Bundesinstitut für Arzneimittel
und Medizinprodukte

Decentralised Procedure

Public Assessment Report

Ceftriaxone Farmaplus 500 mg powder for solution for injection
Ceftriaxone Farmaplus 1 g powder for solution for injection
Ceftriaxone Farmaplus 2 g powder for solution for infusion

Ceftriaxone (as ceftriaxone sodium)

DE/H/2951/001-003/DC

Applicant: Farmaplus AS
Norway

Reference Member State	DE

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ADMINISTRATIVE INFORMATION

Proposed name of the medicinal product in the RMS	Ceftriaxon FarmaPlus 500 mg Pulver zur Herstellung einer Injektionslösung Ceftriaxone FarmaPlus1 g Pulver zur Herstellung einer Injektionslösung Ceftriaxone FarmaPlus2 g Pulver zur Herstellung einer Infusionslösung
INN (or common name) of the active substance(s):	Ceftriaxone (as ceftriaxone sodium)
Pharmaco-therapeutic group (ATC Code):	Antibacterials for systemic use, Third-generation cephalosporins (J01 DD04)
Pharmaceutical form(s) and strength(s):	Powder for solution for injection; 500 mg Powder for solution for injection; 1 g Powder for solution for infusion; 2 g
Reference Number for the Decentralised Procedure	DE/H/2951/01-03/DC
Reference Member State:	DE
Member States concerned:	DK, FI, IS, NO, PL, SE, and UK
Applicant (name and address)	Farmaplus AS, Sørkedalsveien 10 B, NO-0369 Oslo, Norway

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the application for Ceftriaxone Farmaplus 500 mg / 1 g Powder for Solution for Injection/Infusion and Ceftriaxone Farmaplus 2 g Powder for Solution for Infusion, in the treatment of bacterial infections (for details see SmPC section 4.1) is approved.
The product information was adapted during the current DCP to the harmonised product information resulting from the finalised procedure in accordance with Article 30 (2) Referral of Council Directive 2001/83/EC, Procedure no: EMEA/H/A-30/1302, for Rocephin/Roche with the active substance ceftriaxone.

II. EXECUTIVE SUMMARY

II.1 Problem statement

The applications concerned are decentralised applications submitted according to Directive 2001/83/EC (as amended) under Article 10 (1) and 10 (3), as so called 'generic applications' and 'hybrid application', respectively, depending on the fact whether an own marketing authorisation of the originator exist in the different CMS for the strengths concerned, the applicant states as follows:

> The legal base for this submission is Article 10 due to the fact that for some countries and strengths, this product is not registered. Here are the details:
>
> - Article 10(1) for all strengths: GERMANY (RMS) and DENMARK (CMS).
> - Article 10(1) for the 1 g and 2 g strength: ICELAND, SWEDEN.
>
> - * Article 10(3) for all strengths: FINLAND, NORWAY, POLAND and UNITED KINGDOM
> - * Article 10(3) for the 500 mg strength: ICELAND, SWEDEN.

The originator product is Rocephin/Roche with the active substance ceftriaxone.

Rocephin® 500 mg
Pulver und Lösungsmittel zur Herstellung einer Injektionslösung
Rocephin® i.v. 1 g
Pulver und Lösungsmittel zur Herstellung einer Injektionslösung
Rocephin® zur Infusion 2 g
Pulver und Lösungsmittel zur Herstellung einer Infusionslösung

With Germany as the Reference Member State in this Decentralised Procedure Farmaplus AS, 0369 Oslo, Norway, is applying for the Marketing Authorisations for Ceftriaxone FarmaPlus in DK, FI, IS, NO, PL, SE and UK.

II.2 About the product

The applicant applies for 3 medicinal products in 3 different strengths; all 3 medicinal products are applied for intravenous injection and infusion, the 500 mg and 1g strengths for intramuscular use as well.
The active substance ceftriaxone is a parenteral cephalosporin for intravenous and intramuscular injection and intravenous infusion. Ceftriaxone is indicated for the treatment of various and serious infections caused by several Gram-positive and Gram-negative bacterial pathogens.
The applicant claims essential similarity with the German originator products by Roche Pharma AG, Emil-Barell-Str. 1, 79639 Grenzach-Wyhlen, registered since 1996-02-15.

Rocephin. 500 mg Pulver und Lösungsmittel zur Herstellung einer Injektionslösung (Powder and solvent for solution for injection) 32904.00.00 -> for intramuscular and intravenous use
Rocephin i.v. 1 g Pulver und Lösungsmittel zur Herstellung einer Injektionslösung (Powder and solvent for solution for injection) 32904.01.00 -> for intravenous use
Rocephin zur Infusion 2 g Pulver und Lösungsmittel zur Herstellung einer Infusionslösung (Powder and solvent for solution for infusion) ->32906.00.01-> for intravenous use
After adoption of the harmonised product information the indications are:
Ceftriaxone 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*

Ceftriaxone 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

Ceftriaxone should be co-administered with other antibacterial agents whenever the possible range of causative bacteria would not fall within its spectrum (see section 4.4).

Consideration should be given to official local guidance on the appropriate use of antibacterial agents.

Ceftriaxone has bactericidal activity resulting from the inhibition of bacterial cell wall synthesis by inhibiting PBPs, leading to cell death.
Ceftriaxone is active against organisms producing some types of beta- lactamase, for example TEM-1.
Bacterial resistance may be caused by inactivation (hydrolysation) of ceftriaxone by beta-lactamases, especially extended spectrum betalactamases, ESBLs, e.g of Escherichia coli oder Klebsiella pneumoniae, or chromosomal beta-lactamases of AmpC-type, e.g. of Enterobacter cloacae, or by reduced affinity of penicillin-binding proteins, or by bacterial impermeability or by bacterial drug efflux pumps.
Ceftriaxone is administered once daily. The target population ranges from newborn children to adults, the dosage from 20- 100mg per kg bodyweight in the peaediatric population to 2-4g in adults.
The most important pharmacokinetic-pharmacodynamic index correlating with in vivo efficacy has been shown to be the time during which the unbound concentration remains above the minimum inhibitory concentration (MIC) for the target species (i.e. % T>MIC).
Among others ceftriaxone is contraindicated in premature newborn and also in fullterm newborn with jaundice, hypalbuminaemia and acidosis and if they require or are expected to require iv-calcium-treatment. There is a risk of ceftriaxone-calcium-praecipitation in lungs and kidneys with reported fatal outcomes in this paediatric subgroup.

In this respect a discussion in the Pharmakovigilance Working Party was initiated which ended with an agreed wording for the SmPC (and PL) published in September 2009 (http://www.hma.eu/222.html, "Ceftriaxone and the risk of precipitation when given with calcium-containing solutions", Doc. Ref.: CMDh/PhVWP/005/2009) which has been considered in the harmonised product information.
The procedure in accordance with Article 30 (2) Referral of Council Directive 2001/83/EC, Procedure no: EMEA/H/A-30/1302, for the SmPC harmonisation of the medicinal product Rocephin/Roche with the active substance ceftriaxone is finalised. The harmonised product information is available: http://ec.europa.eu/health/documents/community-register/html/ho25150.htm.

II.3 General comments on the submitted dossier

This decentralised application concerns a generic version of Ceftriaxone Sodium. The applicant followed the Guideline on the investigation of bioequivalence CPMP/QWP/EWP/1401/98 rev1; 20 January 2010, as he didn't submit a bioequivalence study because the applied generic medicinal products are intended for intramuscular and intravenous use (injection and infusion) for which the proof of bioequivalence to the reference originator product is not required. The applicant followed the NfG on Evaluation of Medicinal Products Indicated for Treatment of Bacterial Infections (CPMP/EWP/558/95 rev 1) regarding the format of section 5.1 of the SmPC.

II.4 General comments on compliance with GMP, GLP, GCP and agreed ethical principles

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product except for the drug substance manufacturer performing drug product manufacturer activities (sterilisation of the drug substance). For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.
Declarations from the Qualified Person of the manufacturer responsible for batch release has been provided stating that the manufacturer is producing in compliance with the detailed guidelines on GMP.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

Drug Substance
The drug substance is Ceftriaxone sodium. CEPs are provided. Information on the sterilisation process was provided. The packaging material is stated on the CEP (anodised aluminium tin sealed with chlorobutyl rubber stopper secured by an aluminium ring seal). The re-test period 12 months is acceptable. The information presented is considered sufficient for the drug substance.

Drug Product
The drug product is a powder for solution for injection/infusion filled in type I glass vials. The compatibility of the solutions stated in the SmPC is substantiated by data. The sterile Ceftriaxone sodium powder is filled into the containers under nitrogen atmosphere. The manufacture of the finished product is adequately described. The product specifications cover appropriate parameters for this dosage forms with acceptable limits. For release and stability testing the methods of the Ph.Eur. are applied. Validation data were provided for assay, related substances, bacterial endotoxins, and sterility. Sufficient batch data have been provided. The information about the packaging material is sufficient. The test frequencies used in the stability studies are according to the ICH stability guideline. Long-term and accelerated testing has been performed. A shelf-life of two years is accepted. The storage precautions (do not store above 25°C; keep the vial(s) in the outer carton, in order to protect from light) are. As all Cephalosporins having an N-oxime moiety, Ceftriaxone is light-sensitive.

III.2 Non-clinical aspects

There are no objections to approval of Ceftriaxone FarmaPlus Solution for Injection and Infusion from a non-clinical point of view.

III.3 Clinical aspects

Pharmacokinetics
Bioequivalence studies are not required to support the application of the parenteral medicinal products.

Pharmacodynamics
The resistance situation across the EU of the pathogens most relevant in the indications is represented in section 5.1 of the SmPC.

Clinical efficacy
The product information of the reference product Rocephin/Roche was harmonised.

Clinical safety
Ceftriaxone has generally a well-recognised efficacy and an acceptable level of safety in the newly proposed indications, and corresponding products have been widely used in many countries. Considering the fact that ceftriaxone is an old active substance and the originator product is licensed nationally throughout Europe the differences in the national SmPCs will be cleared up in the on-going Art30-procedure. Aspects considering the risk of ceftriaxone-calcium-praecipitation in lungs and kidneys with reported fatal outcomes in premature newborn and also in fullterm newborn if they require or are expected to require iv-calcium-treatment have been regarded in the SmPC.

User testing
The applicant provided the user-testing results of his originally applied and submitted PL. The results are acceptable. Nevertheless, the PL is replaced by the implementation of the harmonised PL.

Pharmacovigilance system
The Applicant/Proposed Future MAH has submitted a signed Summary of the Applicant's/Proposed Future MAH's Pharmacovigilance System and asked the RMS to replace the previously submitted DDPS with the new Summary of Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the RMS accepts this substitution.

Risk Management Plan
Ceftriaxone has generally a well-recognised efficacy and an acceptable level of safety in the proposed indications, and corresponding products have been widely used in many countries. Therefore, Ceftriaxone FarmaPlus 500mg, powder for solution for injection, Ceftriaxone FarmaPlus 1g, powder for solution for injection, Ceftriaxone FarmaPlus 2g, powder for solution for infusion, with the indications mentioned above does currently not require additional risk minimisation measures beyond the Product Information and routine pharmacovigilance activities. A Risk Management Plan has therefore not been established for the originator product and is also considered not necessary for the applied products.

Periodic Safety Update Report (PSUR)
With regard to PSUR submission, the MAH should take the following into account:
For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.

IV. BENEFIT RISK ASSESSMENT

The application is approved.
For intermediate amendments see current product information.