Decentralised Procedure

Public Assessment Report

Cefepim Dotopharma 0,5 g / 1 g / 2 g Pulver zur Herstellung einer Injektions- bzw. Infusionslösung

Cefepime dihydrochloride monohydrate

DE/H/3453/001-003/DC

Applicant:
Dotopharma UG
Rosenstr. 141
58095 Hagen
Germany

Reference Member State	DE

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ADMINISTRATIVE INFORMATION

Proposed name of the medicinal product in the RMS	Cefepim Dotopharma 0,5 g / 1 g / 2 g Pulver zur Herstellung einer Injektions- bzw. Infusionslösung
Name of the drug substance (INN name):	Cefepime (as dihydrochloride monohydrate)
Pharmaco-therapeutic group (ATC Code):	Other beta-lactam antibacterials, fourth-generation cephalosporins (J01DE01)
Pharmaceutical form(s) and strength(s):	Powder for solution for infusion/injection: 0.5 g, 1 g, 2 g
Reference Number(s) for the Decentralised Procedure	DE/H/3453/001-003/DC
Reference Member State:	DE
Concerned Member States:	FR, PL
Applicant (name and address)	Dotopharma UG Rosenstr. 141 58095 Hagen Germany

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the application for Cefepim Dotopharma 0,5 g / 1 g / 2 g Pulver zur Herstellung einer Injektions- bzw. Infusionslösung with reference to the German originator products Maxipime® 0,5 g, Pulver zur Herstellung einer Injektions- bzw. Infusionslösung, 44319.00.00; Maxipime 1,0 g, Pulver zur Herstellung einer Injektions- bzw. Infusionslösung, 44320.00.00, and Maxipime 2,0 g, Pulver zur Herstellung einer Injektions- bzw. Infusionslösung, 44321.00.00., Bristol-Myers Squibb GmbH & Co. KGaA, in the indications:

Adults and adolescents

For the treatment of infections caused by cefepime-susceptible pathogens:

- severe pneumonia
- complicated urinary tract infections
- intra-abdominal infections, including peritonitis; combination therapy with another antibiotic, taking into consideration the individual risk profile of the patient and the expected or established pathogens, is recommended, as needed.
- biliary tract infections (gallbladder and bile duct)
- in patients with moderate (neutrophil granulocytes $\leq 1000/mm^3$) or severe (neutrophil granulocytes $\leq 500/mm^3$) neutropenic fever that is suspected to be due to bacterial infection. In patients at high risk for severe infection (for example, patients with a history of recent bone marrow transplantation, with hypotension at presentation, with an underlying hematologic malignancy, or with severe or prolonged neutropenia), antimicrobial monotherapy may not be appropriate. Insufficient data exist to support the efficacy of cefepime monotherapy in such patients.
  Combination therapy with an antibiotic from the group of aminoglycosides or glycopeptides is recommended, taking into account the individual risk profile of the patient.
- treatment of patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above.

Children

For the treatment of infections caused by cefepime-susceptible pathogens:

- severe pneumonia
- complicated urinary tract infections
- bacterial meningitis
- in patients with moderate (neutrophil granulocytes $\leq 1000/mm^3$) or severe (neutrophil granulocytes $\leq 500/mm^3$) neutropenic fever that is suspected to be due to bacterial infection. In patients at high risk for severe infection (for example, patients with a history of recent bone marrow transplantation, with hypotension at presentation, with an underlying hematologic malignancy, or with severe or prolonged neutropenia), antimicrobial monotherapy may not be appropriate. Insufficient data exist to support the efficacy of cefepime monotherapy in such patients.
  If necessary, a combination therapy with an antibiotic from the group of aminoglycosides or glycopeptides is recommended, taking into account the individual risk profile of the patient.

Considerations should be given to official guidance on the appropriate use of antibacterial agents.

is approved.

II. EXECUTIVE SUMMARY

II.1 Problem statement

The application for Cefepime Dotopharma 0,5g/1g/2g, powder for solution for injection or infusion was switched by the applicant from a hybrid application according to article 10(3) to an generic application according to Art 10(1) of Directive 2001/83/EC with reference to the German originator products Maxipime® 0,5 g; Maxipime 1,0 g, and Maxipime 2,0 g. All 3 German originator products are licensed for intravenous use only.

II.2 About the product

Cefepime - the active substance of the applied medicinal products - is a parenteral "fourth-generation" broad-spectrum cephalosporin being active against Gram-negative including *Pseudomonas aeruginosa* as well as against Gram-positive pathogens. Compared with the third generation cephalosporin Ceftazidime, Cefepime exerts comparable or enhanced activity in vitro against Gram-positive bacteria, including methicillin-sensitive *Staphylococcus aureus* and *Streptococcus pneumoniae* in various infection models. Cefepime is used in hospitals for the parenteral treatment in its approved indications in adult, adolescent and paediatric patients.
The approved indications and the qualification regarding their severity vary across Europe.

Cefepime similar to other cephalosporins distributes widely into most body tissues and fluids, although its hydrophilic nature limits distribution into lipophilic areas.
Protein binding is about 16%.
Cefepime is metabolized to N-methyl-pyrrolidine (NMP) which is rapidly converted to the N-oxide (NMP-N-oxide), the 7-epimer of Cefepime and NMP, comprising 6.8, 2.5 and <1% of the total radioactivity excreted in urine, respectively. The NMP N-oxide is the predominant metabolite and represents also the major metabolites found in the urine.
The majority of the administered dose (66-91%) is eliminated as unchanged drug by glomerular filtration and negligible tubular secretion with an elimination half-life of about 2 hours. The renal clearance of Cefepime is significantly reduced in patients with renal impairment. Therefore, in patients with renal dysfunction, Cefepime dosage should be reduced according to the decline in creatinine clearance. Cefepime is dialysable. Biliary excretion or enterohepatic recycling of Cefepime has not been reported.

Cefepime exhibits bactericidal activity by inhibition of bacterial wall synthesis and 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 contributes to the overall bactericidal activity of Cefepime.

Efficacy is correlated with the length of time during which drug levels exceed the minimal inhibitory concentration (MIC) of the pathogen concerned.
Serum concentrations 10 and 12 hours after i.v.- or i.m.-injection of a 2g dose are above the MICs of the most commonly encountered pathogens
There is partial or complete cross resistance between Cefepime and other cephalosporins and penicillins.

The indications in the various national licensures of the originator product by Bristol-Myers Squibb vary throughout Europe. Regarding the severity of infections Cefepime is mostly approved for the treatment of severe infections with respective qualification of the infections in section 4.1 of SmPC. Other approved indications are severe per se.

The indications claimed for the applied medicinal products are in line with the indications authorised for the reference medicinal products in Germany:

Adults and adolescents
For the treatment of infections caused by cefepime-susceptible pathogens:

- severe pneumonia
- complicated urinary tract infections
- intra-abdominal infections, including peritonitis; combination therapy with another antibiotic, taking into consideration the individual risk profile of the patient and the expected or established pathogens, is recommended, as needed.
- biliary tract infections (gallbladder and bile duct)
- the empirical treatment of febrile episodes in patients with moderate (neutrophil granulocytes $\leq 1000/mm^3$) or severe (neutrophil granulocytes $\leq 500/mm^3$) neutropenia. In patients at high risk for severe infection (for example, patients with a history of recent bone marrow transplantation, with hypotension at presentation, with an underlying hematologic malignancy, or with severe or prolonged neutropenia), antimicrobial monotherapy may not be appropriate. Insufficient data

exist to support the efficacy of cefepime monotherapy in such patients.
Combination therapy with an antibiotic from the group of aminoglycosides or glycopeptides is recommended, taking into account the individual risk profile of the patient.
- treatment of patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above.

Children
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- empirical treatment of febrile episodes in patients with moderate (neutrophil granulocytes $\leq 1000/mm^3$) or severe (neutrophil granulocytes $\leq 500/mm^3$) neutropenia. In patients at high risk for severe infection (for example, patients with a history of recent bone marrow transplantation, with hypotension at presentation, with an underlying hematologic malignancy, or with severe or prolonged neutropenia), antimicrobial monotherapy may not be appropriate. Insufficient data exist to support the efficacy of cefepime monotherapy in such patients.
If necessary, a combination therapy with an antibiotic from the group of aminoglycosides or glycopeptides is recommended, taking into account the individual risk profile of the patient.

Considerations should be given to official guidance on the appropriate use of antibacterial agents.

Dosage recommendations for adults and adolescents are usually given in a range from 2g, 12 hourly up to 8-hourly.
Paediatric dosage recommendations of 50 mg/kg 12hourly up to 8 hourly are given for children from the age of 2 months until 12 years.
Dosage recommendations for children vary regarding the starting age of 1 month or 2 months in the MAs throughout Europe.

II.3 General comments on the submitted dossier
The applicant provided 192 literature references including 2 references to the German national project ZARS (Zentralstelle für die Auswertung von Resistenzdaten bei systemisch wirkenden Antibiotika) and to the European Committee on Antimicrobial Susceptibility Testing (EUCAST): Breakpoint tables for interpretation of MICs and zone diameters, Version 4.0, valid from 2014-01-01.
These references present data on the prevalence of resistance of the indication most relevant pathogens from current resistance surveillance programs (see new literature references) in line with the recommendations in the NfG on Evaluation of Medicinal Products Indicated for Treatment of Bacterial Infections" (CPMP/EWP/558/95, rev 1 and rev 2) which support the categorisation of these pathogens in section 5.1 in the SmPC.

II.4 General comments on compliance with GMP, GLP, GCP and agreed ethical principles
The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.
For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.
A declaration from the Qualified Person has been provided declaring that Cefepime dihydrochloride monohydrate is manufactured by the same company in accordance with the current detailed guidelines on Good Manufacturing Practice for starting materials.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

Drug substance

The manufacture is described by two ASMFs from the same holder for two different synthesis processes (Process A and Process B). Sufficient letters of access have been provided.

The synthesis is described in sufficient detail in general. The QP declaration is sufficient.

The information with regard to structure elucidation is considered plausible. The characterization of impurities including concrete information on potential genotoxic compounds used during synthesis is satisfactory.

Ph. Eur. specifications and methods are used for control of the drug substance.

Batch analysis results showing the compliance with the proposed drug substance specification are given.

Cefepime dihydrochloride monohydrate is packaged in a three-bag packaging system consisting of LDPE and a multi-layer aluminium polyethylene bag. Sufficient descriptions are given. Demonstration of compliance with current EU food legislation and with the Ph. Eur. requirements for polyolefines is provided.

The provided stability results support the proposed re-test period of 36 months for drug substance manufactured with process A. For process B, the re-test period is 24 months.

Drug Product

GMP compliance is sufficiently demonstrated.

The drug product consists of the sterile mixture of Cefepime dihydrochloride monohydrate and L-Arginine filled into 20 mL type I glass vials, stoppered with bromobutyl rubber stoppers. The drug product is identical to the Originator.

The manufacturing process including in-process controls is described. Holding times are adequately defined. The process validation data are sufficient.

The data for the excipient used during manufacture (L-Arginine) are sufficient.

The proposed release and shelf-life specifications contain the quality relevant characteristics required for this pharmaceutical form. The shelf-life specification contains the same tests as the release specification.

The analytical methods used are derived from Ph. Eur. The description is sufficient. The validation data are acceptable.

CoAs showing compliance with the proposed specifications are provided.

Information on the packaging material is sufficient.

A shelf-life of 36 months if stored below 30°C is accepted.

The results presented for in-use stability / compatibility support the in-use stability claim of 24 hours at 2-8°C for the solutions mentioned in the SmPC (WFI, 0.9 % NaCl, 0.9 % NaCl with 5 % Glucose, 5 % and 10 % Glucose, Lactate Ringer's solution with and without 5 % Glucose, and 1/6 M Sodium Lactate solution).

III.2 Non-clinical aspects

There are no objections to approval of Cefepime Dotopharma Powder for solution for infusion/injection from a non-clinical point of view. The wording of SmPC's section 4.6 and 5.3 is adequate.

Environmental Risk Assessment (ERA)

Evaluation of the potential environmental risk posed by the medicinal product has not been provided. As it concerns a generic product which is intended for substitution of the innovator, such an evaluation is deemed unnecessary since no additional amount of Cefepime will be introduced in the environment.

III.3 Clinical aspects

Pharmacokinetics

Please refer to section II.2.

Pharmacodynamics

Please refer to section II.2.

Clinical efficacy
The clinical efficacy of cefepime in the indications authorised for the German reference products is well-known. The indications are represented in various authorisations throughout Europe. The applicant did not claim the indication bacteraemia for children as authorised for the German originator products.

Clinical safety
We refer to the CSP 2009 for Cefepime regarding sections 4.3 to 4.9.

Legal Status
For prescription only

User Testing
According to the applicant's information the wording of the package leaflet of the present product Cefepime Dotopharma 0,5 g powder for solution for injection or infusion is similar to that of Cefepim Sandoz 0,5 g - Pulver zur Herstellung einer Injektionslösung. It must be assumed that the user testing of the PIL of Cefepim Sandoz 0,5 g - Pulver zur Herstellung einer Injektionslösung to which the PIL submitted in the current application is bridged itself was bridged which obviously was accepted during the DCP (AT/H/298, finalised in 2010).
Due to the fact that the 'mother- and daughter'-PL in the current procedure are of the same active substance and same pharmaceutical formulations, the bridging and thus the exception from a user testing is accepted on the basis of the information provided by the applicant.

Summary Pharmacovigilance system
The Applicant/Proposed Future MAH has submitted a signed Summary of the Applicant's/Proposed Future MAH's Pharmacovigilance System and asked the RMS to replace the previously submitted DDPS with the new Summary of Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the RMS accepts this substitution.

Risk Management Plan
Cefepime has generally a well-recognised efficacy and an acceptable level of safety in the indications approved for the German reference originator product Maxipime and corresponding products have been widely used in many countries.

Therefore, the Cefepime Dotopharma products with the following indications

Adults and adolescents

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do not require additional risk minimisation measures beyond the Product Information and routine pharmacovigilance activities. A Risk Management Plan has therefore not been established for the originator product and is also considered not necessary for Cefepime Dotopharma. The approved SmPC of the German originator reference product Maxipime reflects the known safety profile of Cefepime.

Periodic Safety Update Report (PSUR)
The submission of further PSURs should follow the provisions as laid down in the EURD list when coming into effect and where relevant in line with the EU work sharing project http://www.hma.eu/80.html.

IV. BENEFIT RISK ASSESSMENT

The benefit risk assessment is considered positive.
The application is approved.
For intermediate amendments see current product information.