In vitro* studies have shown that ceftriaxone, like some other cephalosporins, can displace bilirubin from serum albumin. Caution should be exercised before Rocephin is administered to hyperbilirubinaemic neonates, especially if they are premature. Rocephin should not be used in neonates (especially prematures) at risk of developing bilirubin encephalopathy.

During treatment, the blood cell count should be checked regularly.

Each gram of Rocephin contains approximately 3.6 mmol sodium. To be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

No impairment of renal function has been observed in man after simultaneous administration of Rocephin with diuretics.

No interference with the action or increase in nephrotoxicity of aminoglycosides has been observed during simultaneous administration with Rocephin.

The ceftriaxone molecule does not contain the N-methylthio-tetrazole substituent which has been associated with a disulfiram-like effect when alcohol is taken during therapy with certain cephalosporins.

Simultaneous administration of probenecid does not reduce the elimination of Rocephin and its use with Rocephin is not indicated.

In vitro, chloramphenicol has been shown to be antagonistic with respect to ceftriaxone and other cephalosporins. The clinical relevance of this finding is unknown, but caution is advised if concurrent administration of ceftriaxone with chloramphenicol is proposed.

In patients treated with Rocephin, the Coombs' test may rarely become false-positive. Rocephin, like other antibiotics, may result in false-positive tests for galactosaemia. Likewise, non-enzymatic methods for glucose determination in urine may give false-positive results. For this reason, urine-glucose determination during therapy with Rocephin should be done enzymatically.

Ceftriaxone may adversely affect the efficacy of oral hormonal contraceptives. Consequently, it is advisable to use supplementary (non-hormonal) contraceptive measures during treatment and for seven days after treatment.

4.6 Pregnancy and lactation

Pregnancy

For ceftriaxone limited clinical data on exposed pregnancies are available. Ceftriaxone crosses the placental barrier. Reproductive studies in animals have shown no evidence of embryotoxicity, foetotoxicity, teratogenicity or adverse effects on male or female fertility, birth or perinatal and postnatal development. In primates, no embryotoxicity or teratogenicity has been observed. Since safety in human pregnancy is not established ceftriaxone should not be used unless absolutely indicated.

Lactation

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

4.7 Effects on ability to drive and use machines

None.

4.8 Undesirable effects

Rarely severe adverse reactions have been reported in preterm and full-term newborns. These reactions have caused death in some cases. These newborns had been treated with intravenous ceftriaxone and calcium. Some of them had received ceftriaxone and calcium at different times and on different intravenous lines. Precipitation of ceftriaxone-calcium salt has been observed in lungs and kidneys of these dead preterm newborns. The high risk of precipitation is due to the low blood volume of the newborns. Moreover the half life is longer than in adults (see sections 4.3, 4.4 and 6.2).

The most frequently reported adverse events for ceftriaxone are diarrhoea, nausea and vomiting. Other reported adverse events include hypersensitivity reactions such as allergic skin reactions and anaphylactic reactions, secondary infections with yeast, fungi or resistant organisms as well as changes in blood cell counts.

Infections and infestations

Rare ($\geq 0.01\%$ - $< 0.1\%$): Mycosis of the genital tract.

Superinfections of various sites with yeasts, fungi or other resistant organisms are possible.

Blood and lymphatic system disorders

Rare ($\geq 0.01\%$ - $< 0.1\%$): Neutropenia, leucopenia, eosinophilia, thrombocytopenia, anaemia (including haemolytic anaemia), slight prolongation of the prothrombin time.

Vary rare ($< 0.01\%$) including isolated reports: Positive Coombs' test, coagulation disorders, agranulocytosis ($< 500/m^3$), mostly after 10 days of treatment and following total doses of 20g ceftriaxone and more.

Immune system disorders

Rare ($\geq 0.01\%$ - $< 0.1\%$): Anaphylactic (e.g. bronchospasm) and anaphylactoid reactions (see section 4.4)

Nervous system disorders

Rare ($\geq 0.01\%$ - $< 0.1\%$): Headache, dizziness.

Gastrointestinal disorders

Common ($\geq 1\%$ - $< 10\%$): Loose stools or diarrhoea, nausea, vomiting.

Rare ($\geq 0.01\%$ - $< 0.1\%$): Stomatitis, glossitis. These side effects are usually mild and commonly disappear during treatment or after discontinuation of treatment.

Very rare ($< 0.01\%$) including isolated reports: Pseudomembranous colitis (mostly caused by *Clostridium difficile*), pancreatitis (possibly caused by obstruction of the bile ducts).

Hepato-biliary disorders

Rare ($\geq 0.01\%$ - $< 0.1\%$): Increase in liver serum enzymes (AST, ALT, alkaline phosphatase), jaundice.

Precipitation of ceftriaxone calcium salt in the gallbladder had been observed (see section 4.4), mostly in patients treated with doses higher than the recommended standard dose. In children, prospective studies have shown a variable incidence of precipitation with intravenous application, in some studies to above 30%. The incidence seems to be lower with slow infusion (20-30 minutes). This effect is usually asymptomatic, but in rare cases, the precipitations have been accompanied by clinical symptoms such as pain, nausea and vomiting. Symptomatic treatment is recommended in these cases. Precipitation is usually reversible upon discontinuation of ceftriaxone.

Skin and subcutaneous tissue disorders

Uncommon ($\geq 0.1\%$ - $< 1\%$): Allergic skin reactions such as maculopapular rash or exanthema, urticaria, dermatitis, pruritis, oedema.

Very rare ($< 0.01\%$) including isolated reports: Erythema multiforme, Stevens Johnson Syndrome, Lyell's Syndrome/toxic epidermal necrolysis.

Renal and urinary disorders

Rare ($\geq 0.01\%$ - $< 0.1\%$): Increase in serum creatinine, oliguria, glycosuria, haematuria.

Very rare ($< 0.01\%$) including isolated reports: Renal precipitation, mostly in children older than 3 years who have been treated with either high daily doses (80mg/kg/day and more) or total doses exceeding 10g and with other risk factors such as dehydration or immobilisation. Renal precipitation is reversible upon discontinuation of ceftriaxone. Anuria and renal impairment have been reported in association.

General disorders and administration site conditions

Rare ($\geq 0.01\%$ - $< 0.1\%$): Phlebitis and injection site pain following intravenous administration. This can be minimised by slow injection over at least 2-4 minutes. Rigors, pyrexia.

An intramuscular injection without lidocaine is painful.

4.9 Overdose

In the case of overdosage, drug concentrations would not be reduced by haemodialysis or peritoneal dialysis. There is no specific antidote. Treatment should be symptomatic.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Ceftriaxone is a long-acting, broad spectrum cephalosporin antibiotic for parenteral use.

The bactericidal activity of ceftriaxone results from inhibition of cell wall synthesis. Ceftriaxone exerts *in vitro* activity against a wide range of Gram-negative and Gram-positive organisms including both aerobic and anaerobic species. Ceftriaxone is highly stable to most beta-lactamases, both penicillinases and cephalosporinases, of Gram-positive and Gram-negative bacteria.

The outstanding feature of Rocephin is its relatively long plasma elimination half-life of approximately 8 hours, which makes single or once-daily dosage of the drug appropriate for most patients.

Microbiology

Ceftriaxone is usually active against the following micro-organisms *in vitro* and in clinical infections (see section 4.1 Therapeutic indications). The list is not exhaustive and focuses on those organisms of particular clinical interest.

Gram-positive aerobes

Staphylococcus aureus (including penicillinase-producing strains)

Staphylococcus epidermidis

Streptococcus pneumoniae

Streptococcus group A (*Streptococcus pyogenes*)

Streptococcus group B (*Streptococcus agalactiae*)

Streptococcus viridans

Streptococcus bovis

Note

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

Gram-negative aerobes

Aeromonas spp.
Alcaligenes spp.
Moraxella catarrhalis (beta-lactamase negative and positive)
Citrobacter spp.
Enterobacter spp. (some strains are resistant)
Escherichia coli
Haemophilus ducreyi
Haemophilus influenzae (including penicillinase-producing strains)
Haemophilus parainfluenzae
Klebsiella spp. (including *K. pneumoniae*)
Moraxella spp.
Morganella morganii (= *Proteus morganii*)
Neisseria gonorrhoeae (including penicillinase-producing strains)
Neisseria meningitidis
Plesiomonas shigelloides
Proteus mirabilis
Proteus vulgaris
Providencia spp.
Pseudomonas spp. (some strains are resistant)
Salmonella spp. (including *S. typhi*)
Serratia spp. (including *S. marcescens*)
Shigella spp.
Vibrio spp. (including *V. cholerae*)
Yersinia spp. (including *Y. enterocolitica*)

Note

Many strains of the above organisms multiply resistant to other antibiotics, e.g. penicillins, older cephalosporins and aminoglycosides, are susceptible to ceftriaxone. *Treponema pallidum* is sensitive *in vitro* and in animal experiments. Clinical investigations indicate that primary and secondary syphilis respond well to ceftriaxone therapy. With a few exceptions clinical *P. aeruginosa* isolates are resistant to ceftriaxone.

Synergy between Rocephin and aminoglycosides has been demonstrated with many Gram-negative bacilli under experimental conditions. Although enhanced activity of such combinations is not always predictable, it should be considered in severe, life-threatening infections due to organisms such as *Pseudomonas aeruginosa*. Because of physical incompatibility the two drugs must be administered separately at the recommended dosages.

Anaerobic organisms

Bacteroides spp. (many strains notably *B. fragilis* are resistant)
Clostridium spp. (except *C. difficile*)
Fusobacterium spp. (except *F. mortiferum* and *F. varium*)
Gaffkia anaerobica (formerly *peptococcus*)
Peptostreptococcus spp.

Susceptibility to ceftriaxone can be determined by the disc diffusion test or by the agar or broth dilution test using standardised techniques for susceptibility testing such as those recommended by the National Committee for Clinical Laboratory Standards (NCCLS). The NCCLS issued the following interpretative breakpoints for ceftriaxone:

Dilution susceptibility testing

Susceptible ≤ 8mg/litre; moderately susceptible 16 - 32mg/litre; resistant ≥ 64mg/litre.

Diffusion susceptibility testing using a 30 microgram ceftriaxone disc

Susceptible ≥ 21 mm; moderately susceptible 20 - 14mm; resistant ≤ 13 mm.

Organisms should be tested with the ceftriaxone disc since it has been shown by *in vitro* tests to be active against certain strains resistant to cephalosporin class discs.

Where NCCLS recommendations are not in daily use, alternative, well standardised, susceptibility interpretative guidelines such as those issued by DIN, ICS and others may be substituted.

5.2 Pharmacokinetic properties

The pharmacokinetics of Rocephin are largely determined by its concentration-dependent binding to serum albumin. The plasma free (unbound) fraction of the drug in man is approximately 5% over most of the therapeutic concentration range, increasing to 15% at concentrations of 300mg/l. Owing to the lower albumin content, the proportion of free ceftriaxone in interstitial fluid is correspondingly higher than in plasma.

Plasma concentrations

Mean peak concentrations after bolus intravenous injection are about 120mg/l following a 500mg dose and about 200mg/l following a 1g dose; mean levels of 250mg/l are achieved after infusion of 2g over 30 minutes. Intramuscular injection of 500mg Rocephin in 1.06% Lidocaine produces mean peak plasma concentrations of 40 - 70mg/l within 1 hour. Bioavailability after intramuscular injection is 100%.

Excretion

Rocephin is eliminated mainly as unchanged ceftriaxone, approximately 60% of the dose being excreted in the urine (almost exclusively by glomerular filtration) and the remainder via the biliary and intestinal tracts. The total plasma clearance is 10 - 22ml/min. The renal clearance is 5 - 12ml/min. The elimination half-life in adults is about 8 hours. The half-life is not significantly affected by the dose, the route of administration or by repeated administration. Due to its high protein binding, ceftriaxone is not dialysable.

Pharmacokinetics in special clinical situations

In neonates, urinary recovery accounts for about 70% of the dose. In infants less than 8 days and in elderly persons aged over 75 years, the average elimination half-life is usually 2 to 3 times longer than in the young adult group. Dosage in the elderly need not be altered except as indicated under renal dysfunction.

In patients with renal or hepatic dysfunction, the pharmacokinetics of ceftriaxone are only minimally altered and the elimination half-life is only slightly increased. If kidney function alone is impaired, biliary elimination of ceftriaxone is increased; if liver function alone is impaired, renal elimination is increased.

Cerebrospinal fluid

Rocephin crosses non-inflamed and inflamed meninges, attaining concentrations 4 – 17% of the simultaneous plasma concentration.

5.3 Preclinical safety data

Not applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None.

6.2 Incompatibilities

Rocephin should not be mixed in the same syringe with any drug other than 1.06 % Lidocaine Injection (for intramuscular injection only).

Rocephin is not compatible with calcium-containing solutions such as Hartmann's solution and Ringer's solution (see sections 4.3, 4.4 and 4.8).

Based on literature reports ceftriaxone is not compatible with ampicillin, vancomycin, fluconazole or aminoglycosides.

6.3 Shelf Life

Three years.

Reconstituted product: Chemical and physical in-use stability has been demonstrated for 6 hours at or below 25°C or 24 hours at 2-8°C. The product must be protected from light. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless reconstitution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Do not store above 25°C. Keep vial in the outer carton in order to protect from light.

For storage of reconstituted product see section 6.3

6.5 Nature and contents of container

Type I Ph. Eur. clear glass vials with teflonised rubber stopper and aluminium cap containing a sterile, white to yellowish orange crystalline powder.

A plastic loop is attached to the vial for suspending the vial for use as an intravenous drip.

Rocephin 2 g vials, in packs of 1.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Preparation of solutions for injection and infusion

The use of freshly prepared solutions is recommended.

For single use only. Discard any unused content.

When reconstituted for intramuscular or intravenous injection or intravenous infusion, the white to yellowish-orange crystalline powder gives a pale yellow to amber solution. The displacement value of 250 mg of Rocephin is 0.194 ml.

Each gram of Rocephin contains approximately 3.6 mmol sodium.

Intramuscular injection

1 g Rocephin should be dissolved in 3.5 ml of 1.06 % Lidocaine Injection. The solution should be administered by deep intramuscular injection. Dosages greater than 1 g should be divided and injected at more than one site.

Solutions in Lidocaine must not be administered intravenously.

Intravenous injection

1 g Rocephin should be dissolved in 10 ml of Water for Injections BP. The injection should be administered over 2 -4 minutes, directly into the vein or via the tubing of an intravenous infusion.

Intravenous infusion: 2 g of Rocephin should be dissolved in 40 ml of one of the following calcium-free solutions: Dextrose Injection BP 5 % or 10 %, Sodium Chloride Injection BP, Sodium Chloride and Dextrose Injection BP (0.45 % sodium chloride and 2.5 % dextrose), dextran 6 % in Dextrose Injection BP 5 %, hydroxyethyl starch 6- 10 % infusions, sterile water for injection. The infusion should be administered over at least 30 minutes.

Solutions containing Rocephin should not be mixed with or added to solutions containing other agents. In particular, Rocephin is not compatible with calcium-containing solutions such as Hartmann's solution and Ringer's solution.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

PA 0050/062/007

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 2nd November 1983

Date of last renewal: 2nd November 2008

10 DATE OF REVISION OF THE TEXT

November 2009