

Annex II

Scientific conclusions and grounds for the variation to the terms of the Marketing Authorisation

Scientific conclusions

Overall summary of the scientific evaluation of Rocephin and associated names (see Annex I)

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 is approved in 19 EU Member States with different nationally approved Summaries of Product Characteristics (SmPCs). 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 informations for the above-mentioned products and thus to harmonise them across the EU.

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 summarised below.

Section 4.1 - Therapeutic indications

Bacterial Meningitis

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)

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).

- 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)

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.

- Acute exacerbations of chronic bronchitis (AECB)

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)

The CHMP noted that most of the clinical data stem from studies labeled complicated IAI (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 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-bacterial agent would be prescribed or appropriate in truly uncomplicated UTIs (uUTI). Therefore the CHMP limited the indication to complicated UTI (cUTI), including pyelonephritis.

Infections of bones and joints

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)

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 with the wording proposed of "complicated skin and soft tissue infections".

Bacterial endocarditis

The MAH's clinical trial data all stem from open, retrospective or observational uncontrolled studies enrolling small numbers of patients. 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.

Bacteraemia

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 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)

Overall, there is evidence from controlled clinical trials that ceftriaxone is effective in the treatment of AOM.

Prophylaxis of perioperative infections

There is evidence for the efficacy of ceftriaxone in the perioperative prophylaxis of infections in several types of surgery such as cardiac surgery, orthopaedic surgery, genitourinary surgery and transurethral resection of the prostate (TURP).

Gonorrhoea, gonococcal arthritis, gonococcal eye infection

Ceftriaxone was demonstrated to have good clinical efficacy in the treatment of gonorrhoea when used as a single dose treatment. The CHMP considered that there was insufficient data to justify the disease subsets of gonococcal arthritis and gonococcal eye infection as separate indications, and therefore these were deleted as specific indications in the SmPC.

Syphilis including neurosyphilis

Limited clinical data are available in support of the efficacy of ceftriaxone in the treatment of 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

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

Dose recommendations have been listed in tabular format according to dosage schedules for each indication for: Adults and children over 12 years of age (≥ 50 kg), Neonates, infants and children 15 days to 12 years of age (< 50 kg) and Neonates 0-14 days.

Rocephin can be administered by intravenous infusion over at least 30 minutes (preferred route) or by slow intravenous injection over 5 minutes, or by deep intramuscular injection. 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.

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.

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, 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.

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 a Rocephin Periodic Safety Update Report (PSUR) work sharing procedure.

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 5.2 - Pharmacokinetic properties

Information on absorption, distribution, metabolism and elimination has been provided. Ceftriaxone distributes primarily into the extracellular space. Ceftriaxone is not metabolised systemically; but is converted to inactive metabolites by the gut flora. 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.

Special populations such as patients with renal and hepatic impairment and the paediatric population have also been included. 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.

Section 5.3 - Preclinical safety data

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 is 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.

Grounds for the variation to the terms of the marketing authorisation(s)

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 regarding with respect to the therapeutic indications, posology and method of administration sections, 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).