

**PUBLIC ASSESSMENT REPORT
of the Medicines Evaluation Board
in the Netherlands**

**Cefepim Fresenius Kabi 1 g and 2 g, powder for solution for
injection or infusion
Fresenius Kabi Nederlands B.V., the Netherlands**

cefepime (as dihydrochloride monohydrate)

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.

It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.

This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

**EU-procedure number: NL/H/1370/001-002/DC
Registration number in the Netherlands: RVG 102543-4**

27 August 2010

Pharmacotherapeutic group:	fourth-generation cephalosporins
ATC code:	J01DE01
Route of administration:	parenteral
Therapeutic indication:	Severe infections. <i>In adults and children over 12 years of age</i> - Nosocomial pneumonia; Complicated urinary tract infections; complicated intra-abdominal infections; peritonitis associated with dialysis in patients on CAPD; <i>in children aged 2 months up to 12 years and with a body weight of ≤ 40 kg</i> - nosocomial pneumonia; complicated urinary tract infections.
Prescription status:	prescription only
Date of authorisation in NL:	20 August 2010
Concerned Member States:	Decentralised procedure with BE, BG, CY, EL, ES, PL, RO, SI and PT (only 1 g)
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Cefepim Fresenius Kabi 1 g and 2 g, powder for solution for injection or infusion, from Fresenius Kabi Nederland B.V. The date of authorisation was on 20 August 2010 in the Netherlands. The product is indicated for treatment of severe infections, see below.

In adults and children over 12 years of age:

- Nosocomial pneumonia
- Complicated urinary tract infections
- Complicated intra-abdominal infections
- Peritonitis associated with dialysis in patients on CAPD

Cefepime may be used in the management of neutropenic patients with fever that is suspected to be due to a bacterial infection.

In children aged 2 months up to 12 years and with a body weight of ≤ 40 kg:

- Nosocomial pneumonia
- Complicated urinary tract infections

Cefepime may be used in the management of neutropenic patients with fever that is suspected to be due to a bacterial infection. Cefepime should be co-administered with other antibacterial agents whenever the possible range of causative bacteria would not fall within its spectrum of activity. Consideration should be given to official guidelines on the appropriate use of antibacterial agents.

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

Cefepime is a broad-spectrum antibiotic with *in vitro* bactericidal activity against a large number of Gram-positive and Gram-negative bacteria. Cefepime exercises its bactericide action by inhibition of bacterial wall synthesis.

Cefepime exhibits rapid penetration into Gram-negative bacterial cells. It possesses a high affinity to penicillin-binding proteins (PBP), in particular PBP3 of *Escherichia coli* and *Enterobacter cloacae*, but also to PBP2. The moderate affinity to PBP1a and 1b probably also contributes to the overall bactericidal activity of cefepime.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Maxipime 1g and 2 g powder for solution (NL license RVG 17207) which has been registered in the Netherlands by Bristol-Myers Squibb B.V. since 1994 (original product). On 31 December 2000 this product was withdrawn from the Dutch market for commercial reasons.

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. As Cefepim Fresenius Kabi is a product for parenteral use, it is exempted for biostudy (*NfG CPMP/EWP/QWP 1401/98*). The current product can be used instead of its reference product.

No scientific advice has been given to the MAH with respect to these products, and no paediatric development programme has been submitted, as this is not required for generic medicinal products.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice

The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active 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. Cefepime shows optical rotation due to the presence of two asymmetric carbons at position 6 and 7, deriving from 7-ACA molecule. During the reaction that transforms the starting material 7-ACA in cefepime there is no variation of the stereochemistry of the molecule, and new stereogenic carbons are not formed. The CEP procedure is followed for the drug 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 new 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, the official handbook in which methods of analysis with specifications for substances are laid down by the authorities of the EU.

Manufacture

The starting material for the synthesis of cefepime is converted in a three step reaction to form cefepime dihydrochloride monohydrate. A list of the solvents used for the synthesis has been provided. The drug substance has been adequately characterised. The specification is acceptable in view of the route of synthesis and the various European guidelines.

Quality control of drug substance

The drug substance specification is in line with the Ph.Eur. and with additional requirements for particulate matter and solvents. The specification is acceptable. Batch analytical data demonstrating compliance with the proposed drug substance specification have been provided for three commercial-scale batches.

Stability of drug substance

Stability data on the active substance have been provided for three batches stored at 25°C/60%RH for 12 or 6 months and at 40°C/75%RH for 6 months. The batches were adequately stored. When stored at long term conditions, a decrease in assay has been observed. The initially claimed retest period of 24 months was reduced to 6 months. A retest period of 6 months is justified when stored in a sterile, airtight, tamper-proof container.

Medicinal Product

Composition

The products are formulated as powder (white to pale yellow) for solution for injection or infusion. The powder needs to be reconstituted prior to application. The pH of the reconstituted solution is 4.0-6.0.

The powder for solution for injection or infusion is packed in:

Cefepime Kabi 1 g: 15 ml Type III glass vial closed with chlorobutyl rubber stopper containing 1 g cefepime. Each vial contains 1 g cefepime (as 1189.2 mg cefepime dihydrochloride monohydrate).

Cefepime Kabi 2 g: 15 ml Type III glass vial closed with chlorobutyl rubber stopper containing 2 g cefepime. Each vial contains 2 g cefepime (as 2378.5 mg cefepime dihydrochloride monohydrate).

L-arginine is used as excipient (buffer).

The excipient and packaging are usual for this type of dosage form.

Pharmaceutical development

The development of the product has been described, the choice of the excipient L-arginine is justified and its function explained. The composition of the applicant's drug products per vial is identical to that of the originator's drug product (Maxipime of Bristol-Myers Squibb). The comparability of the MAH's and the originator's products with regard to the physicochemical characteristics (appearance of reconstituted solution, pH and particulate matter), as well as the assay and the impurity profile has been confirmed by results of batch analyses provided for both the MAH's products and samples of the reference products. Since the product is a generic product for parenteral use it is exempted from bioequivalence study. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

Sterile cefepime and sterile L-arginine are mixed and filled into vials aseptically. The manufacturing process was adequately validated on three production batches per strength for both manufacturing sites. Aseptic filling has also been validated by process simulation.

Excipients

L-arginine is the only excipient used. The provided specification is in compliance with the Ph.Eur. monograph for L-arginine.

Quality control of drug product

The specifications for the analysis of the intermediate sterile cefepime L-arginine bulk product by the intermediate bulk manufacturer, as well as for retest of the sterile bulk by the final product manufacturer have been provided. The specifications and methods for both manufacturers are identical, and in accordance with the criteria and methods of the Ph.Eur., and with the USP* monograph for cefepime for injection. The specification is acceptable.

In addition, the specifications for release and end-of-shelf life for the final products have been provided. The specification includes tests for appearance, identification by TLC and HPLC, appearance of reconstituted solution, pH, water content, assay, related substances, particulate matter, content uniformity, N-methylpyrrolidine, sterility, bacterial endotoxins and reconstitution time. The analytical methods have been adequately described and validated. The specifications are acceptable. Batch analytical results of three production- scale batches per strength demonstrating compliance with the specification have been provided.

Compatibility

The MAH provided the results of an in-use compatibility study. The study was performed at 25°C for 2 hours with different dilutions (1 mg/ml, 100 mg/ml and 200 mg/ml) in water for injection, sodium chloride 0.9% and glucose 5%. Samples were tested at time-points 0, 1 and 2 hour for appearance of reconstituted solution (clarity, colour, visible particles), pH, particulate contamination, assay and related substances. The limits were set in accordance with the shelf-life specifications.

No specified impurities were detected above the limit of 0.05%. No unspecified impurities were detected above the identification threshold of 0.10%. The dilutions of 100 mg/ml and 200 mg/ml are in accordance

with the recommended dilution volume of 10 ml as recommended in the SPC. The low concentration (1 mg/ml) is also acceptable. The results of this study adequately demonstrate that the drug product is stable for 2 hours after reconstitution / dilution with water for injection, sodium chloride 0.9% and glucose 5%. The statement in the SPC "*Reconstituted solutions are stable for two hours at 25°C*" is justified.

Stability tests on the finished product

Stability data on the product have been provided for both the sterile cefepime L-arginine bulk as well as for the final product. The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in commercial packaging.

Stability data on the sterile bulk have been provided for two batches stored at 25°C/60%RH (12 months) and at 40°C/75%RH (6 months). No significant changes have been observed. The obtained results are well within the proposed specification limit of NMT 1.0%.

Stability data on the final product have been provided for three full-scale batches of both strengths stored at 25°C/60%RH (24 months) and at 40°C/75%RH (6 months).. The claimed shelf life of 24 months with the storage condition "*Do not store above 25°C*" and "*Keep the vial in the outer carton in order to protect from light*" is justified.

After reconstitution with the IV fluids water for injection, glucose 5% and sodium chloride 0.9% the solution was demonstrated to remain stable for 2 hours at 25°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.

* *Ph.Eur. and USP are official handbooks pharmacopoeias in which methods of analysis with specifications for substances are laid down by the authorities of the EU and USA respectively.*

II.2 Non clinical aspects

This product is a generic formulation of Maxipime, which is available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

Environmental risk assessment

The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of cefepime released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Pharmacokinetics/ Pharmacodynamics

Pharmacodynamic and pharmacokinetic properties of cefepime are well known. As cefepime is a widely used, well-known active substance, and a solution for injection, no further studies are required and the MAH provided none. An overview based on literature review is, thus, appropriate and adequate.

Clinical efficacy & Clinical safety

No new clinical (pharmacodynamic and pharmacokinetic) data have been submitted and none are required for an application of this type.

On request of the MEB the clinical overview was largely rewritten during the procedure. The MAH included a wider selection of publications, and provided an adequate discussion of the claimed indications in nosocomial pneumonia, empiric therapy in febrile neutropenic patients and urinary tract infections. Safety is reviewed in the clinical overview which also includes a discussion of recent critical publications that question the safety of cefepime. The overview is now considered adequate.

In the Clinical Overview, the MAH did not discuss the clinical evidence underlying the indications of “*complicated intra-abdominal infections*” and “*peritonitis associated with dialysis in patients on CAPD*” in children under 12 years of age, nor did the MAH provide a dose recommendation for children under 12 in section 4.2 of the SmPC for these indications. It was therefore suggested to limit these indications to patients over the age of 12 years. The MAH agreed, and has updated section 4.1 of the SmPC accordingly. See the SPC.

Based on the submitted clinical overview, relevant treatment guidelines, and a recent review by the FDA, the benefit/risk of intravenous cefepime in adults and children over the age of 12 years can be considered positive in the following indications from a clinical point of view:

- *Nosocomial pneumonia*
- *Complicated urinary tract infections*
- *Complicated intra-abdominal infections*
- *Peritonitis associated with dialysis in patients on CAPD*

Cefepime may be used in the management of neutropenic patients with fever that is suspected to be due to a bacterial infection.

The benefit/risk of intravenous cefepime can be considered positive for the following indications in children between the ages of 2 months and 12 years and with a body weight of ≤ 40 kg) from a clinical point of view:

- *Nosocomial pneumonia*
- *Complicated urinary tract infections*

Mortality

Yahav et al. (2007) demonstrated in a meta-analysis that cefepime when used in the management of neutropenic patients with fever is associated with an increased risk of mortality. A thorough and more inclusive meta-analysis performed by the FDA did not confirm this finding, and demonstrated no evidence of an increased risk of mortality. Considering the proposed indications, and the reassurance given by the FDA-meta-analysis that there is no evidence for an increased risk of mortality associated with treatment with cefepime, the Benefit Risk can be considered positive in the following indication in patients over the age of 2 months:

Cefepime may be used in the management of neutropenic patients with fever that is suspected to be due to a bacterial infection.

Risk management plan

Cefepime was first approved in 1993, and there is now more than 10 years post-authorisation experience with the active substance. The FDA has finished its analysis of a possible risk of higher death with cefepime, an antibiotic, as compared to patients treated with similar drugs. The FDA has determined that the data do not indicate a higher rate of death in cefepime-treated patients.

The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. The MAH and committed to continue closely monitoring of fatal cases and thoroughly discuss them in the PSURs.

Product information

SPC

The MAH was requested to include an additional warning in section 4.4 of the SPC following recent referral procedures for Tienam and Fortem.

Readability test

The package leaflet 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 overall impression of the readability test is good.

After one pilot phase with 5 person some amendments were made in the PL. After the two test runs with each 10 persons no additional amendments were made. The PL is well organised and patient friendly wording is used.

The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

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

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

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

The SPC, package leaflet and labelling are in the agreed templates. The MAH was requested to include an additional warning in section 4.4 of the SPC following recent referral procedures for Tienam and Fortem.

Cefepim Fresenius Kabi 1 g and 2 g, powder for solution for injection or infusion was discussed in the Board meetings of 17 July 2008 and 11 February 2010. Primary subject were issues regarding the compatibility study for the finished product, and the initially insufficient clinical overview presented by the MAH.

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 Cefepim Fresenius Kabi 1 g and 2 g, powder for solution for injection with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 8 July 2010. Cefepim Fresenius Kabi 1 g and 2 g, powder for solution for injection is authorised in the Netherlands on 20 August 2010.

A European harmonised birth date has been allocated (29 June 1993) and subsequently the first data lock point for cefepime is June 2012. The first PSUR will cover the period from August 2010 to June 2012, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: 1 August 2015.

The following post-approval commitment was made during the procedure:

Safety

- The MAH has committed to continue monitoring closely fatal cases and thoroughly discuss them in the PSURs according to the requirements of Volume 9a.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C _{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
t _{1/2}	Half-life
t _{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

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