PUBLIC ASSESSMENT REPORT
of the Medicines Evaluation Board
in the Netherlands

Ceftazidim Mylan 500 mg, powder for solution
for injection,
Ceftazidim Mylan 1000 mg, powder for solution
for injection or infusion
Ceftazidim Mylan 2000 mg, powder for solution
for injection or infusion

Mylan B.V., the Netherlands

ceftazidime

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/1090/01-03/DC
Registration number in the Netherlands: RVG 100278, 100281, 100282

28 September 2009

Pharmacotherapeutic group: third-generation cephalosporins
ATC code: J01DD02
Route of administration: intramuscular; intravenous
Therapeutic indication: parenteral treatment of infections when caused by pathogens susceptible to ceftazidim

Prescription status: prescription only
Date of authorisation in NL: 3 October 2008
Concerned Member States: Decentralised procedure with AT, BE, CZ, EL, ES, HU, PT, SI (only 1000 mg), SK, UK

Application type/legal basis: Directive 2001/83/EC, Articles 10(1) and 10(3)

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 Ceftazidim Mylan 500, 1000 and 2000 mg, powder for solution for injection or infusion, from Mylan B.V. The date of authorisation was on 3 October 2008 in the Netherlands.

The product is indicated for the parenteral treatment of the following infections when caused by pathogens susceptible to ceftazidim:

- Respiratory tract infections, including lower respiratory tract infections in patients with cystic fibrosis
- Urinary tract infections
- Skin and soft tissue infections
- Biliary tract infections
- Intra-abdominal infections
- Bone and joint infections
- Infections associated peritoneal dialysis and with continuous ambulatory peritoneal dialysis (CAPD)
- Meningitis due to aerobic gram-negative organisms.

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

Ceftazidime is a semi-synthetic bactericidal antibacterial agent of the cephalosporin class. Like other beta-lactam drugs, ceftazidime exerts antibacterial activity by binding to and inhibiting the action of certain bacterial cell wall synthetic enzymes (transpeptidases). Inhibition of one or more of these essential penicillin-binding proteins results in the interruption of cell wall biosynthesis at the final stage of peptidoglycan production, resulting in bacterial cell lysis and death.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Fortum (NL RVG 12847 (500 mg), RVG 10540 (1000 mg) and RVG 12848 (2000 mg)) which has been registered in the Netherlands by GlaxoSmithKline since 1985 (1000 mg strength) and 1989 (500 and 2000 mg). In addition, reference is made to Fortum authorisations in the individual member states (reference product).

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC. In Austria, however, the marketing authorisation for all three strengths was granted based on article 10(3) of Directive 2001/83/EC (hybrid application). In Greece the same applies for the 500 mg strength.

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 Ceftazidim Mylan 500, 1000 and 2000 mg are products for parenteral use, these are exempted for biostudy (NfG CPMP/EWP/QWP 1401/98). The current products can be used instead of their reference products.

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

No scientific advice has been given to the MAH with respect to these products.

No paediatric development programme has been submitted.
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 these product types 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 ceftazidime pentahydrate, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). The powder for solution for injection is subject of an USP monograph.

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 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.

Specification
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. with additional specifications for residual solvents, sterility and particulate matter. Batch analytical data demonstrating compliance with this specification have been provided for 3 production scaled batches.

Stability
Stability data has been obtained during storage at 25°C/60% RH and 40°C/75% RH. The drug substance was packaged in the commercial packaging, i.e. an aluminium container. Based on the stability data provided, the claimed retest period of 2 years with no special storage conditions, was granted.

* 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 the USA, respectively.

Medicinal Product

Composition
Ceftazidime Mylan 500/1000/2000 mg contain as active substance ceftazidime pentahydrate corresponding to 500/1000/2000 mg of ceftazidime, and is a white or almost white, crystalline powder.

The 500 mg and 1000 mg powder for solution for injection or infusion are packed in a type III glass vial, closed with a chlorobutyl rubber stopper and a flip-off aluminium cap. The 2000 mg product is packed in a type II glass vial, closed with a chlorobutyl rubber stopper and a flip-off aluminium cap.

The only excipient used is anhydrous sodium carbonate. There is no overage.

Pharmaceutical development
The development of the product is adequately described. The first two production steps are performed at the plant of the API manufacturer. The intermediate (buffered ceftazidime pentahydrate) is aseptically filled in vials. The packaging materials are usual and suitable for the products at issue.

Manufacturing process
The manufacturing process of ceftazidime pentahydrate sterile, is a non-stop dosing procedure in aseptic conditions of the sterile active ingredient. The active compound, premixed with the buffer substance sodium carbonate, is filled in the proper containers; no additional excipient and no anti-microbial
preservative are present. The MAH makes use of the ready to fill sterile mixture ceftazidime pentahydrate/sodium carbonate, received from the API manufacturer.

Ceftazidime cannot be sterilised by dry heat at 160°C, or with alternative combination of time and of temperature or with alternative sterilization methods like ionising, radiation or filtration through a microbial retentive filter. For this reasons, according to the guideline on "Decisions trees for the selection of sterilisation method" (Re: CPMP/QWP/054/98), the filling in aseptic conditions is the only viable method. This procedure is one of the critical aspects of the manufacturing process.

The manufacturing process has been sufficiently described and validated. The MAH has validated eight pilot batches to ensure that the process is reproducible and will consistently yield a product of the required quality and complying with all previously established specifications. The bulk product is validated on a production scale and the aseptic filling is adequately validated. Therefore, the process is considered to be sufficiently validated.

Compatibility
Buffered pentahydrate ceftazidime is compatible with the most popular diluents for infusion, like sodium chloride 0.9 %, glucose, dextrose, sodium lactate, etc. The compatibility of the drug product with the reconstitution diluents is clearly demonstrated by the stability studies performed on the reconstituted solution. No evidence of significant degradation phenomena and no difference between the various tested diluents were shown during the studies. The product, as any injectable beta-lactamic product, is not chemically stable and must be used in a limited time. The stability data demonstrate that the product must be used within 8 hours if stored at temperature not exceeding 25°C and within 48 hours if stored in refrigerator (2-8°C), when reconstituted with the diluents reported in the Summary of Product Characteristics. As usual rule, from a microbiological point of view, the product should be used immediately after the reconstitution as suggested by the Note for Guidance on "Maximum shelf-life for sterile products for human use after first opening or following reconstitution"(CPMP/QWP/159/96).

Product specification
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specifications are in line with the Ph.Eur. and USP (ceftazidime for injection). These include tests for identification, appearance, appearance of solution, pH, water, related substances, pyridine, uniformity of mass, uniformity of dosage units, ceftazidime content, sodium carbonate content, sterility, bacterial endotoxine and particulate contamination. 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 analyses data of two pilot scale batches of each strength has been provided. All batches comply with the specifications.

Container Closure System
The primary container is a colourless neutral glass type III vial for ceftazidime 500 mg and 1 g (usable capacity 10 ml) A glass type II vial is the primary container for ceftazidime 2 g for infusion (usable capacity 50 ml). The primary container is closed with a chlorobutyl rubber (according to Eur. Ph. current ed.) of grey colour with medium level of silicone oil. Specifications for all the primary materials are provided and are adequate. Certificates of analysis are provided and the materials are complying with Ph.Eur. 3.2.

Stability tests on the finished product
The vials have been stored at 25°C/60% RH and 40°C/75% RH (upright and inverse). The stability results show that all results are within the requirement. An increasing trend is seen for the amount of pyridine and a decrease of assay at long term and at accelerated conditions; these trends are more pronounced at accelerated conditions. The claimed shelf-life of 24 months and no special storage conditions was granted.

In-use stability results with different diluents show 8 hours at 25°C and 48 hours at 2-4°C stability for reconstitution in water for injection, sodium chloride 0.9%, glucose 10% and sodium lactate solution. Reconstitution in dextrans 10% shows only stability for 4 hours at 25°C and 24 hours at 2°-4°C.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.2 Non clinical aspects

This product is a generic formulation of the innovator product Fortum, 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 ceftazidime 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

Ceftazidime is a well-known active substance with established efficacy and tolerability.

Ceftazidim Mylan 500, 1000 and 2000 mg, powder for solution for injection or infusion are parenteral formulations and fulfil 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 (NIG CPMP/EWP/QWP 1401/98). The quantitative composition of Ceftazidim Mylan 500, 1000 and 2000 mg is entirely the same as the originator. Therefore, these 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 products can be used instead of their reference products.

**Risk management plan**

Ceftazidime was first approved in 1983, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of ceftazidime can be considered to be well established and no product specific pharmacovigilance issues were identified pre or post authorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

**Product information**

**SPC**

The SPC is derived from the final SPC for procedure UK/H/663/MR, except for the product specific sections and section 4.8. This section is derived from a recent update of this section within the SPC of the innovator. Moreover, the MAH committed to perform a type II variation to harmonise the SPC in accordance with the article 30 procedure for the innovator product Fortum.

**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. Two cohorts of 10 participants were recruited. It was of sufficiently diverse demographic and sociologic criteria. Each cohort participated in one stage of research; per stage 14 questions were asked.

The test results were presented per stage, focusing on the questions not found and/or answered correctly. In the first stage it concerned 4 questions, in the second stage 3 questions.
The PIL successfully passed the test in both stages. The user test showed that the leaflet enabled 90% of participants to find, and 90% of those to express in their own words each piece of information tested. However, a number of changes to the PIL were deemed necessary. The MAH indicated which changes were implemented in the final PIL. The member states agree with the new leaflet submitted. The readability test has been sufficiently performed.
III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Ceftazidim Mylan 500, 1000 and 2000 mg, powder for solution for injection or infusion have a proven chemical-pharmaceutical quality and are generic forms of Fortum. Fortum 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.

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 and are in agreement with other ceftazidime containing products.

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 concerned member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Ceftazidim Mylan 500, 1000 and 2000 mg, powder for solution for injection or infusion with the reference products, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 12 May 2008. Ceftazidim Mylan 500, 1000 and 2000 mg were authorised in the Netherlands on 3 October 2008.

A European harmonised birth date has been allocated (17 October 1983) and subsequently the first data lock point for ceftazidime is October 2009. The first PSUR will cover the period from May 2008 to October 2009, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: 12 May 2013.

The following post-approval commitment has been made during the procedure:

Product information
- The MAH committed to perform a type II variation to harmonise the SPC in accordance with the outcome of the article 30 procedure for the innovator product Fortum.
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\textsubscript{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\textfrac{1}{2} Half-life
t\textsubscript{max} Time for maximum concentration
TSE    Transmissible Spongiform Encephalopathy
USP    Pharmacopoeia in the United States
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<th>Procedure number</th>
<th>Type of modification</th>
<th>Date of start of the procedure</th>
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