CBG MEB

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

# Valsartan/Hydrochloorthiazide Mylan 80 mg/12.5 mg, 160 mg/12.5 mg, 160 mg/25 mg, 320 mg/12.5 mg and 320 mg/25 mg, film-coated tablets Mylan B.V., the Netherlands

## valsartan/hydrochlorothiazide

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/2360/001-005/DC**
**Registration number in the Netherlands: RVG 109823-109824, 109839, 109843-109844**

**24 October 2012**

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|---|---|
| Pharmacotherapeutic group: | angiotensin II antagonists and diuretics |
| ATC code: | C09DA03 |
| Route of administration: | oral |
| Therapeutic indication: | essential hypertension in adults, whose blood pressure is not adequately controlled on valsartan or hydrochlorothiazide monotherapy |
| Prescription status: | prescription only |
| Date of authorisation in NL: | 31 July 2012 (80 mg/12.5 mg, 160 mg/12.5 mg, 160 mg/25 mg only) |
| Concerned Member States: | Decentralised procedure with AT, BE, DE, DK, EL, ES, FI, FR, HU, LU, NO, PL, PT and SE |
| 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 Valsartan/Hydrochloorthiazide Mylan 80 mg/12.5 mg, 160 mg/12.5 mg and 160 mg/25 mg, film-coated tablets from Mylan B.V. The date of authorisation was on 31 July 2012 in the Netherlands.

The product is indicated for treatment of essential hypertension in adults.
Valsartan/Hydrochloorthiazide Mylan fixed-dose combination is indicated in patients whose blood pressure is not adequately controlled on valsartan or hydrochlorothiazide monotherapy.

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

Based on the review of the data on quality, safety and efficacy, the member states consider that the applications for Valsartan/Hydrochlorothiazide Mylan 320 mg/12.5 mg and 320 mg/25 mg are not approvable since a potential serious risk to public health remains, which precludes a recommendation for marketing authorisation at the present time. A biowaiver could not be granted for these strengths. The details of this potential serious risk to public health are provided in section II.3 'Clinical aspects'.

Valsartan is an orally active and specific angiotensin II (Ang II) receptor antagonist. It acts selectively on the $AT_1$ receptor subtype, which is responsible for the known actions of angiotensin II. The increased plasma levels of Ang II following $AT_1$ receptor blockade with valsartan may stimulate the unblocked $AT_2$ receptor, which appears to counterbalance the effect of the $AT_1$ receptor. Valsartan does not exhibit any partial agonist activity at the $AT_1$ receptor and has much (about 20,000 fold) greater affinity for the $AT_1$ receptor than for the $AT_2$ receptor. Valsartan is not known to bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

The site of action of thiazide diuretics is primarily in the renal distal convoluted tubule. It has been shown that there is a high-affinity receptor in the renal cortex as the primary binding site for the thiazide diuretic action and inhibition of NaCl transport in the distal convoluted tubule. The mode of action of thiazides is through inhibition of the $Na^+Cl^-$ symporter perhaps by competing for the $Cl^-$ site, thereby affecting electrolyte reabsorption mechanisms:directly increasing sodium and chloride excretion to an approximately equal extent, and indirectly by this diuretic action reducing plasma volume, with consequent increases in plasma renin activity, aldosterone secretion and urinary potassium loss, and a decrease in serum potassium. The renin-aldosterone link is mediated by angiotensin II, so with co-administration of valsartan the reduction in serum potassium is less pronounced as observed under monotherapy with hyrochlorothiazide.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Co-Diovan 80 mg/12.5 mg film-coated tablets which has been registered in Germany by Novartis Pharma since 21 October 1997 (original product). Co-Diovan 160 mg/12.5 mg and Co-Diovan forte Filmtabletten 160 mg/25 mg were approved in Germany on 16 December 2002 and 9 February 2004, respectively. On 13 April 2007 the 320 mg/12.5 mg and 320 mg/25 mg strengths were registered. Co-Diovan has been approved via MRP (SE/H/0565) in all CMSs involved in this procedure.

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 two bioequivalence studies in which the pharmacokinetic profile of the 160/12.5 mg and 160/25 mg formulations is compared with the pharmacokinetic profile of the reference product Co-Tareg, which is

the name of the reference product Co-Diovan as registered in France. 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. This generic product can be used instead of its reference product.

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 a generic application.

# 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 substances**
***Valsartan***
The active substance valsartan is an established active substance described in the European Pharmacopoeia (Ph.Eur.*). It is a white or almost white, hygroscopic powder, which is practically insoluble in water, freely soluble in anhydrous ethanol and sparingly soluble in methylene chloride. Valsartan is known to exists in two polymorphic forms: amorphous and crystalline forms. The amorphous form is used.

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 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.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The specification is compliant with the Ph.Eur. monograph and general ICH requirements for specifications and includes limits on particle size distribution. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance
The active substance is stable for 5 years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

** 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.*

***Hydrochlorothiazide***
The active substance hydrochlorothiazide is an established active substance described in the European Pharmacopoeia (Ph.Eur.*). It is a white or almost white, crystalline powder, which is very slightly soluble in water, soluble in acetone and sparingly soluble in ethanol. It dissolves in dilute solutions of alkali hydroxides.

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 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.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The specification is compliant with the Ph.Eur. monograph and general ICH requirements for specifications and includes limits on particle size distribution. Batch analytical data demonstrating compliance with this specification have been provided.

Stability of drug substance
The active substance is stable for 5 years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

**Medicinal Product**

Composition
Valsartan/Hydrochloorthiazide Mylan 80 mg/12.5 mg is a light orange, oval, biconvex film-coated tablet (12.5 x 6.4 mm) debossed with “VH1” on one side of the tablet and “M” on other side.
Valsartan/Hydrochloorthiazide Mylan 160 mg/12.5 mg is a reddish, oval, biconvex film-coated tablet (16.1 x 7.6 mm) debossed with “VH2” on one side of the tablet and “M” on other side.
Valsartan/Hydrochloorthiazide Mylan 160 mg/25 mg is a brown, oval, biconvex film-coated tablet (16.1 x 7.6 mm) debossed with “VH3” on one side of the tablet and “M” on other side

The 320 mg/12.5 mg and 320 mg/25 mg products have not been approved.

The film-coated tablets are packed in HDPE bottles with PP screw cap or OPA/Al/PVC-Aluminium blister packs.

The excipients are:
*Tablet core*
silica, colloidal anhydrous
magnesium stearate/sodium lauryl sulphate
cellulose, microcrystalline
pregelatinised maize starch
lactose monohydrate
crospovidone
povidone
Stear-o-wet M [Magnesium stearate/ Sodium lauryl sulphate (94/6)]

*Film-coating*
hypromellose
titanium dioxide (E171)
macrogol
talc
iron oxide (E172):
80 mg/12.5 mg: yellow & red iron oxide
160 mg/12.5 mg: red iron oxide
160 mg/25 mg: yellow, red & black iron oxide

The 80/12.5 mg tablets are dose proportional with the 160/25 mg tablets. The 160/12.5 mg tablet differs from the 160/25 mg tablets in the amount of hydrochlorothiazide.

Pharmaceutical development
The product composition is adequately described. The excipients used are commonly employed. The packaging materials are standard and shown suitable by the presented stability studies.
Comparative dissolution profiles of the generic product and the French reference product Cotareg® tablets were generated in pH 6.8 Phosphate buffer (release media), 0.1N HCl and pH 4.5 acetate buffer. For both valsartan and hydrochlorothiazide more than 85% of the labelled amount of drug is released within 15 minutes from both test and reference product. Therefore, as per the provisions mentioned in CPMP guideline on the Investigation of Bio-equivalence, CPMP/EWP/QWP/1401/98-Rev 01 January 2010, the dissolution profiles can be considered similar without further mathematical calculations.
The development of the product has been satisfactorily performed and explained.

Manufacturing process
The product manufacture is standard and consists of three stages: preparation of hydrochlorothiazide intermediate, preparation of valsartan granules and preparation of valsartan/hydrochlorothiazide tablets. Manufacturing process validation data have been provided on three batches per strength.

Control of excipients
Al excipient with the exception of the colorants and Stear-o-wet M (Magnesium stearate/Sodium lauryl sulphate (94/6)) comply with the Ph.Eur. The individual compendial components used in the manufacturing of opadry coating material comply with the monographs in Ph.Eur./USP NF. The individual components of Stear-o-wet M comply with the Ph.Eur. These specifications are acceptable.

Quality control of drug product
The finished product specification is standard for the pharmaceutical form and includes description, identification, dissolution, assay, related substances, uniformity of dosage units by content uniformity, water content and microbiological tests. The release and shelf-life specifications are identical. Batch analysis data of 3 pilot-scale batches of each tablet strength have been provided, showing compliance with the release requirements.

Stability of drug product
Stability data have been provided for 3 pilot-scale batches of each strength stored in the proposed market packagings. Results at long term and accelerated storage were within specification. At accelerated conditions a decrease in assay was observed. When stored under long term conditions, the assay values of both drug substances show a large variance. Photostability of the product has been demonstrated.
A shelf-life of 24 months stored without special storage conditions when packed in Al-Al blisters or HDPE containers was granted on the basis of the presented data.
The in-use studies for the HDPE container demonstrated compliance with the shelf-life parameters up to 3 months after opening.
Bulk tablet storage can be accepted for up to 12 months when stored in LDPE bags placed in triple laminated bags with a 10g silicabag placed in a HDPE container.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Lactose monohydrate is made milk that is sourced from healthy animals in the same conditions as milk collected for human consumption. The lactose is prepared without the use of other ruminant materials than milk and calf rennet. Magnesium stearate is derived from vegetable origin.

## II.2 Non-clinical aspects

This product is a generic formulation of Co-Diovan, which is available on the European market. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

**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 valsartan or hydrochlorothiazide 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

Valsartan and hydrochlorothiazide are well-known active substances with established efficacy and tolerability.
A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted two bioequivalence studies in which the pharmacokinetic profile of the test products Valsartan/Hydrochloorthiazide Mylan 160 mg/12.5 mg and 160 mg/25 mg (Mylan B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference products Co-Tareg 160 mg/12.5 mg and 160 mg/25 mg film-coated tablets (Novartis Pharma S.A.S., France).

*The choice of the reference products*
The choice of the reference products in the bioequivalence studies has been justified by comparison of dissolution results and compositions of reference products.
The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

***Bioequivalence study I – 160/12.5 mg***
*Design*
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 48 healthy male subjects, aged 18-50 years. Each subject received a single dose (160/12.5 mg) of one of the 2 valsartan/hydrochlorothiazide formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least 10 hours. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.50, 1.0, 1.50, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 8.0, 10.0, 12.0, 16.0, 24.0 and 36.0 hours after administration of the products.
The overall study design is considered acceptable considering the absorption rate and half-lives. Also the washout period is acceptable.

*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*
One subject was withdrawn as he did not show up for the second period. The remaining 47 subjects were included in the analysis.

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

| **Treatment N=47** | **$AUC_{0-t}$** ug.h/ml | **$AUC_{0-\infty}$** ug.h/ml | **$C_{max}$** ug/ml | **$t_{max}$** h | **$t_{1/2}$** h |
|---|---|---|---|---|---|

| | | | | | |
|---|---|---|---|---|---|
| **Test** | 34.8 ± 12.9 | 35.6 ± 13.2 | 5.81 ± 2.09 | 3.0 (1.5 – 5.0) | 6.6 ± 1.4 |
| **Reference** | 32.9 ± 13.3 | 33.6 ± 13.8 | 5.23 ± 2.05 | 3.0 (1.5 – 6.0) | 6.4 ± 1.1 |
| ***Ratio (90% CI)** | 1.07 (1.00 – 1.16) | 1.07 (1.00 – 1.16) | 1.13 (1.02 – 1.25) | -- | -- |
| **CV (%)** | 21.8 | 21.6 | 29.4 | -- | -- |

**$AUC_{0-\infty}$** area under the plasma concentration-time curve from time zero to infinity
**$AUC_{0-t}$** 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*

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

| **Treatment N=47** | **$AUC_{0-t}$** ug.h/ml | **$AUC_{0-\infty}$** ug.h/ml | **$C_{max}$** ug/ml | **$t_{max}$** h | **$t_{1/2}$** h |
|---|---|---|---|---|---|
| **Test** | 593 ± 146 | 639 ± 147 | 80.7 ± 22.2 | 2.0 (1.0 – 4.0) | 9.2 ± 1.2 |
| **Reference** | 591 ± 152 | 635 ± 154 | 76.7 ± 15.6 | 2.0 (1.5 – 4.5) | 9.2 ± 1.2 |
| ***Ratio (90% CI)** | 1.01 (0.95 – 1.06) | 1.01 (0.96 -1.06) | 1.04 (0.98 – 1.10) | -- | -- |
| **CV (%)** | 16.2 | 14.3 | 16.2 | -- | -- |

**$AUC_{0-\infty}$** area under the plasma concentration-time curve from time zero to infinity
**$AUC_{0-t}$** 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 valsartan and hydrochlorothiazide under fasted conditions, it can be concluded that Valsartan/Hydrochloorthiazide Mylan 160 mg/12.5 mg and Co-Tareg 160 mg/12.5 mg film-coated tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

***Bioequivalence study II – 160/25 mg***

*Design*

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 48 healthy male subjects, aged 18-50 years. Each subject received a single dose (160/25 mg) of one of the 2 valsartan/hydrochlorothiazide formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least 10 hours. There were 2 dosing periods, separated by a washout period of 8 days.

Blood samples were collected pre-dose and at 0.50, 1.0, 1.50, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 8.0, 10.0, 12.0, 16.0, 24.0 and 36.0 hours after administration of the products.

The overall study design is considered acceptable considering the absorption rate and half-lives. Also the washout period is acceptable.

*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*
Three subjects were withdrawn as they did not show up for the second period. The remaining 45 subjects were included in the analysis.

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, $t_{max}$ (median, range)) of valsartan under fasted conditions.

| **Treatment N=45** | **$AUC_{0-t}$** ug.h/ml | **$AUC_{0-\infty}$** ug.h/ml | **$C_{max}$** ug/ml | **$t_{max}$** h | **$t_{1/2}$** h |
|---|---|---|---|---|---|
| **Test** | 41.7 ± 16.9 | 42.7 ± 17.2 | 6.61 ± 2.66 | 3.5 (1.5 – 5.0) | 6.4 ± 1.3 |
| **Reference** | 39.5 ± 16.3 | 40.5 ± 16.5 | 6.09 ± 2.57 | 3.5 (1.5 – 5.0) | 6.5 ± 1.4 |
| ***Ratio (90% CI)** | 1.05 (0.94 – 1.17) | 1.05 (0.94 – 1.17) | 1.09 (0.95 – 1.24) | -- | -- |
| **CV (%)** | 31.6 | 31.4 | 38.4 | -- | -- |

**$AUC_{0-\infty}$** area under the plasma concentration-time curve from time zero to infinity
**$AUC_{0-t}$** 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*

Table 4. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, $t_{max}$ (median, range)) of hydrochlorothiazide under fasted conditions.

| **Treatment N=45** | **$AUC_{0-t}$** ug.h/ml | **$AUC_{0-\infty}$** ug.h/ml | **$C_{max}$** ug/ml | **$t_{max}$** h | **$t_{1/2}$** h |
|---|---|---|---|---|---|
| **Test** | 1124 ± 247 | 1187 ± 257 | 149 ± 42 | 2.0 (1.0 – 3.5) | 9.5 ± 1.4 |
| **Reference** | 1122 ± 250 | 1191 ± 260 | 142 ± 39 | 2.5 (1.5 – 4.5) | 9.5 ± 1.4 |
| ***Ratio (90% CI)** | 1.00 (0.94 – 1.07) | 1.00 (0.94 – 1.06) | 1.05 (0.98 – 1.13) | -- | -- |
| **CV (%)** | 17.5 | 16.4 | 22.4 | -- | -- |

**$AUC_{0-\infty}$** area under the plasma concentration-time curve from time zero to infinity
**$AUC_{0-t}$** 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 valsartan and hydrochlorothiazide under fasted conditions, it can be concluded that Valsartan/Hydrochloorthiazide Mylan 160 mg/25 mg and Co-Tareg 160 mg/25 mg film-coated tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Valsartan/HCTZ may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of valsartan/HCTZ. 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.

The MEB has been assured that the bioequivalence studies have 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).

Biowaiver

A request for a biowaiver was submitted for the 80/12.5 mg, 320 mg/12.5 mg and 320 mg/25 mg film-coated tablets. At day 70, the RMS concluded that the request for a biowaiver could be granted for all strengths.

The MAH states in his extensive argumentation that the 80/12.5 mg tablets are dose proportional with the 160/25 mg tablets for which bioequivalence was established. The same holds for the 320/25 mg film-coated tablets that are dose proportional with the investigated 160/12.5 mg tablet formulation and that the 320/12.5 mg film-coated tablets only differ from the 320/25 mg film-coated tablets in the amount of hydrochlorothiazide (less than 5% of the total weight). The MAH also provided dissolution tests with the different strengths.

In addition the MAH mentioned that the reference product of valsartan/hydrochlorothiazide 320 mg/25 mg was not available during the conduct of the bioequivalence studies for this application. The MAH has therefore performed a bioequivalence study on valsartan/hydrochlorothiazide 160 mg/12.5 mg film-coated tablets which is the scale down version of valsartan/hydrochlorothiazide 320 mg/25 mg film-coated tablets

However the assessment at day 70 was not in line with the current Guideline on the Investigation of Bioequivalence (CHMP/QWP/EWP/1401/98 Rev. 1) and recent decisions for other procedures. According to the Guideline on the Investigation of Bioequivalence, two conditions have to be fulfilled in order to waive a study with the highest dose strength (chapter 4.1.6): the pharmacokinetic has to be linear and the drug substance is highly soluble.

While linearity over the therapeutic dose range is given for valsartan, it is practically insoluble in water. Hence, bioequivalence testing has to be performed with the highest strength applied for.

Selection of a lower dose in the bioequivalence study could also be acceptable if the highest dose of the active substance could not be administered to healthy volunteers due to safety/tolerability reasons. Since there is sufficient experience that valsartan/hydrochlorothiazide 320 mg/25 mg tablet is reasonably well tolerated when administered to healthy volunteers, the bioequivalence study should have been conducted with the highest strength. In conclusion, during the procedure it became evident that the request for a biowaiver for the 320 mg/12.5 mg and 320 mg/25 mg film-coated tablets cannot be granted and these strengths were not approved.

The assessment of the biowaiver for the 80 mg/12.5 mg tablet is positive. The 80 mg/12.5 mg film-coated tablets comply with the requirements for a biowaiver and thus a biowaiver can be granted for this strength.

Risk management plan

The combination of valsartan and HCTZ was first approved in 1997, and there is now more than 10 years post-authorisation experience with the active substances. The safety profile of valsartan/HCTZ 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 almost identical to the Art. 30 referral text for the innovator Co-Diovan and is updated according to the recently agreed wording for the use of ACE-inhibitors or AIIRAs in combination with hydrochlorothiazide during pregnancy and lactation.

Readability test
The package leaflet has not been evaluated via a user consultation study. The MAH submitted a bridging report in which the proposed PL for Valsartan/Hydrochlorothiazide Mylan (daughter PL) is being bridged to a tested PL of Candesartan cilexetil/Hydrochlorothiazide (parent PL). The MAH states that the two products belong to the same class of medicinal products, are both combination products and have the same oral route of administration. The same safety issues were also identified.
As the majority of the information on the daughter PL is common to that on the parent PL, the results from the readability testing study of the parent PL can be extrapolated to that of the daughter PL.
The MAH performed a bridging study which focused on the following issues:
- Target patient population
- Key safety messages
- Design and layout issues
- Content issues.

The target patient population is identified as the same for both the parent and daughter PLs. The MAH compared the key safety messages in both PLs and concluded that these were similar.
Design and lay-out issues of both PLs were compared. The layout and design of the parent PL and daughter PL are the same and reflect the MAH's in-house style. This in-house style is used in several other successfully user-tested PLs.
The messages and language used in the two leaflets are very similar and there is no reason to consider the daughter PL to be any less readable than the Parent PL.
The member states agree with the conclusions of the MAH. The daughter PL can be brigded to the parent PL. Separate user testing is not required.

## III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Valsartan/Hydrochloorthiazide Mylan 80 mg/12.5 mg, 160 mg/12.5 mg and 160 mg/25 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Co-Diovan 80 mg/12.5 mg, 160 mg/12.5 mg and 160 mg/25 mg, film-coated tablets. Co-Diovan is a well-known medicinal product with an established favourable efficacy and safety profile.

For the 80 mg/12.5 mg, 160 mg/12.5 mg and 160 mg/25 mg strengths, bioequivalence has been shown to be in compliance with the requirements of European guidance documents. For Valsartan/Hydrochlorothiazide Mylan 320 mg/12.5 mg and 320 mg/25 mg a biowaiver could not be accepted in line with the current Guideline on the Investigation of Bioequivalence. These strengths were not approved and no marketing authorisation was granted.

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

The SPC is consistent with that of the reference product. The SPC, package leaflet and labelling are in the agreed templates.

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 Valsartan/Hydrochloorthiazide Mylan 80 mg/12.5 mg, 160 mg/12.5 mg and 160 mg/25 mg, film-coated tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 10 May 2012. Valsartan/Hydrochloorthiazide Mylan 80 mg/12.5 mg, 160 mg/12.5 mg and 160 mg/25 mg, film-coated tablets were authorised in the Netherlands on 31 July 2012.

The date for the first renewal will be: 30 March 2015.

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

Quality - medicinal product

- The MAH committed to validate the environmental conditions during transportation of the bulk shipment packs, according to the protocol provided, by monitoring environmental conditions throughout the transit period by placing the data logger along with the consignment. The data should be available upon request and should be submitted if unexpected events or results occur or if out of specification results are observed
- The MAH committed to perform process validation studies on the first 3 production-scale batches of tablets manufactured.
- The MAH committed to place 3 production-scale batches per strength for up to 6 months under accelerated stability conditions (i.e. 40 ± 2°C/75 ± 5% RH) and up to 36 months under long term stability conditions (i.e. 25 ± 2°C/60 ± 5% RH).
- The MAH committed to revisit the proposed shelf-life limits once complete stability data up to 36 months are available for the ongoing stability studies on production-scale batches.

## List of abbreviations

| | |
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| 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 |
| HCTZ | Hydrochlorothiazide |
| 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 |
| $t_{½}$ | 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 |
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