CBG MEB

Public Assessment Report

Scientific discussion

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

(cefepime)

NL/H/2986/001-002/DC

Date: 22 July 2015

This module reflects the scientific discussion for the approval of Cefepime-MIP 1 g and 2 g, powder for solution for injection or infusion. The procedure was finalised on 27 November 2014. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

I. INTRODUCTION

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

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 Germany since 23 January 2004 by Bristol-Myers Squibb GmbH & Co.

The concerned member states (CMS) involved in this procedure were Austria, Belgium, Bulgaria, Czech Republic, Denmark, Estonia, Finland, Germany, Hungary, Lithuania, Latvia, Norway, Poland, Romania, Slovakia, Spain and Sweden.

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.

Cefepime-MIP 1 g is supplied in 15 ml colourless type I glass vials closed with bromobutyl rubber stoppers and flip-off seal, containing a white to pale yellow powder.
Cefepime-MIP 2 g is supplied in 50 ml colourless type II glass vials closed with bromobutyl rubber stoppers and flip-off seal.

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 European Pharmacopoeia.

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

Quality control of drug substance
The drug substance specification is in line with the Ph.Eur. and the CEP. The MAH included two additional tests. The specification is acceptable. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three full-scale batches.

Stability of drug substance
The active substance is stable for 2 years when stored at 2-8°C 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. Critical parameters being relevant for an appropriate quality of the final product have been identified and are monitored by suitable in-process controls, assuring a good batch-to-batch consistency and homogeneity. The manufacturing process takes place under aseptic conditions. The blend of cefepime, sterile and L-arginine, sterile is manufactured at the drug substance manufacturing site. In turn the blend is transported to the drug product manufacturing site where it is filled into the final packaging. The choice of aseptic filling of presterilised individual components is justified. The composition of the drug product and the innovator product are considered to be similar.
Since the drug product is a solution for injection or infusion no bioavailability studies are required.
The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process of the medicinal product consists of the manufacture of a bulk mixture of active ingredient and buffer substance being filled into the primary packaging containers as a sterile powder. Process validation data on the product has been provided on two pilot scaled batches per strength and four production batches of two other, comparable cephalosporin products with the same process, including al critical aspects.
The manufacturing process is considered to be a non-standard manufacturing process, and has been sufficiently validated on full-scale batches according to relevant European guidelines.

Control of excipients
The excipient, L-arginine sterile, complies with the European Pharmacopoeia with additional tests for sterility, bacterial endotoxins, colour, clarity and particulate matter. The specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, identity of cefepime, arginine and chloride, appearance of solution, dissolution time, pH, water content, osmolality, particulate contamination, sterility, bacterial endotoxins, uniformity of dosage units, related substances and assay of cefepime and arginine. The release and shelf-life limits are identical with the exception of the limits for pH, impurities and cefepime assay. The specification is acceptable.
The analytical methods have been adequately described. A product-specific validation of the analytical procedure for the determination of identity, content and purity of cefepime in the finished medicinal product has been provided including a forced degradation study.
Batch analytical data from the proposed production site have been provided on two pilot-scale batches per strength, demonstrating compliance with the release specification.

Microbiological attributes
According to 5.1.4 of the Ph.Eur., the finished medicinal product belongs to category 1 which is required to be sterile as requested by the general monograph Parenteral Preparations of the European Pharmacopoeia.
Due to the sensitivity of the active substance, no terminal sterilisation of the closed container can be performed in the manufacturing process. A strictly aseptic regime has to be applied to guarantee the sterility of the finished medicinal product. In order to show that the medicinal product does not bear any risk of accumulation of microbes, the microbiological status of the dosage form is investigated also in the framework of stability testing. The proposed limits for the drug product are acceptable.

Stability of drug product
Stability data on the product has been provided of four pilot-scale batches. The stability batches were stored at 25°C/60% RH (24 months), 30°/65% RH (12 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the proposed packaging.
At 40°C/75% RH out-of-specification results were observed for particulate matter in three of the four batches. Furthermore an increase in impurities was observed.
At 30°C/65% RH and at 25°C/60% RH particulate contamination increased but remained within the specification limit. No other trends are observed. Based on the Ph.Eur. monograph of cefepime and arginine both substances are considered to be sensitive to light. Hence, no photostability study has been conducted.
Based on the submitted data a shelf-life of 27 months and storage condition ‘Do not store above 30°C; Keep the vial in the outer carton in order to protect from light’ is justified.

In order to demonstrate the stability of the reconstituted solution in water for injections, 5% glucose solution, physiological sodium chloride solution (0.9%) and 1% lidocaine solution at ambient temperature and for storage in a refrigerator (2-8°C), a study has been performed. The in-use shelf life of 2 hours is justified at room temperature and 24 hours at 2-8°C, based on adequate in-use results.

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-MIP 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-MIP 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-MIP 1 g and 2 g powder for solution for injection or infusion is a generic and contains the same drug substance, cefepime hydrochloride, in the same pharmaceutical form, powder to prepare injectable solutions, at the same strengths, 1.0 and 2.0 g, as the originator brand Maxipime by Bristol-Myers Squibb Company. Since this cefepime formulation is administered as a solution by the intravenous route (or intramuscular route), the bioavailability of the product is considered 100%.
No additional studies are deemed necessary to confirm the bioavailability of Cefepime-MIP for this intravenous formulation and the bioequivalence with the reference medicinal product. This is in accordance with the NfG on the "Investigation of bioavailability and bioequivalence" (CPMP/EWP/QWP/1401/98).

IV.3 Clinical efficacy and safety

Therapeutic indications
Pneumonia
On the basis of the submitted studies as referred to in the Clinical Overview, supported by the current International Guidelines on the treatment of pneumonia, and with reference to the positive outcome of DCP NL/H/1370/001-002/DC and the approved SmPC of the ERP, RMS considers cefepime a useful effective and safe drug in the treatment of pneumonia. Cefepime should be reserved for severe pneumonia.

The following indication for cefepime is considered approvable: ***"Severe pneumonia in adults, adolescents and children aged 2 months to 12 years old and with a body weight of ≤ 40 kg".***

Urinary tract infections
On the basis of the submitted studies as referred to in the Clinical Overview, supported by the current International Guidelines on the treatment of urinary tract infections, and with reference to the positive outcome of DCP NL/H/1370/001-002/DC and the approved SmPC of the ERP, RMS considers cefepime a useful effective and safe drug in the treatment of "nosocomial, severe *complicated* urinary

tract infections (including pyelonephritis) in adults, adolescents and children aged 2 months to 12 years and with a body weight of ≤ 40 kg.

The following indication for cefepime is considered approvable:
"Severe, complicated urinary tract infections (including pyelonephritis) in adults, adolescents and children aged 2 months to 12 years old and with a body weight of ≤ 40 kg".

Skin and soft tissue infections
Only four publications of studies were submitted in support of this indication and all of these publications were over 10 years old providing at most weak evidence for efficacy and safety of cefepime. Moreover, cefepime is not mentioned as an option for the treatment of SSTIs in what could considered relevant guidelines for the treatment of skin and soft tissue infections[1]. This indication has not been accepted for the German ERP either, nor in the approved Cefepime Fresenius Kabi (DCP NL/H/1370/001-002/DC), nor in the former registered Dutch innovator Maxipime. The requested indication "Skin and soft tissue infections" is therefore considered not approvable unless better justified by the MAH.

The following indication "Skin and soft-tissue infections (adults and adolesents)" is considered not approvable for cefepime unless better justified by the MAH.

Severe/complicated intra-abdominal infections
Taken into consideration the submitted studies as referred to in the Clinical Overview, supported by the current International Guidelines on the treatment of intra-abdominal infections, and with reference to the positive outcome of DCP NL/H/1370/001-002/DC, and the approved SmPC of the ERP, RMS considers cefepime an useful effective and safe drug in the treatment of "severe, complicated intra-abdominal infections in adults and children over 12 years of age" and in the treatment of "Severe, acute biliary tract infections in adult patients".

The following indications for cefepime are considered approvable:
"Severe, complicated intra-abdominal infections in adults and children over 12 years of age"
"Severe, acute biliary tract infections in adults"

Peritonitis due to dialysis in patients undergoing CAPD
On the basis of the submitted studies as referred to in the Clinical Overview, supported by the current International Guidelines on the treatment of peritoneal dialysis-related infections, and with reference to the positive outcome of DCP NL/H/1370/001-002/DC and the approved SmPC (section 4.2) of the ERP, RMS considers cefepime a useful effective and safe drug in the treatment of "Severe, peritonitis associated with dialysis in patients on CAPD in adults and children over 12 years of age".

The following indication for cefepime is considered approvable:
"Severe peritonitis associated with dialysis in patients on CAPD"

Prophylaxis in intra-abdominal surgery
Only two supportive studies were submitted. The use of cefepime is not recommended in relevant recent updated guidelines (IDSA 2013). This indication is not approved in the SmPC of the German ERP nor in the SmPC of Cefepime Fresenius Kabi (NL/H/1370/001-002/DC). The risk of development of resistance following a wide-spread prophylactic use, is considered a major concern by RMS and for these reasons the assessor considers "Prophylactic use of cefepime in intra-abdominal surgery" not acceptable.
The claimed indication for cefepime "Prophylaxis in intra-abdominal surgery (in adults and adolescents)" is considered not acceptable.

Bacterial meningitis in children
With reference to the submitted studies as referred to in the Clinical Overview, supported by existing guidelines on the treatment of bacterial meningitis, and based upon the approval of this indication in the approved SmPC of the ERP, RMS considers cefepime a useful effective and safe drug in the

[1] IDSA Guidelines – "Practice Guidelines for the Diagnosis and Management of Skin and Soft-Tissue Infections" - CID 2005:41 (15 November) • 1373-1406.

treatment of “bacterial meningitis in children aged 2 months to 12 years and with a body weight of ≤ 40 kg”.

The following indication for cefepime is considered approvable:
”Bacterial meningitis in children aged 2 months to 12 years old and with a body weight of ≤ 40 kg”

Empirical treatment of patients with febrile neutropenia
On the basis of the submitted studies (conducted in adults and in the pediatric population) as referred to in the Clinical Overview, supported by the existing International Guidelines on the treatment of Empirical treatment of patients with febrile neutropenia, and with reference to the approved SmPC of Cefepime Fresenius Kabi 1 g and 2 g (DCP NL/H/1370/001-002/DC), and the approved SmPC of the ERP, the member states consider cefepime a useful effective and safe drug in the management of neutropenic patients with fever that is suspected to be due to a bacterial infection in adults, adolescents and children aged 2 months to 12 years old and with a body weight of ≤ 40 kg.

The following indication for cefepime is considered approvable: ***”Cefepime may be used in empirical treatment of patients with febrile neutropenia that is suspected to be due to a bacterial infection in adults, adolescents and children aged 2 months to 12 years old and with a body weight of ≤ 40 kg). Cefepime as monotherapy is indicated in patients with febrile neutropenia. In patients at high risk of severe infections (e.g. patients with recent bone marrow transplantation, with hypotension at presentation, with an underlying haematological malignancy, or severe or prolonged neutropenia), antimicrobial monotherapy may be not appropriate. Insufficient data exist to support the efficacy of cefepime monotherapy in such patients. Combination therapy with an aminoglycoside or glycopeptide antibiotic may be advisable, taking into consideration the individual risk profile of the patient”.***

Treatment of patients with bacteraemia
The CHMP adopted the following harmonised indication:
”*Treatment of patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above* (i.e. referring to the list of indications approved)”.
According to to the Addendum to the NfG on antibacterials (CPMP/EWP/558/95 REV 2) “It may be possible to accumulate sufficient clinical data to support an indication for use of an antibacterial agent in the treatment of bacteraemia that is associated with specific types of infection, with or without restriction to certain pathogens. For example, in the case of agents that have been in use for many years and are indicated for use in a broad range of infections the total evidence may be considered sufficient for an indication that reads “Treatment of patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above (i.e. referring to the list of indications approved)”.
The member states consider that based on the submitted studies as referred to in the Clinical Overview sufficient supportive clinical data have been submitted by the MAH to justify this CHMP harmonised indication in the SmPC of Cefepime MIP.

The following indication for cefepime is considered acceptable:
“Treatment of patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above”

IV.4 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-MIP 1 g and 2 g.

Summary of safety concerns	
Important identified risks	• Previous hypersensitivity reactions to any component of the formulation, the cephalosporin class of antibiotics, penicillins or other beta-lactam antibiotics (monobactams and carbapenems) or to the excipient L-arginine • Acidosis and hyperkalemia • Increased risk for neurotoxicity and severe adverse events in patients with renal impairment (especially elderly patients with renal insufficiency) • Overgrowth of non-susceptible microorganisms • Concomitant use of loop diuretics or aminoglycosides • Hypersensitivity reactions to other medicinal products • History of asthma or allergic diathesis
Important potential risks	-
Important missing information	• Use of cefepime during pregnancy • Use of cefepime during lactation • Use of cefepime in children below 2 months of age

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

IV.5 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Maxipime. 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 not been evaluated via a user consultation study. The MAH submitted a bridging report making reference to the successfully user tested PLs for several comparable products, i.e. other cephalosporin antibiotics. Their dosage form is identical or comparable in all cases and all products are intended for administration to the patient by healthcare professionals. Also the indications are comparable for all products are used for the treatment of severe bacterial infections. Therefore, also the safety profiles of the products and the key safety messages are identical.
The bridging report is in full compliance with the demands of the readability guideline and is therefore accepted. Separate user testing is not required.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Cefepime-MIP 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.

In the Board meeting of 27 November 2014, the dossier was discussed. The Board concluded that sufficient data have been provided to demonstrate the adequate control of the finished product and its manufacturing process.

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-MIP 1 g and 2 g, powder for solution for injection or infusion with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 27 November 2014.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached