IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

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 Cefotaxime 500 mg, 1 g and 2 g powder for solution or injection/infusion from Noridem Enterprises Limited on 26th June 2020 for treatment of severe infections when known to or thought very likely to be caused by bacteria that are susceptible to cefotaxime and perioperative prophylaxis for surgical operations with increased risk of infection with anaerobic pathogens (see Section 4.1 of the SmPC)

This application was submitted under Article 10 (1) *of Directive 2001/83/EC* referred to as a generic application, with Ireland as reference member state and the following as concerned member states: France; Belgium and Luxembourg.

The Summary of Product Characteristics for (SmPC) for this medicinal product is available on the HPRA's website.

Name of the product	Cefotaxime 500 mg, 1 g and 2 g powder for solution for injection/infusion
Name(s) of the active substance(s) (INN)	Cefotaxime sodium
Pharmacotherapeutic classification (ATC code)	J01DD01
Pharmaceutical form and strength(s)	Powder for solution for injection/infusion; 500 mg, 1 g and 2 g
Marketing Authorisation Number(s) in Ireland (PA)	PA1122/019/001-003
Marketing Authorisation Holder	Noridem Enterprises Ltd
MRP/DCP No.	IE/H/491/001-003/DC
Reference Member State	IE
Concerned Member State	FR BE LU EL CY

II. QUALITY ASPECTS

II.1. Introduction

This application is for Cefotaxime 500 mg, 1 g and 2 g powder for solution for injection/infusion.

II.2 Drug substance

The active substance is Cefotaxime sodium, an established active substance 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

The excipients in the medicinal product are listed in section 6.1 of the SmPC.
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/*Ancillary Substances*)

All ingredients comply with Ph. Eur.

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 site have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.7 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. requirements.

P.8 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 Cefotaxime 500 mg, 1 g and 2 g powder for solution for injection/infusion.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Cefotaxime Noriden is a generic formulation of Claforan with the same active substance, cefotaxime sodium. No new preclinical data have been submitted.

The pharmacodynamic, pharmacokinetic and toxicological properties of cefotaxime sodium are well known. As cefotaxime sodium is a widely used, well-known active substance, the applicant has not provided additional studies. An overview based on literature review is acceptable for this type of application.

III.2 Ecotoxicity/environmental risk assessment

Since Cefotaxime Noriden is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.3 Discussion on the non-clinical aspects

The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology provided is adequate. As cefotaxime sodium is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Non-clinical findings are adequately represented in the appropriate sections of the SmPC.

IV. CLINICAL ASPECTS

IV.1 Introduction

Cefotaxime is a well known active substance with established efficacy and tolerability.

The content of the SmPC approved during the decentralised procedure is in accordance with that accepted for the reference product Claforan marketed by Sanofi-Aventis and has been modified during the course of the procedure to be in line with recent decentralised procedures for cefotaxime.

No bioequivalence studies were submitted as Bioequivalence studies are generally not required if the test product is to be administered as an aqueous intravenous solution containing the same active substance as the currently approved reference product.

IV.2 Pharmacokinetics

Cefotaxime is for parenteral application. Mean peak concentrations 5 minutes after intravenous administration are about 81 – 102 mg / L following a 1 g dose of cefotaxime and about 167 – 214 mg / L 8 minutes after a 2 g dose. Intramuscular injection produces mean peak plasma concentrations of 20 mg / L within 30 minutes following a 1 g dose.

Distribution
Cefotaxime has good penetration into different compartments. Therapeutic drug levels exceeding the minimum inhibitory levels for common pathogens can rapidly be achieved. Cerebrospinal fluid concentrations are low when the meninges are not inflamed but cefotaxime usually passes the bloodbrain barrier in levels above the MIC of the sensitive pathogens when the meninges are inflamed (3- 30 µg / mL). Cefotaxime concentrations (0.2 – 5.4 µg / mL), inhibitory for most gramnegative bacteria, are attained in purulent sputum, bronchial secretions and pleural fluid after doses of 1or 2 g.
Concentrations likely to be effective against most sensitive organisms are similarly attained in female reproductive organs, otitis media effusions, prostatic tissue, interstitial fluid, peritoneal fluid and gall bladder wall, after therapeutic doses. High concentrations of cefotaxime and O-desacetyl-cefotaxime are achieved in bile. Cefotaxime passes the placenta and attains high concentrations in foetal fluid and tissues (up to 6 mg / kg). Small amounts of cefotaxime diffuse into the breast milk.
Protein binding for cefotaxime is approximately 25 – 40%.
The apparent distribution volume for cefotaxime is 21-37 l after 1 g intravenous infusion over 30 minutes.

Biotransformation
Cefotaxime is partly metabolised in humans. Approximately 15-25% of a parenteral dose are metabolised to the O-desacetyl-cefotaxime metabolite, which also has antibiotic properties.
Elimination
The main route of excretion of cefotaxime and O-desacetyl-cefotaxime is through the kidneys. Only a small amount (2%) of cefotaxime is excreted in the bile. In the urine collected within 6 hours 40 – 60% of the administered dose of cefotaxime is recovered as unchanged cefotaxime and 20% is found as Odesacetylcefotaxime. After administration of radioactive labelled cefotaxime more than 80% can be recovered in the urine; 50 – 60% of this fraction is unchanged cefotaxime and the rest contains metabolites. The total clearance of cefotaxime is 240 – 390 mL / min and the renal clearance is 130 – 150 mL / min.
The serum half-lives of cefotaxime and O-desacetyl-cefotaxime are normally about 50 – 80 and 90 minutes, respectively. In elderly, the serum half-life of cefotaxime is 120 – 150 min.
In patients with severely impaired renal function (creatinine clearance 3 – 10 mL / min) the serum halflife of cefotaxime can be increased to 2.5 – 3.6 hours.
There is no accumulation following administration of 1000 mg intravenously or 500 mg intramuscularly for 10 or 14 days.
In neonates the pharmacokinetics are influenced by gestation and chronological age, the half-life being prolonged in premature and low birth weight neonates of the same age.
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IV.3 Pharmacodynamics

Cefotaxime is a third generation cephalosporin antibiotic. The bactericidal activity of cefotaxime results from the inhibition of bacterial cell wall synthesis (during the period of growth) caused by an inhibition of penicillin-binding proteins (PBPs) like transpeptidases.

IV.4 Clinical Efficacy

The clinical efficacy of cefotaxime is well characterised. No new clinical efficacy data are required for these applications and none have been submitted controlled, inclusion criteria,

IV.5 Clinical Safety

The clinical safety of cefotaxime is well characterised.

Risk Management Plan

The Applicant 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 cefotaxime 500mg, 1g & 2g powder for solution for injection/infusion.
The RMP (version 1.0, date of final sign-off: 24/12/2019) is acceptable. Routine pharmacovigilance and routine risk minimisation are considered sufficient.

Summary table of safety concerns as approved in RMP

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

An updated RMP should be submitted:

- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

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

The efficacy and safety of cefotaxime is well characterised. No bioequivalence studies were required as the product is for intravenous or intra-muscular use.
For generic applications: brief explanation that abridged applications avoid the need for repetitive tests on humans. Reference to the reference medicinal product. For these applications the bioequivalence studies are pivotal and should be described.

V. OVERALL CONCLUSIONS

Cefotaxime 500 mg, 1 g and 2 g powder for solution or injection/infusion from Noridem Enterprises Limited is a generic form of Calforan. Claforan is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

No bioequivalence studies were submitted as Bioequivalence studies are generally not required if the test product is to be administered as an aqueous intravenous solution containing the same active substance as the currently approved reference product.

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 Cefotaxime 500 mg, 1 g and 2 g powder for solution or injection/infusion is similar to the reference product and has a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

VI. REVISION DATE

23.02.2025