COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Cefepime Noridem 1 g and 2 g, powder for solution for injection or infusion

(cefepime dihydrochloride monohydrate)

NL/H/4045/001-002/DC

Date: 28 November 2018

This module reflects the scientific discussion for the approval of Cefepime Noridem 1 g and 2 g, powder for solution for injection or infusion. The procedure was finalised at 5 July 2018. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Cefepime Noridem 1 g and 2 g, powder for solution for injection or infusion, from Noridem Enterprises Ltd.

The product is indicated for the treatment of the severe infections listed below caused by cefepime-susceptible pathogens (see sections 4.4 and 5.1 of the approved SmPC).

In adults and children over 12 years of age and with a body weight of ≥ 40 kg:
- Pneumonia
- Complicated urinary tract infections (including pyelonephritis)
- Complicated intra-abdominal infections
- Peritonitis associated with dialysis in patients on CAPD.

In adults:
- Acute biliary tract infections

In children aged 2 months up to 12 years and with a body weight of ≤ 40 kg:
- Pneumonia
- Complicated urinary tract infections (including pyelonephritis)
- Bacterial meningitis.

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

Cefepime may be used in the empirical treatment of adults, adolescents and children aged 2 months to 12 years with febrile neutropenia that is suspected to be due to a bacterial infection. In patients at high risk of severe infections (e.g. patients with recent bone marrow transplantation, hypotension at presentation, underlying haematological malignancy, or severe or prolonged neutropenia), antimicrobial monotherapy may be inappropriate. No sufficient data exist to support the efficacy of cefepime monotherapy in such patients. A combination therapy with an aminoglycoside or glycopeptide antibiotic may be advisable, taking into consideration the patient's individual risk profile.

Cefepime should be co-administered with other antibacterial agents whenever the possible range of causative bacteria would not fall within its spectrum of activity.

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the European reference products (ERP) Maxipime 1 g and 2 g powder for solution for injection/infusion, which have been registered in Belgium since 6 May 1994 by Bristol-Myers Squibb Belgium SA. As no registration of Maxipime powder for solution for injection/infusion

containing cefepime has been granted in the Netherlands, the Belgium product is used as European Reference Product .

The concerned member states (CMS) involved in this procedure were Belgium, Czech Republic, France, Luxembourg and the Slovak Republic.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Cefepime-MIP is a white to pale yellow powder. The powder needs to be reconstituted prior to application. The pH of the reconstituted solution is 4.0-7.0.

The powder for solution for injection or infusion is packed in glass (Type III) vials closed with a rubber closure with an aluminium cap with a flip-top plastic cover.

Each vial contains 1.189 g or 2.378 g cefepime dihydrochloride monohydrate corresponding to 1 g or 2 g cefepime.

The only excipient is L-arginine.

II.2 Drug Substance

The active substance is cefepime, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is freely soluble in water and in methanol, practically insoluble in methylene chloride. It is a white to almost white, crystalline powder. It has a specific optical rotation of +40° to +45°.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process

A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specification has not been provided, although a justification for the specification has been provided stating that the tests and limits are in compliance with the Ph.Eur. monograph with additional test for residual solvents.
Batch analyses data on three production scaled batches have been provided and comply with the Ph.Eur monograph.

Stability of drug substance
The active substance is stable for 2 years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The main development studies performed were essential similarity/comparative analysis. The choices of the packaging are justified. As the test and innovator drug products are to be administered as an aqueous intravenous infusion and contain the same active substance (i.e. cefepime dihydrochloride monohydrate) and excipient (L-arginine) in the same quantities as the reference products, no bioequivalence study is required in accordance with the Guideline on the investigation of bioequivalence.
The pharmaceutical development of the drug product has been adequately performed. The manufacturing process development justified the selection of the sterilisation method. The finished is prepared by aseptic compounding and filling using pre-sterilised individual components. Compatibility data demonstrated that the drug product can be diluted with 0.9% sodium chloride solution, 5% dextrose solution and sodium chloride 0.9% and dextrose 5% solution.

Manufacturing process
The manufacturing process of the medicinal product consists of mixing and filling of the sterile blend into pre-sterilised vials performed by two different parties under aseptic conditions. The control of the intermediate drug product and information on the control of critical steps in the manufacture of the sterile intermediate drug product are provided. The intermediate product specifications comply with the final product specifications. The process has been validated according to relevant European guidelines. Process validation data on the product have been presented for three full scaled batches in accordance with the relevant European guidelines.

Control of excipients
The sterile arginine used in the preparation of the sterile blend is of Ph.Eur. quality with additional requirements for bacterial endotoxins, sterility, colour and clarity and particulate matter according to the Ph.Eur. These specifications are acceptable.

Microbiological attributes

The product is filled under aseptic conditions (under nitrogen atmosphere) in sterilised glass vials which are closed with sterilised rubber closures and sealed with sterilised aluminium flip-off caps. In addition, in process control during sealing of the vials confirms the integrity of the container closure system.

The information provided is considered sufficient. The product is a sterile product. Sterility and bacterial endotoxins are controlled as part of the finished product specification.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, identity, reconstitution time, pH, clarity of the solution, water, assay, related substances, N-methylpyrrolidine, uniformity of dosage units, particulate contamination, sterility and bacterial endotoxins. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from the proposed production sites have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for three full scaled batches stored at 25°C/60% RH (up to 18 months) and 40°C/75% RH (up to 6 months). The condition used in accordance with applicable European guidelines. The batches were stored in the proposed packaging. The stability data showed no clear trends or changes in any of the tested parameters at both storage conditions. Results of a photostability study showed that the product is not photo stable in the immediate conditions. Therefore, on the basis of the data submitted, a shelf life was granted of 30 months with the storage conditions: 'Store below 25°C. Keep the vials in the outer carton in order to protect from light.'

The chemical and physical stability of the preparation after dilution has been demonstrated for 7 days when stored at 2°C - 8°C or for 24 hours when stored at 23°C - 27°C. From a microbiological point of view, the product should be used immediately. If not used immediately in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C - 8°C.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Cefepime Noridem has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Cefepime Noridem 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.2 Discussion on the non-clinical aspects

This product is a generic formulation of Maxipime which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Cefepime is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

IV.2 Pharmacokinetics

Biowaiver

Cefepime Noridem 1 g and 2 g, powder for solution for injection or infusion is a parenteral formulation and therefore fulfils the exemption mentioned in the Note for Guidance on bioequivalence “5.1.6 parenteral solutions”, which states that a bioequivalence study is not required if the product is administered as an aqueous intravenous solution containing the same active substance in the same concentration as the currently authorized reference medicinal product (NfG CPMP/EWP/QWP 1401/98). The quantitative composition of Cefepime Noridem is entirely the same as the originator. Therefore, it may be considered as therapeutic equivalent, with the same efficacy/safety profile as known for the active substance of the reference medicinal product. The current product can be used instead of its reference product.

IV.3 Risk Management Plan

The MAH 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 Cefepime Noridem

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	- Hypersensitivity, anaphylaxis - Pseudomembranous colitis - Renal failure
Important potential risks	- Increased risk of adverse events in patient with renal impairment - Interaction with drugs with nephrotoxic potential - Medication error (wrong dose) in children - Overdose especially in the elderly - Superinfection
Missing information	- Exposure during pregnancy and lactation - Data on use in infants under the age of 2 months - Effectiveness of cefepime monotherapy in patients with febrile neutropenia

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Maxipime 1 g and 2 g powder for solution for injection/infusion. No new clinical studies were conducted. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet (PL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of two rounds with 10 participants each. A questionnaire of 15 questions on the leaflet content was used, sufficiently addressing the key safety and usage messages, and 6 additional questions to obtain feedback on the general layout and appearance of the leaflet. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.

The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Cefepime Noridem 1 g and 2 g, powder for solution for injection or infusion have a proven chemical-pharmaceutical quality and are generic forms of Maxipime 1 g and 2 g powder for solution for injection/infusion. Maxipime is a well-known medicinal product with an established favourable efficacy and safety profile.

Since both the reference and current product are intended for parenteral use, no bioequivalence study is deemed necessary. A biowaiver has been granted.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Cefepime Noridem with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 5 July 2018.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse