PUBLIC ASSESSMENT REPORT
of the Medicines Evaluation Board
in the Netherlands

Cilazapril Mylan 0.5, 1, 2.5 and 5 mg film-coated tablets
Mylan B.V., the Netherlands

cilazapril (as 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/1386/001-004/DC
Registration number in the Netherlands: RVG 102536, 102538-102540

24 February 2010

Pharmacotherapeutic group: ACE inhibitors, plain
ATC code: C09AA08
Route of administration: oral
Therapeutic indication: essential hypertension; chronic heart failure as an adjunctive therapy with digitalis and/or diuretics.
Prescription status: prescription only
Date of authorisation in NL: 3 November 2009
Concerned Member States: Decentralised procedure with AT, PL, CZ (2.5 and 5 mg only), PT (1, 2.5 and 5 mg only)
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 Cilazapril Mylan 0.5, 1, 2.5 and 5 mg film-coated tablets, from Mylan B.V. The date of authorisation was on 3 November 2009 in the Netherlands.

The product is indicated for all grades of essential hypertension. Cilazapril Mylan is also indicated for the treatment of chronic heart failure as an adjunctive therapy with digitalis and/or diuretics.

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

Cilazapril Mylan is a specific, long-acting angiotensin-converting enzyme (ACE) inhibitor that suppresses the renin-angiotensin-aldosterone system, thereby causing a reduction in the systolic and diastolic blood pressure, both in supine and standing position, in most cases without an orthostatic component.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator products Vascase 0.5 mg, 1 mg, 2.5 mg and 5 mg tablets which have been registered in Ireland by Roche Product Limited since 1991. In the Netherlands, Vascase 0.5, 1, 2.5 and 5 mg film-coated tablets (NL License RVG 15132-15135) have been registered by Roche Nederland BV since 18 February 1992. In addition, reference is made to Vascase authorisations in the individual member states (reference product).

The MAH proposed to re-introduce the 1 mg strength on the Dutch market, as it was withdrawn in the Netherlands in 1997 for commercial reasons. The 1 mg strength fits into the dosage regimen as described in the SPC.

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

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. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. To this end the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Vascase 2.5 mg tablets, registered in Greece. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. These generic 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, 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 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 cilazapril monohydrate, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). The active substance is slightly soluble in water. The drug substance has three chiral centers. Only one enantiomer has been manufactured, the other enantiomer is regarded as an impurity, which is limited according to the Ph.Eur.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or ‘know-how’ of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMEA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process
The manufacturing process has been adequately described.

Quality control of drug substance
The drug substance specification is in line with the Ph.Eur., with additional requirements for residual solvents. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for five production-scale batches.

Stability of drug substance
Stability data on the active substance have been provided for five production-scale batches stored at 25°C/60% RH (24 months) and 40°C/75% RH (6 months). The batches were adequately stored. There are no other trends or changes. A photostability study according to the NfG on photostability testing has been included. The drug substance is not sensitive to light. The claimed retest period of 24 months is justified and no special storage conditions are required.

* Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.

Medicinal Product

Composition
Cilazapril Mylan 0.5 mg is a pink, oblong presenting a one sided score, film-coated tablet.
Cilazapril Mylan 1 mg is a pink, oblong presenting a one sided score, with the mark C1 engraved one one side, film-coated tablet,
Cilazapril Mylan 2.5 mg is a brown, oblong presenting a one sided score, film-coated tablet.
Cilazapril Mylan 5 mg is a brown, oblong presenting a one sided score, with the mark C5 engraved one one side, film-coated tablet.
The tablets can be divided into equal halves.

The film-coated tablets are packed in Aluminium-Aluminium/PVC blister packs.
The excipients are: lactose monohydrate, maize starch, hypromellose (E464), talc (E553b), sodium stearyl fumarate,
Colourants - Opadry pink (for 0.5 and 1.0 mg strengths): hypromellose, talc, titanium dioxide (E171), Macrogol 400, iron oxide red (E172) and iron oxide yellow (E172).
Opadry brown (for 2.5 and 5.0 mg strengths): hypromellose, talc, titanium dioxide (E171), Macrogol 400, iron oxide red (E172).
The composition of the 0.5 and 1 mg strength is dose-proportional and the composition of the 2.5 and 5.0 mg strength is also dose-proportional.
The composition of the 0.5 and 2.5 mg tablets is comparable, i.e. a little different quantity of lactose, due to a larger quantity of active drug substance, and another coating colour have been used. The same is true for the 1 and 5.0 mg tablets.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The qualitative composition of the test and reference product is the same. The 2.5 mg tablets are used in bioequivalence study. Dissolution profiles of all four strengths in three different pHs are comparable, more than 85% is dissolved in 15 minutes.
The pharmaceutical development of the product has in general been adequately performed. The influence of the particle size and polymorphic form on the dissolution has been discussed. The particle size does not influence the dissolution rate. The daily dose is low, resulting in a good and fast dissolution in water.

Manufacturing process
The manufacturing process consists of several mixing, drying and sieving steps, after which the final blend is compressed into tablets and the tablets are coated. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for two pilot-scale batches of each strength. The 0.5 and 1.0 mg tablets are manufactured using a non-standard process (low strength), however, given the experience of the MAH with low-dose tablets and the commitment to validate full-scale batches prior to marketing, process validation on pilot-scale batches is considered sufficient.

Excipients
Except for Opadry, the excipients comply with the Ph.Eur. The specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, identity, assay, degradation, dissolution, uniformity of mass and content, disintegration, subdivision of tablets (all strengths), loss on drying and microbial quality. Except for dissolution, one impurity and total impurities, the requirements at release and shelf-life are the same. The test for uniformity of content is the same as the test for uniformity of dosage units. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on two pilot-scale batches of all strengths, demonstrating compliance with the release specification. The validation on three production-scale batches will be performed for the strengths 0.5 mg and 1 mg prior to release on the market.

Stability of drug product
Stability data on the product has been provided two pilot-scale batches of all strengths stored at 25°C/60% RH (36 months) and 30°C/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 Al-Al/PVC blisters.
At long term and intermediate storage conditions no significant trends or changes are observed. At accelerated conditions an out of specification result is encountered for one impurity. A shelf-life of 3 years and the storage condition Store below 25°C could be granted in view of these stability data. Results of a photostability study were provided, demonstrating that the drug product is sensitive to light. Therefore, the storage condition Store in the original package to protect from light is applicable.
The MAH committed to perform the test for subdivision of tablets at the end of the stability studies. Stability studies will be performed for the first three production-scale batches on long term and accelerated studies.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies. Lactose is derived from animal source, but a TSE declaration has been included. The milk used is sourced from healthy animals under the same condition as milk for human consumption. The other excipients are not of human or animal origin.

II.2 Non clinical aspects

These products are generic formulations of Vascase 0.5 mg, 1 mg, 2.5 mg and 5 mg tablets, which are 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 cilazapril 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

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

For this generic application, the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Cilazapril Mylan 2.5 mg (Mylan B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference product Vascase 2.5 mg tablets (Roche, Greece).

The choice of the reference product
The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of reference products in different member states.

The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 28 healthy male subjects, aged 22-42 years. Each subject received a single dose (2.5 mg) of one of the 2 cilazapril formulations. The tablet was orally administered with 240 ml water after a 10 hour overnight fast. The first standard meal was served 5 hours after dosing. There were 2 dosing periods, separated by a washout period of 14 days.

Blood samples were collected at 0, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 6, 9, 12, 24, 48, 72, 96 and 144 hours after administration of the products.

Analytical/statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
Twenty-six individuals completed both treatment periods and 24 individuals were included in the pharmacokinetic analyses per protocol with 2 individuals as backup individuals (total 26). Twenty-six individuals were included in the safety analysis. No major adverse events were identified.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of cilazapril under fasted conditions.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC_{0-t} ng.h/ml</th>
<th>AUC_{0-\infty} ng.h/ml</th>
<th>C_{max} ng/ml</th>
<th>t_{max} h</th>
<th>t_{1/2} h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>87.6 ± 40.0</td>
<td>90.3 ± 39.2</td>
<td>52.29 ± 22.01</td>
<td>1.0 (0.5-1.5)</td>
<td>1.11 ± 0.52</td>
</tr>
<tr>
<td>Reference</td>
<td>87.4 ± 45.7</td>
<td>91.1 ± 44.6</td>
<td>51.82 ± 23.14</td>
<td>1.0 (0.5-1.25)</td>
<td>1.10 ± 0.51</td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td>1.02 (0.90-1.16)</td>
<td>1.01 (0.91-1.13)</td>
<td>1.02 (0.94-1.11)</td>
<td>--</td>
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</tr>
<tr>
<td>CV (%)</td>
<td>26</td>
<td>23</td>
<td>17</td>
<td>--</td>
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</tr>
</tbody>
</table>

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
AUC_{0-\infty} area under the plasma concentration-time curve from time zero to infinity
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
t_{1/2} half-life

*ln-transformed values

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of cilazaprilate under fasted conditions.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC_{0-t} ng.h/ml</th>
<th>AUC_{0-\infty} ng.h/ml</th>
<th>C_{max} ng/ml</th>
<th>t_{max} h</th>
<th>t_{1/2} h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>422.1 ± 115.5</td>
<td>478.5 ± 143.9</td>
<td>53.40 ± 17.90</td>
<td>2.0 (1.25-3.0)</td>
<td>44.76 ± 21.30</td>
</tr>
<tr>
<td>Reference</td>
<td>442.9 ± 125.2</td>
<td>496.7 ± 136.2</td>
<td>52.37 ± 18.45</td>
<td>2.0 (1.25-3.0)</td>
<td>41.96 ± 12.53</td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td>1.03 (0.88-1.03)</td>
<td>0.96 (0.88-1.04)</td>
<td>1.02 (0.92-1.12)</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>CV (%)</td>
<td>16</td>
<td>18</td>
<td>19</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

AUC_{0-t} area under the plasma concentration-time curve from time zero to infinity
AUC_{0-\infty} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
t_{1/2} half-life

*ln-transformed values

The 90% confidence intervals calculated for AUC_{0-t}, AUC_{0-\infty} and C_{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the pharmacokinetic parameters of cilazapril under fasted conditions, supported by the data for cilazaprilate, it can be concluded that Cilazapril Mylan 2.5 mg and Vascase 2.5 mg tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.
Cilazapril may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of cilazapril. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

**Extrapolation to different strengths**
The 0.5 mg and the 1 mg tablets are dose proportional, as are the the 2.5 mg and 5 mg tablets. The ratio of the composition of the 0.5 mg tablet compared to the 2.5 mg, as well as the 1 mg and the 5 mg tablet, are similar and the weight of the active ingredient is within 5% of the total weight of the tablets for all strengths. Also, the manufacturing process and dissolution profiles of the different strengths are comparable. The tablets are all made by the same manufacturer. The results of the bioequivalence study performed with the 2.5 mg tablets therefore apply to the other strengths.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

**Risk management plan**
Cilazapril was first approved in 1990, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of cilazapril can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or postauthorisation 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 MAH committed to adopt the wording of the SPC to the outcome of the upcoming article 30 referral for cilazapril.

**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 test consisted of a pilot test with 3 participants, followed by two rounds with 10 participants each. The composition of the subject population is acceptable as far as age, gender and education are concerned.
During the pilot round, all participants located and understood all of the information for all but four questions. The results of the pilot test were used to adapt the PIL, especially by the removal of unnecessary technical information and the improvement of the clarity of many sections of the PIL. The changes made as a result of the pilot test are clearly indicated in the user test report. The amended PIL was used in the first round of the user test.
During the first round, the results of the 10 subjects met the study objectives. However, some questions which led to difficulties in responding indicated the sections of the PIL which needed amendments. As a result of the first testing round, the PIL was further adapted. The amended PIL was used in the second round of the user test.
The results of the second testing round also met the objectives. The second round of testing led to some final adaptations of the PIL.
The readability test itself and the evaluation report are of an acceptable quality. There were sufficient questions about the critical sections. The conclusions are clear, concise and clearly presented. Furthermore, the questions covered the following areas sufficiently: traceability, comprehensibility and applicability.
III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Cilazapril Mylan 0.5, 1, 2.5 and 5 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Vascase 0.5, 1, 2.5 and 5 mg tablets. Vascase 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 and are in agreement with other cilazapril 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 member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Cilazapril Mylan 0.5, 1, 2.5 and 5 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 20 July 2009. Cilazapril Mylan 0.5, 1, 2.5 and 5 mg film-coated tablets were authorised in the Netherlands on 3 November 2009.

A European harmonised birth date has been allocated (21 February 1990) and subsequently the first data lock point for cilazapril is December 2011. The first PSUR will cover the period from July 2009 to December 2011, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: 31 August 2012.

The following post-approval commitments have been made during the procedure:

Quality - medicinal product
- The MAH committed to validate three production-scale batches for the strengths 0.5 mg and 1 mg prior to release on the market.
- The MAH committed to perform the test for subdivision of tablets at the end of the stability studies.
- The MAH committed to perform stability studies for the first three production-scale batches on long term and accelerated studies.

Product information – SPC
- The MAH committed to adopt the wording of the SPC to the outcome of the upcoming article 30 referral for cilazapril.
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
Cmax   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
t½     Half-life
tmax   Time for maximum concentration
TSE    Transmissible Spongiform Encephalopathy
USP    Pharmacopoeia in the United States
### STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Type of modification</th>
<th>Date of start of the procedure</th>
<th>Date of end of the procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached</th>
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