IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Ceftriaxone 1g powder for solution for injection/infusion
Ceftriaxone sodium
PA23183/006/001

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

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I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Ceftriaxone 1g powder for solution for injection/infusion, from JED Pharma Limited on 10th of March 2023.
This is a generic product and the legal basis for this application is article 10 (1) of Directive 2001/83/EC as amended.
This medicinal product has been approved with the following indications:
Ceftriaxone is indicated in 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 causitive bacteria would not fall within its spectrum.

This medicinal product is subject to prescription, which may not be renewed.
The Summary of Product Characteristics (SmPC) for this medicinal product is available on the HPRA's website at www.hpra.ie.

Name of the product	Ceftriaxone 1g powder for solution for injection/infusion
Name(s) of the active substance(s) (INN)	CEFTRIAXONE SODIUM
Pharmacotherapeutic classification (ATC code)	Ceftriaxone-J01DD04
Pharmaceutical form and strength(s)	Powder for solution for injection/infusion, 1000 milligrams
Marketing Authorisation Number(s) in Ireland (PA)	PA23183/006/001
Marketing Authorisation Holder	JED Pharma Limited

II. QUALITY ASPECTS

II.1. Introduction
This application is for Ceftriaxone 1g powder for solution for injection/infusion

II.2 Drug substance
The active substance is Ceftriaxone sodium an established active substance described in the European Pharmacopoeia, and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP)

The active substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition

Composition of the medicinal product includes 1.193 g of active substance ceftriaxone sodium which is the equivalent to 1.000 g of ceftriaxone.

The drug product does not contain any excipients.
A visual description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European/ICH guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients)

The drug product does not contain any excipients or other substances.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for the dosage form, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production sites have been provided and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that the packaging complies with Ph. Eur./EU legislation for use with foodstuffs requirements.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Ceftriaxone 1g powder for solution for injection/infusion.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This active substance is a generic formulation of Rocephin 1g powder for solution for injection/infusion on the European market. No new preclinical data have been submitted. As such, no pre-clinical assessment has been made on the application. This is acceptable for this type of application.

III.2 Ecotoxicity/environmental risk assessment
Since Ceftriaxone 1g/vial solution for injection/infusion is a generic product, an increased exposure to the environment is not anticipated. A justification for the absence of ERA studies on the basis of generic substitution was provided.

III.3 Discussion on the non-clinical aspects
Pharmacodynamic, pharmacokinetic and toxicological properties of Ceftriaxone are well known. As Ceftriaxone is a widely used, well-known active substance, the applicant has not provided additional nonclinical studies and further studies are not required.

IV. CLINICAL ASPECTS

IV.1 Introduction
Ceftriaxone is a well known active substance with established efficacy and tolerability.

The content of the SmPC approved during this national procedure is in accordance with that accepted for the reference product Rocephin 1g powder for solution for injection/infusion, PA2307/008/003, marketed by Roche Products (Ireland) Ltd.

For this generic application, the applicant was not required to perform bioequivalence studies in compliance with the CHMP guideline on the Investigation of Bioequivalence (CPMP/PWP/EWP/1401/98 Rev 1/Corr**) regarding parenteral solutions. The product is an aqueous solution containing the same concentration of the same active substance and the same excipients in similar amounts as the medicinal product currently approved.

IV.2 Pharmacokinetics
The pharmacokinetic profile of ceftriaxone is well characterised.

Absorption
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 ceftriaxone produces mean peak plasma concentrations of 40-70 mg/l within one hour, approximately half those observed after intravenous administration of an equivalent dose. Bioavailability after intramuscular injection is 100%.

Distribution
The volume of distribution of ceftriaxone is 7 – 12 l. Steady state is reached in most cases within 48 - 72 hours depending on the route of administration. Ceftriaxone binds reversibly to albumin. The level of binding decreases with increasing ceftriaxone concentrations as plasma protein binding sites become saturated.

Tissue Penetration
Concentrations well above the minimal inhibitory concentrations of most relevant pathogens are detectable in tissue including lung, heart, biliary tract/liver, tonsil, middle ear and nasal mucosa, bone, and in cerebrospinal, pleural, prostatic and synovial fluids. Ceftriaxone penetrates the meninges and is greatest when the meninges are inflamed. Peak ceftriaxone concentrations in CSF are reached approximately 4-6 hours after intravenous injection. Ceftriaxone crosses the placental barrier and is excreted in the breast milk at low concentrations. Ceftriaxone preferentially localises in bile.

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

Elimination
Ceftriaxone is eliminated mainly as unchanged drug, 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 10-22 ml/min. The renal clearance is 5-12 ml/min. The elimination half-life of total ceftriaxone in adults is about 8 hours.
A notable feature of ceftriaxone is its relatively long plasma elimination half-life of approximately eight hours which makes single or once daily dosage of the drug appropriate for most patients. The half-life is not significantly affected by the dose, the route of administration or by repeated administration.

Pharmacokinetic/pharmacodynamic relationship

As with other beta-lactams, the pharmacokinetic-pharmacodynamic index demonstrating the best correlation with *in vivo* efficacy is the percentage of the dosing interval that the unbound concentration remains above the minimum inhibitory concentration (MIC) of ceftriaxone for individual target species (i.e. %T > MIC).

IV.3 Pharmacodynamics

Ceftriaxone is a parenteral third-generation cephalosporin. Ceftriaxone is a bactericidal agent that acts by inhibition of bacterial cell wall synthesis following attachment to penicillin binding proteins (PBPs). This results in the interruption of cell wall (peptidoglycan) biosynthesis, which leads to bacterial cell lysis and death.

Ceftriaxone is stable to a wide range of both Gram-positive and Gram-negative betalactamases, including those which are able to hydrolyse advanced generation penicillin derivatives and other cephalosporins. Bacterial resistance to ceftriaxone may be due to one or more of the following mechanisms:

- hydrolysis by beta-lactamases, including extended-spectrum beta-lactamases (ESBLs), carbapenemases and Amp C enzymes that may be induced or stably derepressed in certain aerobic Gram-negative bacterial species.
- reduced affinity of penicillin-binding proteins for ceftriaxone.
- outer membrane impermeability in Gram-negative organisms.

- bacterial efflux pumps

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections.
Additonal information provided in the clinical overview suggested that Ceftriaxone treatment may be associated with reversible suppression of intestinal microflora. Studies in patients show that ceftriaxone reversibly alters the intestinal flora (suppresses enterobacteria, bifidobacteria, clostridia and *Bacteroides*and increases enterococci and candida), but is associated with the emergence of fewer cephalosporin-resistant Gram- negative bacilli than cefotaxime or cefazolin.

IV.4 Clinical Efficacy

No clinical efficacy data are provided as this is a generic application.

IV.5 Clinical Safety

As this is a generic application, no other clinical safety data are required.

Risk Management Plan (RMP)

The applicant has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Ceftriaxone 1g powder for solution for injection/infusion.
Routine pharmacovigilance and routine risk minimisation activities are considered sufficient.
Summary of safety concerns

Important identified risks	None
Important potential risks	None
Missing information	None

Periodic Safety Update Report (PSUR)

With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c (7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.
- 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.
- For medicinal products that do not fall within the categories waived of the obligation to submit routine PSURs by the revised pharmacovigilance legislation, the MAH should follow the DLP according to the EURD list.

IV.6 Discussion on the clinical aspects

As this approval concerns a generic application, there are no new efficacy or safety studies required, as the applicant can refer to the data of the reference medical products.

V. OVERALL CONCLUSIONS

Ceftriaxone 1g powder for solution for injection/infusion is a generic form of Rocephin 1g powder for solution for injection/infusion, PA2307/008/003, marketed by Roche Products (Ireland) Ltd. Ceftriaxone is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

Bioequivalence was waived in compliance with the CHMP guidance documents. The SmPC is consistent with that of the reference product and Article 30 referral EMEA/H/A-30/1302.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The HPRA, on the basis of the data submitted considered that Ceftriaxone 1g powder for solution for injection/infusion has demonstrated a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

VI. REVISION DATE

5 years from the finalisation of the procedure.

VII. UPDATES

This section reflects the significant changes following finalisation of the initial procedure.

SCOPE	PROCEDURE NUMBER	PRODUCT INFORMATION AFFECTED	DATE OF START OF PROCEDURE	DATE OF END OF PROCEDURE
New National	N/A	SPC Section 1 to 9	10th March 2023	9th March 2028