CMDh/223/2005
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Public Assessment Report

Scientific discussion

Ceftazidim MIP
(Ceftazidime pentahydrate)

NO/H/0243/001-002/DC

Date: 10.04.15

This module reflects the scientific discussion for the approval of Ceftazidim MIP. The procedure was finalised at 12.02.15 (day 210). For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Ceftazidim MIP, powder for solution for injection/infusion, 1 g and 2 g, from MIP Pharma GmbH.
The product is indicated for treatment of the infections caused by Gram-positive and Gram-negative bacteria in adults and children including neonates.

A comprehensive description of the indications and posology is given in the SmPC. Indication and posology are identical with the latest approved product information for the originator Fortum, and in accordance with the Article 30 referral finalised in 2011.

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

Ceftazidime is a third generation cephalosporin (ATC code: J01DD02) with broad spectrum of activity against both Gram-negative and Gram-positive bacteria. Ceftazidime inhibits the biosynthesis of bacterial cell wall peptidoglycan, causing inhibition of bacterial growth or cell lysis and death.

II. QUALITY ASPECTS

II.1 Introduction

The drug products (1 g and 2 g strengths) are sterile white or pale yellow powders for solution for injection or infusion filled in 15 ml (1 g) or 50 ml (2 g) glass vials closed with rubber stoppers and aluminium caps. The only excipient is sodium carbonate, anhydrous added as buffering agent.

II.2 Drug Substance

The drug substance, ceftazidime pentahydrate, is monographed in the Ph. Eur. The drug substance is supplied sterile by the manufacturer Orchid Chemicals and Pharmaceuticals Ltd, India who holds a Certificate of Suitability (CEP). Adequate documentation for drug substance manufacture according to GMP has been provided.

EDQM has assessed the methods of manufacturing, the sterilisation and aseptic packaging of the drug substance. Sterility of the drug substance is critical for the quality of the drug product as there are no additional sterilisation steps for the drug product. Further to the short description of method used for sterilisation as included on the CEP, more detailed information has been made available to the applicant by the drug substance manufacturer/ASMF holder and is also included in the marketing authorisation dossier.

The control tests and specifications for drug substance are adequately drawn up. The batch analysis data presented show compliance with the Ph.Eur. requirements and the additional tests specified.

A re-test period of 2 years is included on the CEP for ceftazidime pentahydrate (sterile) if stored in an aluminium container closed with chlorobutyl rubber stopper and an aluminium cap.

II.3 Medicinal Product

The development of the drug product is described. The composition is justified, and the container closure system is conventional for this product type and found suitable.
Relevant development aspects of the manufacturing processes have been briefly described.

Compatibility has been demonstrated for the drug product and the reconstitution solutions included in the product information. The claimed chemical and physical in-use stability of the solutions is acceptable:

- 6 hours stability at 25°C, except for when reconstituted with lidocaine.
- 12 hours stability at 2-8°, except for when reconstituted with lidocaine.
- Drug product reconstituted with lidocaine should be used immediately.

An acceptable in-use specification has been established.

The drug product manufacture is non-standard since aseptic manufacturing processes are used. The manufacture consists of the main stages of i) manufacture of sterile sodium carbonate, anhydrous (Orchid Chemicals & Pharmaceuticals Ltd., India), ii) manufacture of a sterile powder blend of sterile ceftazidime pentahydrate and sterile sodium carbonate, anhydrous (Orchid Chemicals & Pharmaceuticals Ltd., India) and iii) aseptic filling of the sterile powder blend into vials (Shenzhen Lijian Pharmaceuticals Co., Ltd., China).
Satisfactory documentation for GMP manufacture has been provided for the involved sites.

The manufacture of the drug product (sterile excipient, intermediate drug product, finished drug product) has been described. The descriptions include batch formulae and sizes, flow charts, narrative process descriptions and in-process controls for each stage of manufacture. Data on process validation have been presented. The manufacturing processes are described in sufficient detail, including methods and conditions of sterilisation, applicable holding times and the control of critical parameters, and are supported by the validation data presented. The control of the materials used in manufacture of sterile excipient is described.

The drug product specifications cover appropriate parameters for this dosage form, and acceptable limits are set. Descriptions of analytical methods and the method validation have been presented. Batch analysis has been performed on two batches of each strength. The results show that the finished products meet the specifications proposed.

The conditions used in the stability studies are according to the ICH stability guideline. The stability data presented support the proposed shelf-life of unopened vial of 30 months with the storage claim "Do not store above 30°C" and "Keep the vial in the outer carton in order to protect from light".

II.4 Discussion on chemical, pharmaceutical and biological aspects

Agreement between member states was reached during a written procedure. There are no objections to approval from a quality point of view.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of ceftazidime are well known. As ceftazidime is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is thus appropriate.

The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate.

Proposed text in non-clinical sections of the SmPC (section 4.6 and 5.3) and PIL are identical with the latest approved product information for the originator Fortum, and in accordance with the Article 30 referral finalised in 2011.
There are no objections to approval of Ceftazidim MIP from a non-clinical point of view.

III.2 Pharmacology

NA

III.3 Pharmacokinetics

NA

III.4 Toxicology

NA

III.5 Ecotoxicity/environmental risk assessment (ERA)

Since Ceftazidim 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.6 Discussion on the non-clinical aspects

Agreement between member states was reached during a written procedure. The application is considered approvable from a non-clinical point of view.

IV. CLINICAL ASPECTS

IV.1 Introduction

According to the Guideline on the Investigations of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1.), Appendix II, a biowaver for a parenteral solution can be accepted provided it is administered as an aqueous solution containing the same active substance in the same concentration as the medicinal product already approved (Fortum. GlaxoSmithKline AS). This criterion is fulfilled and Ceftazidim MIP can be considered essentially similar to the original product Fortum "GlaxoSmithKline".

The application contains an adequate review of published clinical data. As Ceftazidim MIP is indicated for parenteral use only, there is no need to show bioequivalence.

Approval is recommended from the clinical point of view.

IV.2 Pharmacokinetics

NA

IV.3 Pharmacodynamics

NA

IV.4 Clinical efficacy

The efficacy of ceftazidime is well known and no clinical studies have been conducted and none is required for this generic parenteral drug.

IV.5 Clinical safety

NA

IV.6 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 Ceftazidim MIP.

IV.7 Discussion on the clinical aspects

The efficacy and safety of ceftazidime is well established and no clinical studies have been conducted and none is required for this generic application.

Agreement between member states was reached during a written procedure. The application is considered approvable from a clinical point of view.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to the User Tests of four parent PILs within the same class of medicinal products (cephalosporins): Ceftriaxone 1 g / 2 g vials, powder for solution for injection/infusion, NO/H/0219/001-002/DC; Cefuroxime 750 mg / 1500 mg vials, powder for solution for injection/infusion, NO/H/0218/001-002/DC; Cefazolin 2 g vials, powder for solution for infusion, FI/H/0778/001/DC; Cefotaxime 1 g / 2 g vials, powder for solution for injection/infusion, DK/H/2158/001-002/DC.
Further, with respect to content, the daughter PIL is identical with the latest approved PIL for the originator Fortum and in accordance with the harmonisation procedure EMEA/H/A-30/1006, finalised in January 2011.

The bridging report submitted by the applicant has thus been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The conclusion of the benefit risk assessment is positive.