



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Pursuant to Article 30 of Directive 2001/83/EC

Rocephin and associated names

International non-proprietary name: CEFTRIAXONE

Procedure No. EMEA/H/A-30/1302

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.



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1. Background information on the procedure

1.1. Background information on the basis of the grounds for referral

On 09 December 2011 the European Commission presented to the European Medicines Agency a referral under Article 30 of Directive 2001/83/EC, in order to harmonise the national summary of product characteristics (SmPC), labelling and package leaflet (PL) of the medicinal products:

Rocephin and associated names (see Annex I of CHMP opinion).

Further to the CHMP's consideration of the matter, the referral procedure was initiated at the February 2012 meeting. The marketing authorisation holder was informed of the start of the procedure.

The CHMP appointed Ian Hudson (UK) as rapporteur and Juris Pokrotnieks (LV) as co-rapporteur. In September 2013 the rapporteurship was transferred to Greg Markey.

Rocephin medicinal products are registered in the following EU Members States: Belgium, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Luxembourg, Malta, the Netherlands, Portugal, Romania, Sweden and United Kingdom and also in Iceland.

2. Scientific discussion during the referral procedure

2.1. Introduction

Rocephin contains ceftriaxone, a cephalosporin antibacterial agent with in-vitro activity against a range of Gram-positive and Gram-negative bacteria. Rocephin inhibits bacterial enzymes necessary for cell-wall synthesis (peptidoglycan synthesis) causing cell death.

Rocephin was first approved in Switzerland on 27 May 1982, which marks its International Birth Date (IBD). National approval was obtained in most of the European countries. Rocephin is approved in 19 EU Member States with different nationally approved Summaries of Product Characteristics (SmPCs).

In Europe, Rocephin is administered parenterally either by intramuscular injection, intravenous injection or infusion. The medicinal product is available in vials as powder for solution for injection or infusion. Strengths available are 250 mg, 500 mg, 1g and 2g. Not all strengths are marketed in all EU Member States. Solvent vials contain either sterile water for injections or 1% lidocaine hydrochloride solution.

Due to the divergent national decisions taken by Member States concerning the authorisation of Rocephin and associated names, the European Commission notified the EMA of an official referral under Article 30 of Directive 2001/83/EC in order to resolve divergences amongst the nationally authorised product information for the above-mentioned products and thus to harmonise them across the EU.

2.2. Critical Evaluation

For the preparation of the harmonised product information, the MAH considered the current registered SmPCs of all EU Member States with an active registration, the published literature and the cumulative safety experience with Rocephin as reported in the company's drug safety database and reflected in the appropriate sections of the company's Core Data Sheet (CDS).

The conclusions of the harmonisation of the different sections of the SmPC are discussed below.

Section 4.1 - Therapeutic indications

Indications that are authorised in at least 1 member state are discussed below:

Bacterial Meningitis

Austria, Belgium, Germany, Greece, Hungary, Ireland, Latvia, Luxembourg, Malta, Portugal, Romania and the UK have implemented the CDS wording "Meningitis". In the Netherlands and Sweden, "Bacterial meningitis" is included as an indication, whereas the SmPCs in Denmark and Iceland, contain the indication "prophylactic treatment of meningococcal disease".

Initial clinical studies were conducted in the 1980s and enrolled almost exclusively paediatric patients. Where available, the causative pathogens were representative for this indication and population. Most studies were open and controlled. Ampicillin, chloramphenicol (or a combination thereof) and cefotaxime were most commonly used as comparators. Concurrent bacteraemia was reportedly successfully treated in a number of cases.

The published clinical trial data that were submitted focus primarily on the paediatric population and mostly from non- European countries. Chloramphenicol was most frequently used as a comparator.

The outcomes reported and the definitions seem to differ quite considerably between these studies, making comparisons difficult. But overall, clinical "success" rates and where reported bacteriological eradication rates with ceftriaxone were high (>> 90%) and the point estimates in the studies were generally at least as good as those of the comparators.

Taking into account the data from clinical studies and considerable clinical experience with ceftriaxone in the treatment of meningitis in adults and children the CHMP agreed with the harmonised indication of "Bacterial meningitis".

Lower Respiratory Tract Infections (LRTI)

In Austria, Greece, Ireland, Portugal and Romania, the indication in the currently approved SmPC is "Respiratory tract infections particularly pneumonia", and in most member states LRTIs are approved in some form.

Current guidelines require indications to be specific where possible, as it was recognised that different clinical conditions summarised under LRTI have different etiology and therefore may require different treatment. For example, whether pneumonia was acquired in a hospital setting or not, provides additional clues to the pathogens involved and have led to definitions of hospital-acquired pneumonia (HAP) and community-acquired pneumonia (CAP).

The MAH has presented a number of small or moderate size studies in patients with LRTI, mostly bronchopneumonia. The studies were controlled, with cefotaxime, amoxicillin, cefamandole, penicillin G and tobramycin as comparators. Most studies were conducted in adults, one study in children enrolled patients aged 1 month to 2 years. The pathogens isolated in these studies suggest that both hospital and community acquired infections are likely to have been present.

Community-acquired pneumonia (CAP)

Ceftriaxone has been used as a comparator in several recently conducted clinical trials of newer antibacterial medicinal products including ceftaroline and ceftobiprole. The studies report similarly high success rates for both ceftriaxone and the comparator regimens. One paediatric study was also submitted by the MAH, which enrolled 48 patients aged 2 months to 5 years.

Overall, the CHMP considered that ceftriaxone, used as a comparator agent in EU licensing trials, is an appropriate agent for the treatment of CAP in adults and children.

Hospital-acquired pneumonia (HAP)

HAP is a respiratory infection developing more than 48 h after hospital admission. HAP can be divided into early- and late-onset. Early-onset disease occurs within 4–5 days of admission and tends to be caused by antibacterial agent-susceptible community-type pathogens, whereas late infections tend to be caused by antibacterial agent-resistant hospital pathogens. In a proportion of patients, HAP is associated with mechanical ventilation, and is commonly known as ventilator-associated pneumonia (VAP).

Four randomised controlled trials in adults were presented, in which ceftriaxone was compared to ceftazidime, moxifloxacin or cefoperazone. A relevant proportion of patients presented with bacteraemia. All except one of the clinical trials used a dose of 2g/ day of ceftriaxone. Mean treatment duration was at least 7 days. The point estimates for the clinical cure rate of ceftriaxone versus the respective comparators is generally lower, although the relatively small sample sizes make it difficult to detect a difference and the statistical analyses were not included in the report.

Overall, the CHMP considered that the evidence for the use of ceftriaxone in HAP was sufficient for accepting the harmonised indication taking into account that HAP is included in the indications LRTI or 'pneumonia', which are currently licensed in the majority of member states.

A limitation to early onset HAP (in view of the lesser likelihood of *P. aeruginosa* as a pathogen in this subset) was not considered to be acceptable as the clinical studies did not make such a distinction. Therefore the indication HAP, without restriction, was accepted by the CHMP.

Acute exacerbations of chronic bronchitis (AECB)

Supportive evidence for the claimed indication AECB is provided by the study by Grassi C et al. (2002)¹, comparing intramuscular ceftriaxone (1g daily) with oral moxifloxacin over a 5 day treatment course. Both agents showed equal efficacy in the per protocol population.

Ceftriaxone has utility in cases of AECB, although the supporting study was small. Nevertheless, ceftriaxone has a place where intravenous treatment is needed. On balance, the CHMP considered that the indication 'Acute exacerbations of chronic obstructive pulmonary disease' is approvable.

Intra-abdominal infections (IAI)

There is considerable divergence in the present nationally approved wording for this indication in the various member states. The CDS wording has been implemented in the SmPCs in Austria, Finland, Greece and Portugal.

In support of this indication, the MAH provided data from initial studies. The initial studies presented included patients with a variety of conditions including non-intra-abdominal infections. The CHMP noted that the studies were generally small, open, and sometimes used multiple and unsuitable comparator agents. Others studies were observational or included populations with specific conditions (such as peritonitis in cirrhotic patients).

Studies from the published literature were also submitted and were overall of better quality, although some of the comparators used in the studies were questionable.

The study by Wacha H et al. (2006)² enrolled a large number of patients with complicated IAI (cIAI). This design feature and the high number of patients with appendiceal origin of infections enrolled

¹ Grassi C, Salvatori E, Rosignoli MT, et al. Randomized, double-blind study of prulifloxacin versus ciprofloxacin in patients with acute exacerbation of chronic bronchitis. *Respiration*. 2002;69:217–22.

probably explains the high overall clinical success rate of around 90% in both groups. However, non-appendiceal infection cure rates were also high. Patients who could not be switched to oral therapy were as expected more severely ill, and success rate was overall lower (ceftriaxone/ metronidazole 62% vs 49% ciprofloxacin/ metronidazole). While ciprofloxacin may not be considered the best standard comparator, this study does provide supportive data for ceftriaxone in the indication cIAI.

Weiss G et al. (2009)³ also enrolled more than 500 adult patients with cIAI. The CHMP noted that the comparator in this open study was moxifloxacin, which is not licensed for use in intra-abdominal infections in the EU. Treatment with ceftriaxone could be switched to co-amoxicillin after 3 days, further hindering interpretation of these data. In this study non-inferiority of moxifloxacin vs ceftriaxone was shown. This was in line with the results observed in a very similar study in 364 patients with cIAI conducted by Solomkin (2009)⁴.

Despite the limitations observed in the studies, the CHMP concluded that overall the data submitted were sufficient to accept an indication in IAI.

The CHMP noted that most of the clinical data stem from studies labeled cIAI, although these studies included a wide variety of conditions. However IAI was accepted as the indication for ceftriaxone as there are increasing discrepancies in the definition of cIAI and a lack of acceptance of the term amongst many clinicians. In addition the draft addendum to the *Note for guidance on evaluation of medicinal products indicated for treatment of bacterial infections (CPMP/EWP/558/95 rev 2)* refers to IAI only. Therefore, the CHMP considered that the wording of the indication IAI acceptable.

Urinary tract infections (UTI), including pyelonephritis

The indication is not specified in the SmPC for Rocephin in Belgium, Luxembourg, Hungary, Latvia, Romania, Malta and the UK. The Finnish, French and Netherlands SmPCs contain variations of the indication included in the CDS.

Uncomplicated UTIs (uUTI) are usually treated with oral antibacterial agents; however acute pyelonephritis is treated with parental antibacterial agents particularly in those cases where bacteraemia and sepsis is suspected.

A complicated UTI (cUTI) is an infection associated with a condition, such as a structural or functional abnormality of the genitourinary tract, or the presence of an underlying disease that interferes with host defense mechanisms, which increase the risks of acquiring infection or of failing therapy. Complicated UTIs are also frequently associated with the presence of a urinary catheter. The bacterial spectrum for cUTI is much larger than in uUTIs, and bacteria are more likely to be resistant to antibacterial agents, especially in a treatment-related cUTI.

A number of studies in both complicated and uncomplicated UTI were presented. These included randomised controlled trials in adults and children on the use of ceftriaxone in pyelonephritis and uncomplicated UTI. In several trials of ceftriaxone versus other beta- lactams or aminoglycosides, success rates similar to the active comparators were observed.

The CHMP was of the opinion that overall, there is sufficient data from randomised controlled trials to support an indication in UTI (including pyelonephritis). It is not expected that a parenteral anti-

² Wacha H, Warren B, Bassaris H, et al. Comparison of sequential intravenous/oral ciprofloxacin plus metronidazole with intravenous ceftriaxone plus metronidazole for treatment of complicated intra-abdominal infections. *Surg Infect (Larchmt)* 2006; 7: 341–54.

³ Weiss G, Reimnitz P, Hampel B, Muehlhofer E, Lippert HAIDA Study Group: Moxifloxacin for the treatment of patients with complicated intra-abdominal infections (the AIDA Study). *J Chemother* 2009 Apr; 21(2): 170-180.

⁴ Joseph Solomkina, Yu-Pei Zhaob, En-Ling Mab, Min-Jun Chenc, Barbara Hampeld, Members of the DRAGON Study Team: Moxifloxacin is non-inferior to combination therapy with ceftriaxone plus metronidazole in patients with community-origin complicated intra-abdominal infections. *Int. J of Antimicrob Agents* 34 (2009) 439–445

bacterial agent would be prescribed or appropriate in truly uUTI. Therefore the CHMP limited the indication to cUTI (including pyelonephritis).

Infections of bones and joints

The following countries reflect the CDS indication: Austria, Finland, Germany, Greece, the Netherlands, Portugal and Romania, whereas the following countries list bone infections only: Hungary, Latvia, the UK and Malta.

The data from clinical studies are limited. Small comparative studies tested ceftriaxone versus oxacillin and ampicillin + gentamycin and showed similar success rates (Kissling and Bergamini⁵). The overall lack of good quality clinical studies in the treatment of bone and joint infections is acknowledged.

A review in 2005 (Lazzarini et al 2005⁶) identified 93 studies of antibiotics in this indication of which 17 were comparative and only 10 of these were randomised. There is no consensus regarding the most appropriate antibiotic regimen as the mostly uncontrolled and small studies do not allow differentiating between different agents. A Cochrane review published in 2009 came to similar conclusions.

In summary, there is some evidence from clinical studies supporting the indication bone and joint infections. Therefore, in view of the available data and the fact that ceftriaxone has been approved by the majority of member states for bone and joint infections, the CHMP agreed with harmonised indication for: infections of bones and joints.

Skin and soft tissue infections (SSTIs)

This indication has been implemented in most EU member state SmPC's except in Belgium, Luxembourg, France and Sweden..

SSTIs can be acute, recurrent and chronic, and occur in the community, as well as being health care-associated. SSTIs may range from simple, uncomplicated superficial infections, such as erysipelas, folliculitis, cellulitis, abscesses, furuncles and wound infections, to deeper complicated infections, such as necrotising fasciitis, myositis, surgical site infections and gas gangrene. A SSTI is considered complicated when it involves deeper skin structures such as fascia or muscle layers, requires significant surgical interventions or arises in the presence of significant co-morbidities, such as in the presence of diabetes mellitus or HIV infections. Simple, uncomplicated SSTI do not usually present with systemic signs of infection and may frequently be treated with topical antibiotics. Parenteral antibiotics are rarely required.

While most of the earlier studies presented by the MAH were non-comparative or conducted with non-licensed comparators (enoxacin), there are data from several randomised controlled clinical trials for ceftriaxone. As expected for a third generation intravenous cephalosporin, these studies were usually conducted in hospitalised patients with a variety of complicated and serious SSTIs. Ceftriaxone (1g or 2g daily) was compared to cephazolin, gentamycin + clindamycin or ampicillin/sulbactam and showed similar efficacy.

⁵ Roche Research Reports.

⁶ Lazzarini L, Lipsky B A, Mader J T: Antibiotic treatment of osteomyelitis: what have we learned from 30 years of clinical trials? International Journal of Infectious Diseases (2005) Volume 9, Issue 3 , Pages 127-138.

A non-comparative study by Fraenkel⁷ included 94 paediatric patients from one month to 18 years of age with serious SSTI, who received doses of 50- 80 mg/kg/day. Reported cure rate was >90%.

In view of the available data, the antimicrobial activity of ceftriaxone in the indication of uncomplicated SSTI (uSSTI) is not considered to be appropriate for this agent. There is sufficient data to harmonise the indication for ceftriaxone in complicated SSTI (cSSTI), since the clinical data presented stem mostly from what was labelled as cSSTI. Therefore CHMP agreed to accept the MAH's proposal of "complicated skin and soft tissue infections".

Bacterial endocarditis

The French SmPC includes treatment of endocarditis as a specific indication. Some SmPCs for other member states cover the treatment of endocarditis under a general statement – "Severe infections caused by pathogens sensitive to ceftriaxone".

Data in this indication are quite limited as may be expected in this relatively infrequent condition. The MAH's clinical trial data all stem from open, retrospective or observational uncontrolled studies enrolling small numbers of patients.

From the published literature, 4 interventional studies (open, no comparator) in patients with streptococcal endocarditis are reported. One of these studies compared monotherapy with ceftriaxone for 4 weeks to combination treatment of ceftriaxone and aminoglycoside. Cure rate was reported to be high and similar in both groups.

The generally good tissue penetration, antibacterial activity, PK and PK/PD considerations provide scientific rationale for use of ceftriaxone in the treatment of bacterial endocarditis.

Very few children (all ≥ 8 years of age) were enrolled in these studies and received 1g of ceftriaxone per day. Clinical and bacteriological cure rates as reported are relatively high, despite shortcomings with regard to the definitions and study design (most notably the lack of a comparator), noted by the CHMP.

Considering the utility that ceftriaxone has in endocarditis, particularly when caused by streptococci, the CHMP agreed to accept this indication.

Bacteraemia

The Rocephin CDS lists sepsis as an indication, and the SmPCs in Austria, Belgium, Luxembourg, Germany, Greece, Portugal, Romania reflect the CDS. In France, the UK, Hungary, Ireland, Malta and Latvia, the SmPC contains the indication septicaemia. In Finland, the SmPC contains the indication 'empiric initial therapy of sepsis'.

From the data presented for the various indications it appears that sufficient patients with bacteraemia were included in the clinical studies, which allow the conclusion that ceftriaxone can be used in the authorised indications when bacteraemia is present. It was noted that the proposal for the indication is aligned with the wording previously agreed on for similar antibiotics.

Infections with impaired defence mechanisms

The above indication listed in the CDS is reflected in the SmPCs in: Austria, Finland, Ireland and Portugal. In the UK, Hungary, Latvia and Romania, the SmPCs list infections in neutropenic patients and the German SmPC states interventional therapy in neutropenic patients.

⁷ Frenkel LD. Once-daily administration of ceftriaxone for the treatment of selected serious bacterial infections in children. *Pediatrics*. 1988; 82(3 Pt 2):486-491.

The clinical studies presented by the MAH include patients with a variety of different underlying diseases and causes for neutropenia, different degrees of severity of neutropenia or granulocytopenia and include different types of infections. Despite the limitations, there is a reasonable amount of data available on ceftriaxone either as monotherapy or in combination with other antibacterial agents in neutropenia.

However the MAH's proposal 'Infections in patients with impaired defence mechanisms' was not considered to be sufficiently supported by data. Therefore the revised indication 'Ceftriaxone may be used in the management of neutropenic patients with fever that is suspected to be due to a bacterial infection' was proposed and considered acceptable by the CHMP.

Acute otitis media (AOM)

France and Finland have a specific indication for acute otitis media whilst Germany, Austria, Greece, Ireland and Portugal all reflect the CDS and list ear, nose and throat infections.

Large comparative trials have been conducted comparing single dose i.m. ceftriaxone (usually 50mg/kg) with oral antibiotics (McGarty T et al. 1996; Cunningham M et al. 1996⁸). In the largest studies, ceftriaxone was shown to be less effective than a 10 day course of amoxicillin/clavulanic acid and as effective as trimethoprim-sulfamethoxazole. In another study ceftriaxone as a single intramuscular injection was less effective after 2 weeks (but not after 4 weeks) than Bicillin C-R (pen) single dose i.m. followed by a 10-day course of oral trimethoprim-sulfamethoxazole (TMP-SMZ).

Several other smaller studies compared ceftriaxone with other antibiotics, particularly co- amoxicillin, and found similar effectiveness.

Overall, there is evidence from controlled clinical trials that ceftriaxone is effective in the treatment of AOM. The CHMP agreed that AOM should be included in the harmonised SmPC.

Prophylaxis of perioperative infections

The wording in most current SmPCs implies that ceftriaxone can be used in most types of surgery, at least when there is an "increased" or "high" risk for infection.

Prophylactic perioperative administration of antibiotics is recommended in some types of surgery for the prevention of surgical site infections (SSI).

In cardiac surgery, 5 studies comparing a single dose of ceftriaxone to multiple doses of cefazolin, cefamandole, cefuroxime, vancomycin, and flucloxacillin+ gentamycin were presented. Point estimates for the "patients free from postoperative infections" in these studies are generally similar for ceftriaxone and comparator.

The MAH presented several studies in orthopaedic surgery, including a large placebo controlled trial in patients with closed fractures. Efficacy in preventing wound infections was demonstrated. Further studies provide supportive evidence in other types of orthopaedic surgery.

Ceftriaxone was shown to reduce postoperative infections when compared to placebo in 2 studies in genitourinary surgery and transurethral resection of the prostate (TURP). Several comparative studies in patients undergoing gastrointestinal and biliary surgery have also been conducted.

In summary, there is evidence for the efficacy of ceftriaxone in the perioperative prophylaxis of infections in several types of surgery.

⁸ Roche Research Reports

Gonorrhoea, gonococcal arthritis, gonococcal eye infection

The Rocephin CDS contains the indication "Genital infections, including gonorrhoea". This indication is not specified in the Rocephin SmPC in Belgium, Luxembourg, France, Romania and Sweden. In Finland, the SmPC contains the indication "gonorrhoea and syphilis". In Hungary, Ireland, Latvia, Malta, The Netherlands and the UK, Rocephin is indicated for the treatment of "Gonorrhoea". In Denmark, the SmPC for Rocephin 500 mg and 1 g powder and solvent for solution for injection contains the indication "gonococcal eye infection".

Multiple randomised controlled studies have been conducted, comparing single dose (i.m.) ceftriaxone to penicillin G + probenecid, cefoxitin, and spectinomycin in uncomplicated anogenital gonorrhoea. Several studies reported bacteriological cure rates for genital and extragenital lesions separately. Success rates were high and similar to the comparators. Ceftriaxone was demonstrated to have good clinical efficacy in the treatment of gonorrhoea when used as a single dose treatment.

In view of the above, the CHMP considered that the most appropriate wording for this indication would be 'gonorrhoea', which is currently included most SmPCs.

The CHMP considered that there was insufficient data to justify the disease subsets of gonococcal arthritis and gonococcal eye infection as separate indications. The MAH agreed with the recommendation that these should be deleted as specific indications in the SmPC.

Syphilis including neurosyphilis

"Syphilis" is listed as an indication in Finland only.

Limited clinical data are available in support of the efficacy of ceftriaxone in the treatment of syphilis. However, available clinical data indicate that ceftriaxone is efficient in treating early syphilis. In the largest and most recent study, Psomas *et al* (2012)⁹ compared the efficacy of ceftriaxone and doxycycline to penicillin in 116 adult patients with early syphilis. The results of this study suggest that ceftriaxone and doxycycline are effective therapeutic alternatives to penicillin. Other studies that have been conducted are small, but together they provide a body of evidence demonstrating the effectiveness of ceftriaxone in syphilis. Data in patients with neurosyphilis are even more limited.

Considering the submitted data, the CHMP was of the view that ceftriaxone is useful in the treatment of syphilis.

Lyme Borreliosis

The indication for Lyme borreliosis or Lyme's disease is approved in most member states with the exception of Hungary, Ireland, Latvia, Malta and the UK.

Lyme borreliosis is commonly divided into 3 stages: early localised, early disseminated and late disseminated disease, but these phases overlap to some extent. In 90% of cases, erythema migrans is the presenting symptom. Borreliae can disseminate (haematogenic or direct) into other organ systems, mainly the nervous system, joints and rarely heart and skin.

Of the initial clinical trials submitted by the MAH, only one study was comparative, investigating ceftriaxone versus doxycycline in early disseminated Lyme disease. While the investigators global assessment score was similar, the sponsor's cure and 75% resolution rates favoured doxycycline, which also had less adverse events. Dattwyler R J *et al* (1997)¹⁰ also compared ceftriaxone (2 g once

⁹ Psomas KC, Brun M, Causse A, et al. Efficacy of ceftriaxone and doxycycline in the treatment of early syphilis. *Med Mal Infect* 2012;42:15–9.

¹⁰ Dattwyler RJ, Luft BJ, Kunkel MJ, Finkel MF, Wormser GP, Rush TJ, et al. Ceftriaxone compared with doxycycline for the treatment of acute disseminated Lyme disease. *N Engl J Med* 1997;337(5):289–94.

daily for 14 days) with oral doxycycline (100 mg twice daily for 21 days) in patients with acute disseminated *B. burgdorferi* infection but without meningitis. Rates of clinical cure at each patient's last evaluation were similar among the patients treated with ceftriaxone (85%) and those treated with doxycycline (88 %). The same author compared ceftriaxone to penicillin in 23 adult patients with clinically active late Lyme disease and found ceftriaxone to be superior (Dattwyler R J *et al* (1988)¹¹). Other small comparative studies showed efficacy in late manifestations of Lyme disease such as neuroborreliosis and arthritis.

Ceftriaxone has been shown to be beneficial in both early (Stage II) and late (Stage III) disseminated Lyme borreliosis and is recommended in current clinical guidelines. Therefore the MAH's proposal to add Stage II and Stage III nomenclature to this indication was considered to be acceptable by the CHMP.

Other indications

The MAH's proposal to delete the indication for sinusitis, pharyngitis and prostatitis due to the scarcity of robust clinical trials in these conditions was agreed by the CHMP.

'Purpura fulminans' was deleted as an indication as it was agreed that the condition is a manifestation of specific infections, all of which are already covered in the list of indications.

Section 4.2 - Posology and method of administration

Posology

Adults

For adults, the Rocephin CDS text states that the usual dose is 1 - 2 g of Rocephin once daily (every 24 hours) and in severe cases or in infections caused by moderately sensitive organisms, the dosage may be raised to 4 g, once daily.

The SmPCs for Austria, Finland, Greece, the Netherlands and Portugal have implemented the CDS wording. In the SmPC in Belgium, Luxembourg, Germany, Malta and the UK, the wording differs slightly but the same dose range is reflected.

Most of the clinical studies presented were conducted with doses of 1- 2g per day. Many studies are however more than 20 years old.

The probability of target attainment (PTA) presented for the various pathogens was based on the MIC distributions of the respective pathogens.

- *Dosage schedules of 1-2g once daily in adults and children over 12 years of age*

Ceftriaxone has been used at a dose of 1 g/day in almost all studies of patients with CAP. Taking into account the PK/PD and clinical data, the MAH has proposed the following dose for the treatment of CAP in adults and children over 12 years of age (≥ 50 kg): 1–2 g once daily.

Most trials of ceftriaxone in intra-abdominal infections have studied a dose of 2 g/day. The clinical data supporting the use of ceftriaxone 1 g/day as the lower dose level in intra-abdominal infections were confirmed by PK/PD modelling. Therefore the MAH has proposed a dose of 1–2 g once daily for intra-abdominal infections.

Several large studies have demonstrated the efficacy of 1 g daily doses of ceftriaxone in patients with urinary tract infections and PK/PD model data have confirmed the efficacy of this dose. In cases of

¹¹ Dattwyler RJ, Halperin JJ, Volkman DJ, Luft BJ. Treatment of late Lyme borreliosis – randomised comparison of ceftriaxone and penicillin. *Lancet* 1988;1(8596):1191–4.

complicated UTIs, including pyelonephritis, PK/PD modelling was not undertaken for these organisms because they do not have established target attainment levels. A dose of 1–2 g once daily was accepted for complicated UTIs, including pyelonephritis.

There were no clinical studies in AOM in adults, but the CHMP considered that extrapolation was possible from paediatric data and a dose of 1-2g has been proposed.

- *Dosage schedules of 2g once daily in adults and children over 12 years of age*

The MAH has proposed a dose of 2g for SSTI and bone and joint infections, for which the PK/PD data suggest that target attainment rates are low for doses < 2g/ 24h in indications where *S. aureus* is a relevant pathogen.

Although early onset HAP is caused by the same pathogens as those implicated in CAP, the clinical trials in this patient population have tended to use a 2 g daily dose of ceftriaxone. Four randomised controlled trials in adults were presented, in which ceftriaxone was compared to ceftazidime, moxifloxacin or cefoperazone. All except one of the clinical trials used a dose of 2g/ day of ceftriaxone. Considering the severity of the illness and the clinical data, the MAH considers that a higher dose of ceftriaxone is warranted and proposed a dose of ceftriaxone of 2 g once daily in this indication in adults and children over 12 years of age (≥ 50 kg).

Specific Monte Carlo simulations were not conducted for *Shigella* or *Salmonella* because these organisms do not have agreed target attainment levels. The MAH has proposed a dose of 2 g once daily for the treatment of severe infections of the gastro-intestinal tract caused by *Shigella* or *Salmonella* in adults and children over 12 years of age (≥ 50 kg), based on pathogen-independent Monte Carlo simulations, intravenous or intramuscular doses of ceftriaxone 2 g daily in adults.

- *Dosage schedules of 2-4g once daily in adults and children over 12 years of age*

Both clinical data and PK/PD data favour a dose of 2g/day in neutropenic patients with bacterial infections. In view of the nature of the condition, i.e. the inability of the immune system to contribute to a normal extend (if at all) to fighting an infection, it is expected that antibiotic doses should be at the higher end of the recommended spectrum. Therefore a once daily dose of 2-4g has been proposed by the MAH.

For the indication endocarditis, the MAH's clinical trial data all stem from open, uncontrolled studies enrolling small numbers of patients, where the vast majority of adult patients received a dose of 2g once per day in combination with an aminoglycoside. A once daily dose of 2-4g has been proposed by the MAH.

The only study in meningitis presented was in adults and used a dose of 4g once daily and a dose of 2-4g has been accepted by the CHMP. Initial clinical studies conducted in the 1980s enrolled almost exclusively paediatric patients.

Specific dosage schedules were discussed and agreed for AOM (single dose of 1-2g or for 3 days in severe cases), gonorrhoea (single dose of 500mg), syphilis (500mg-1g for 10-14 days), pre-operative prophylaxis of surgical site infections (single dose of 2g) and disseminated Lyme borreliosis (2g once daily for 14-21 days).

Since there are no data supporting a separate dose recommendation in infections with bacteraemia, the CHMP was of the view that a general statement should be included in section 4.2, that in cases of severe infections and those with bacteraemia, doses at the higher end of the recommended range should be considered.

Paediatric population

For neonates, infants and children (15 days to 12 years), the dose regimen in the Rocephin CDS is 20 - 80 mg/kg once daily. The Rocephin SmPCs in Hungary, Ireland, Latvia, Malta and the UK state 20-50 mg/kg once daily for neonates, infants and children (15 days to 12 years) and doses up to 80 mg/kg for severe infections. For children and infants, the French SmPC states that the dose should not exceed the adult dose. For neonates (0-14 days), the dose regimen in the CDS is 20-50 mg/kg once daily.

- *Children (15 days to 12 years)*

In almost all studies 100 mg/kg/day given once daily was used, supporting the MAH's dose proposal. There are very few clinical data demonstrating the efficacy of ceftriaxone in doses <50mg/kg, however PK/PD data indicate that for the relevant pathogens in most indications, doses of 20mg/kg results in acceptable PTA. An exception is *S. aureus*, where considerably higher doses are needed to achieve acceptable PTA. Following the review of the paediatric data in accordance with Article 45 of the EU Regulations, a standard dose of 20- 80mg/kg has been accepted in all member states.

Although relevant PK/PD data are not available to support the posology in children with meningitis, there is sufficient evidence from clinical studies to support a dose of 80- 100mg for neonates > 15 days to children 12 years of age with meningitis.

There is evidence from controlled clinical trials that ceftriaxone 50mg/kg i.m. as a single dose is effective in the treatment of AOM.

Based on PK/PD data and the available clinical data the upper dose limit has been increased to 100mg/kg in specific infections.

- *Neonates*

The proposed posology ranging from 20- 50mg in this age group was considered to be acceptable.

Given that meningitis is a severe and life threatening condition, and considering the clinical data, the MAH was of the view that it was not appropriate to propose a ceftriaxone dose range of 20–50 mg/kg for the treatment of meningitis in neonates <15 days as proposed for other infections. Therefore the proposed dose of 50 mg/kg for the treatment of bacterial meningitis in neonates <15 days old was accepted by the CHMP.

There is evidence from controlled clinical trials that ceftriaxone 50mg/kg i.m. as a single dose is effective in the treatment of AOM.

Duration

A general statement has been included in section 4.1 that clinical treatment guidelines should be followed.

According to European Union Concerted Action on Lyme borreliosis (EUCALB) guideline recommendations, duration of Ceftriaxone treatment for early disseminated Lyme borreliosis (neuroborreliosis) is 14 days (range 10-30 days) but for late disseminated Lyme borreliosis (arthritis, cardioborreliosis, or acrodermatitis) is 21 days (14-30 days). Therefore the CHMP agreed to include the option of extending the treatment for up to 21 days.

In the treatment of AOM in the adult and paediatric populations, there is limited data that a 3-day treatment course of 50mg/kg/day in cases where previous treatment had failed results in higher cure rates compared to a single dose of ceftriaxone 50mg/kg/day.

Methods of administration

Intravenous (iv)

In 2010, the company was asked by the PhVWP to provide data to on the possibility of precipitation at the site of injection. The results of the in-vitro study were difficult to interpret and no new information was presented which allowed further characterisation of the important potential risk of precipitate formation during iv bolus injection of ceftriaxone. Since the risk of precipitate formation with fast bolus injection cannot be fully excluded, the CHMP recommended that the SmPC should be further amended with precautionary statements in line with other approved SmPCs, recommending the administration of the bolus injection over approximately 5min.

Intramuscular (im)

For a time-dependent antibiotic like ceftriaxone, administration of antibiotics via the intramuscular route is not expected to pose any problems with regards to efficacy. PK/PD data confirm that i.m. administration results in equal target attainment, as expected from the PK profile. Intramuscular administration can be useful in certain scenarios and increases the flexibility of use, although there is some concern with the tolerability and particularly the safety of the administration, with deep abscesses and nerve damage through inadvertent intra/ perineural administration.

As requested by the CHMP, a statement has been included that a maximum of 1g should be given per injection site and that im injection for doses greater than 2g is not suitable. Also in line with statements accepted in previous harmonisation procedures, a statement that '*Intramuscular administration should only be considered when the intravenous route is not possible or less appropriate for the patient*' has been included.

Subcutaneous (sc)

The MAH has performed only one nonclinical study examining the tolerability of subcutaneous ceftriaxone in rats. Therefore as agreed with the MAH, the CHMP was of the view that there is insufficient data to support the recommendation for subcutaneous administration of ceftriaxone.

Elderly patients

Based on the data presented, the same doses have been recommended for both populations - younger and older adults, provided renal and hepatic function are not relevantly impaired.

Patients with renal and hepatic impairment

The MAH has provided studies indicating that the pharmacokinetics of ceftriaxone are not significantly altered in patients with renal and hepatic impairment, both of which may complicate acute infections. However in cases of severe renal and hepatic impairment, a close clinical monitoring for efficacy and safety has been recommended.

Section 4.3 – Contraindications

There is a low incidence of cross allergy between penicillins and 2nd or 3rd generation cephalosporins. However, the use of ceftriaxone has been precluded if the patient has a history of a severe immediate hypersensitivity reaction to any other beta-lactam agent or any other cephalosporin.

This section also states that ceftriaxone solutions containing lidocaine should never be administered intravenously.

The CHMP agreed with the omission of the contraindications relating to i.m use in pregnancy and lactation, which appear to be based on lack of data rather than supporting evidence.

Other minor changes were included to improve clarity of this section.

Section 4.4 - Special warnings and precautions for use

The information on *C. difficile* and antibiotic-associated colitis was re-worded in line with previous Article 30 harmonisation procedures for beta-lactams and to include hypersensitivity reactions and interactions with calcium-containing products. Rocephin is contraindicated in premature and in full-term neonates at risk of developing bilirubin encephalopathy or receiving calcium-containing intravenous infusions.

In case a lidocaine solution is used as a solvent, ceftriaxone solutions must only be used for intramuscular injection.

Adverse events such as biliary lithiasis, biliary stasis and renal lithiasis have also been included with a cross reference to section 4.8 (undesirable effects).

Section 4.5- Interaction with other medicinal products and other forms of interaction

In order to comply with the Guideline on the Summary of product Characteristics, the statement mentioning incompatibilities with ampicillin, vancomycin, fluconazole & aminoglycosides (which is included in the EU CSP) has been moved to Section 6.2 (Incompatibilities).

The statement on the lack of a disulfiram-like interaction with alcohol has been deleted as there is insufficient evidence to rule it out.

At the request of the CHMP, information on drug-drug interactions (DDI) with anticoagulants was included, with a recommendation that the INR (international normalised ratio) is monitored frequently.

Section 4.6 – Fertility, pregnancy and lactation

The pregnancy statements suggest that there is limited human experience, that animal studies do not indicate an embryotoxic or teratogenic effect, and that caution should be exercised if used during pregnancy.

Amendments were made to the wording for the period of lactation, mentioning the fact that the risk of diarrhoea and fungus infection of the mucous membranes cannot be excluded and that breastfeeding might have to be discontinued due to these effects.

The MAH has provided data to demonstrate that doses of up to 700 mg/kg of ceftriaxone had no significant effect on fertility or embryofoetal development and the studies conducted are considered adequate. On this basis, no further revisions were warranted.

The amended wording was considered to be acceptable by the CHMP.

Section 4.7 - Effects on ability to drive and use machines

The MAH's proposed text was accepted with minor re-wording.

Section 4.8 - Undesirable effects

Data to determine the frequency of Rocephin adverse drug reactions was derived from clinical trials.

The MAH has reassigned adverse events that have not been observed in studies to the additional category, 'Not known', with an added explanatory footnote.

The term convulsions has been added to the tabulated summary of adverse events in section 4.8 of the proposed SmPC following a cumulative review of the events related to convulsions during the Rocephin Periodic Safety Update Report (PSUR) work sharing procedure (LV/H/PSUR/0002/002).

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

Section 4.9 – Overdose

The MAH's proposed text that the symptoms of overdose - nausea, vomiting and diarrhoea cannot be reduced by haemodialysis or peritoneal dialysis and that there is no specific antidote was considered to be acceptable by the CHMP. It is stated that the treatment of overdose should be symptomatic.

Section 5.1 - Pharmacodynamic properties

The MAH has revised the table of species to list organisms relevant to the indications included in section 4.1 of the proposed SmPC.

Species known to produce extended-spectrum beta-lactamase (ESBL) have been categorised in category 2, where some of the Enterobacteriaceae have been moved.

Considering the national and EU-wide resistance situation, sensitivity data have been collected from international publications in particular, publications that provide updated data based on recent surveillance. However, it was not considered appropriate to designate particular geographic areas. Taking into consideration the national and EU-wide resistance situation, the MAH has re-categorised some ESBL-producing *Enterobacteriaceae* and *Staphylococci*.

Section 5.2 - Pharmacokinetic properties

Absorption

Data are available for iv bolus, intravenous and intramuscular absorption. Ceftriaxone is not well absorbed when administered orally.

Distribution,

Ceftriaxone distributes primarily into the extracellular space. Partly due to the saturable protein binding, linearity for total and free ceftriaxone differ. Total ceftriaxone increases less than proportionally with dose, while free (active) ceftriaxone seems to have a linear dose- concentration relationship over the ranges tested. Also, CL (total) and CL (renal) of total (free + bound) ceftriaxone are dose related, while CL (renal) of free ceftriaxone is dose- independent is dose related.

Metabolism

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

Elimination

Ceftriaxone is eliminated unchanged renally (by glomerular filtration) and biliary secretion. The elimination half-life of total ceftriaxone in adults is about 8 hours. Total and renal plasma clearance (of total, i.e. free plus protein bound) ceftriaxone is dose dependent, while renal clearance of free ceftriaxone clearance is not.

Data addressing the drug transport proteins involved in the renal and biliary excretion of ceftriaxone are very limited.

The half-life increases in the elderly, and in older people aged over 75 years the average elimination half-life is usually two to three times that of young adults. However the changes are generally small and dose reduction is not required if renal and hepatic function is satisfactory.

Serum concentration

Ceftriaxone has relatively simple PK; it is not appreciably metabolised and excreted via both renal and biliary routes. It does however have high and saturable protein binding (only unbound drug is active), making PK more complex.

Renal and 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. If kidney function alone is impaired, biliary elimination of ceftriaxone is increased; if liver function alone is impaired, renal elimination is increased.

Paediatric population

There is limited information regarding the pharmacokinetics of ceftriaxone in children and neonatal subjects.

The half-life values reported for ceftriaxone in studies is variable because of the non-linear pharmacokinetics of ceftriaxone. From the studies submitted it appears that the half-life of ceftriaxone in adults is approximately half of that observed in neonatal patients during the first two weeks of life. During childhood, the half-life is lower than in neonatal patients or adults.

Section 5.3 - Preclinical safety data

In Belgium, Luxembourg, France, Hungary, Ireland, Latvia, Malta, Romania and the UK, there is no preclinical information provided in section 5.3 of the Rocephin SmPC. In Austria, Denmark, Iceland, Finland and Portugal, the SmPCs specify that ceftriaxone has not shown reproductive toxicity and mutagenic effects or antigenic activity. In Germany, the SmPC specifies that ceftriaxone has not shown reproductive toxicity and mutagenic effects but does not comment on antigenic activity.

The MAH has proposed wording for section 5.3 of the SmPC, which reflects the relevant non clinical data with Rocephin that may be informative for safe clinical use. Taking into account the additional amendments to bring the wording in line with the recommendations made in the Guideline on the Summary of Product Characteristics (2009), this section was considered to be acceptable by the CHMP.

Package Leaflet (PL)

The changes to the SmPC, when relevant for the user, have also been reflected in the PL and agreed by the CHMP. Readability testing has been performed at a national level.

2.3. Risk Management Plan

The CHMP did not require the MAH to submit a risk management plan.

2.4. Recommendation

Following the assessment of the company's submission the CHMP accepted the following harmonised indication:

'Rocephin is indicated for the treatment of the following infections in adults and children including term neonates (from birth).

Bacterial Meningitis

Community acquired pneumonia

Hospital acquired pneumonia

Acute otitis media

Intra-abdominal infections

Complicated urinary tract infections (including pyelonephritis)

Infections of bones and joints

Complicated skin and soft tissue infections

Gonorrhoea

Syphilis

Bacterial endocarditis.

Rocephin may be used :

For treatment of acute exacerbations of chronic obstructive pulmonary disease in adults

For treatment of disseminated Lyme borreliosis (early (stage II) and late (stage III)) in adults and children including neonates from 15 days of age.

For Pre-operative prophylaxis of surgical site infections

In the management of neutropenic patients with fever that is suspected to be due to a bacterial infection

In the treatment of patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above.'

The indications sinusitis, pharyngitis and prostatitis proposed by the MAH were not accepted due to the scarcity of robust clinical trials in these conditions was agreed by the CHMP. 'Purpura fulminans' was deleted as an indication as it was agreed that the condition is a manifestation of specific infections, all of which are already covered in the list of indications.

The CHMP also maintained that the available strengths are 250 mg, 500 mg, 1g and 2g, although not all strengths are marketed in all EU member states. Some presentations also contain solvent vials containing either sterile water for injections or 1% lidocaine hydrochloride solution.

The parenteral administration of Rocephin either by intramuscular injection, intravenous injection or infusion was also maintained. However the CHMP was of the view that there is insufficient data to support the recommendation for subcutaneous administration of ceftriaxone.

The remaining (non)-clinical sections of the SmPC were also harmonised.

In conclusion, the revised and harmonised of the Product Information for Rocephin was considered acceptable by the CHMP.

2.5. Conclusions

In conclusion, based on the assessment of the proposals submitted by the MAH and the discussions of the Committee, the CHMP adopted the harmonised product information consisting of the summary of product characteristics (SmPC), labelling and package leaflets, for Rocephin and associated names.

Based on the above, the CHMP considers the benefit/risk ratio of Rocephin and associated names to be favourable and the harmonised Product Information documents to be approvable.

Whereas

- The committee considered the referral under Article 30 of Directive 2001/83/EC
- The committee considered the identified divergences for the Rocephin and associated names with respect to the sections therapeutic indications, posology and method of administration, as well as the remaining sections of the SmPC.
- The committee reviewed the data submitted by the MAH from the existing clinical studies, published literature and the cumulative safety experience with Rocephin as reported on the company's drug safety database justifying the proposed harmonisation of the Product Information.
- The committee agreed the harmonisation of the summary of product characteristic, labelling and package leaflet proposed by the marketing authorisation holders.

the CHMP has recommended the variation to the terms of the marketing authorisations for which the summary of product characteristics, labelling and package leaflet are set out in Annex III for Rocephin and associated names (see Annex I).