CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Valsartan/Hydrochloorthiazide Mylan 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/2360/006-007/DC
Registration number in the Netherlands: RVG 112791-112801

3 July 2013

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:	22 May 2013
Concerned Member States:	Decentralised procedure with DE, EL, ES
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/Hydrochloorhiazide Mylan 320 mg/12.5 mg and 320 mg/25 mg, film-coated tablets from Mylan B.V. The date of authorisation was on 22 May 2013 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.

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 hydrochlorothiazide (HCTZ).

This decentralised procedure concerns a line extension to the already approved products Valsartan/Hydrochloorthiazide Mylan 80 mg/12.5 mg, 160 mg/12.5 mg and 160 mg/25 mg, film-coated tablets (NL/H/2360/001-003/DC). This application for the 320 mg/12.5 mg and 320 mg/25 mg tablets was initially submitted as DCP NL/H/2360/004-005, but withdrawn before finalization of the procedure. Based on bioequivalence studies with the 160/12.5 mg and 160/25 mg strengths, a biowaiver could not be granted, as the Guideline on the Investigation of Bioequivalence (CHMP/QWP/EWP/1401/98 Rev. 1) requires a bioequivalence study with the highest strength applied for. Further details can be found in the EPAR for NL/H/2360/001-005/DC.
With the current application, the applicant submitted appropriate bioavailability studies for the 320 mg/12.5 mg and 320 mg/25 mg film-coated tablets to demonstrate bioequivalence with the innovator. The results are discussed in section II.3 ‘Clinical aspects’.

For this generic application, essential similarity is claimed with the innovator product Co-Diovan 320 mg/12.5 mg and Co-Diovan forte 320 mg/25 mg film-coated tablets which have been registered in Europe by Novartis Pharma since 2007. 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 product is compared with the pharmacokinetic profile of the reference products CoDiovan® 320 mg/12.5 mg and CoDiovan® forte 320 mg/ 25 mg tablets, registered in Germany. 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 (HCTZ) 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 HCTZ.

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 320 mg/12.5 mg is a pink, oval, biconvex film-coated tablet (21.1 x 10.7 mm) debossed with “VH4” on one side of the tablet and “M” on other side.
Valsartan/Hydrochloorthiazide Mylan 320 mg/25 mg is a yellow, oval, biconvex film-coated tablet (21.1 x 10.7 mm) debossed with “VH5” on one side of the tablet and “M” on other side.

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
magnesium stearate

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

The 320/12.5 mg tablet has the same amount of excipients as the 320/25 mg strength

Pharmaceutical development
The product composition is adequately described. The development of the product has been satisfactorily performed and explained. The packaging materials are standard and shown suitable by the presented stability studies. The excipients used are commonly employed. bioequivalence studies on both strengths have been performed.

Comparative dissolution profiles of the generic product and the German reference products CoDiovan and CoDiovan Forte 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 packages. 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 320 mg/12.5 mg and 320 mg/25 mg, film-coated tablets (Mylan B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference products CoDiovan® 320 mg/12.5 mg and CoDiovan® Forte 320 mg/25 mg tablets (Novartis Pharma GmbH, Germany).

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.

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

Bioequivalence study I – 320/12.5 mg
Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 48 healthy subjects, aged 19-44 years. Each subject received a single dose (320/12.5 mg) of one of the 2 valsartan/HCTZ formulations. The tablet was orally administered under fasted conditions. There were 2 dosing periods, separated by a washout period of 8 days.

Blood samples were collected pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 8, 10, 12, 16, 24, 36 and 48 hours after administration of the products.

The study design is acceptable. The wash-out and the sampling period are both long enough for these compounds. The sampling scheme is in general adequate to estimate pharmacokinetic parameters.

Results
As 2 subjects were withdrawn, a total of 46 subjects completed the study. One subject did not report to the facility for the 2nd period and another subject withdrew his consent for participation at the check-in of the 2nd period. All 46 subjects were included in the pharmacokinetic and statistical analysis of valsartan. In accordance with the protocol, for the pharmacokinetic and statistical evaluation of hydrochlorothiazide only the first 24 completed subjects were used. Inclusion of only the first 24 completed subjects for pharmacokinetic and statistical evaluation of hydrochlorothiazide is acceptable. There were no protocol deviations reported.

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

Treatment N=46	**AUC_{0-t}** ng/ml/h	**$AUC_{0-\infty}$** ng/ml/h	**C_{max}** ng/ml	**t_{max}** h
Test	70630 ± 27228	72249 ± 27231	8534 ± 3125	2.5 (1.0-5.5)
Reference	68380 ± 23358	70036 ± 23616	8035 ± 2773	2.5 (1.0-5.5)
***Ratio (90% CI)**	1.02 (0.94-1.10)	1.02 (0.94-1.10)	1.05 (0.96-1.15)	--

AUC_{0-t} Area under the plasma concentration curve from administration to last observed concentration at time t.
$AUC_{0-\infty}$ Area under the plasma concentration curve extrapolated to infinite time. $AUC_{0-\infty}$ does not need to be reported when AUC_{0-72h} is reported instead of AUC_{0-t}
C_{max} Maximum plasma concentration
t_{max} Time until C_{max} is reached

**ln-transformed values*

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

Treatment N=24	**AUC_{0-t}** ng/ml/h	**$AUC_{0-\infty}$** ng/ml/h	**C_{max}** ng/ml	**t_{max}** h
Test	502.6 ± 119.3	524.8 ± 120.0	64.3 ± 17.5	2.0 (1.0-4.0)
Reference	504.7 ± 104.7	526.9 ± 100.6	62.2 ± 14.0	2.0 (1.0-4.0)
***Ratio (90% CI)**	0.99 (0.92-1.07)	0.99 (0.92-1.06)	1.03 (0.93-1.13)	--

AUC_{0-t} Area under the plasma concentration curve from administration to last observed concentration at time t.
$AUC_{0-\infty}$ Area under the plasma concentration curve extrapolated to infinite time. $AUC_{0-\infty}$ does not need to be reported when AUC_{0-72h} is reported instead of AUC_{0-t}
C_{max} Maximum plasma concentration
t_{max} Time until C_{max} is reached

**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 320 mg/12.5 mg and Co-Diovan 320 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 I – 320/25 mg

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 48 healthy subjects, aged 19-42 years. Each subject received a single dose (320/25 mg) of one of the 2 valsartan/HCTZ formulations. The tablet was orally administered under fasted conditions. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 8, 10, 12, 16, 24, 36 and 48 hours after administration of the products.

The study design is acceptable. The wash-out and the sampling period are both long enough for these compounds. The sampling scheme is in general adequate to estimate pharmacokinetic parameters.

Results

As 6 subjects were withdrawn, a total of 42 subjects completed the study. One subject was withdrawn from the study due to a positive urine drug screen, two subject did not report to the facility for period 2, two subjects were not willing to participate in the 2nd period and one subject was not willing to participate after the 2nd period. All 42 subjects were included in the pharmacokinetic and statistical analysis of valsartan. . In accordance with the protocol, for the pharmacokinetic and statistical evaluation of hydrochlorothiazide only the first 24 completed subjects were used. Inclusion of only the first 24 completed subjects for pharmacokinetic and statistical evaluation of hydrochlorothiazide is acceptable. There were no protocol deviations reported.

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

Treatment N=42	**AUC_{0-t}** ng/ml/h	**$AUC_{0-\infty}$** ng/ml/h	**C_{max}** ng/ml	**t_{max}** h
Test	47499 ± 17902	49113 ± 17964	6252 ± 2106	2.0 (1.0-6.0)
Reference	43830 ± 14891	45424 ± 14968	5703 ± 1933	2.5 (1.5-6.0)
***Ratio (90% CI)**	1.05 (0.94-1.17)	1.06 (0.97-1.16)	1.07 (0.94-1.22)	--

AUC_{0-t} Area under the plasma concentration curve from administration to last observed concentration at time t.
$AUC_{0-\infty}$ Area under the plasma concentration curve extrapolated to infinite time. $AUC_{0-\infty}$ does not need to be reported when AUC_{0-72h} is reported instead of AUC_{0-t}
C_{max} Maximum plasma concentration
t_{max} Time until C_{max} is reached

**ln-transformed values*

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

Treatment N=24	**AUC_{0-t}** ng/ml/h	**$AUC_{0-\infty}$** ng/ml/h	**C_{max}** ng/ml	**t_{max}** h
Test	999.9 ± 151.6	1025.2 ± 156.8	141.9 ± 25.5	2.0 (1.0-4.5)
Reference	1045.4 ± 161.2	1073.1 ± 163.6	141.4 ± 25.8	2.0 (1.0-4.5)
***Ratio (90% CI)**	0.96 (0.91-1.01)	0.96 (0.91-1.01)	1.01 (0.95-1.07)	--

AUC_{0-t} Area under the plasma concentration curve from administration to last observed concentration at time t.
$AUC_{0-\infty}$ Area under the plasma concentration curve extrapolated to infinite time. $AUC_{0-\infty}$ does not need to be reported when AUC_{0-72h} is reported instead of AUC_{0-t}
C_{max} Maximum plasma concentration
t_{max} Time until C_{max} is reached

**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 320 mg/25 mg and Co-Diovan 320 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.

Safety
In the first study a total of 6 adverse events were reported in 3 subjects. One subject experienced abdominal pain during the reference formulation period. Post study, two subjects were reported with elevated eosinophil levels and eosinophil (ABS) levels. In one of them an elevated platelet count level was reported as well.
In the second study only one adverse event was reported during the study: a subject 36 experienced a burning sensation in the abdomen approximately one hour after dosing of the reference treatment.

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).

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. 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.
The MAH states that based on the information available in the public domain, the following safety concerns apply to this product:

Important identified risks	– Hyperkalaemia – Hypotension – Foetotoxicity
Important potential risks	– Elevation of liver function values – Renal impairment – Hypersensitivity reactions incl. angioedema and serum sickness – Decrease in haemoglobin and/or hematocrit
Important missing information	– Exposure in children

The proposed safety specification is acceptable.

Product information

SPC
The new strengths are added to the existing product information of NL/H/2360/001-003 including additional wordings relevant for the higher strengths. The MAH committed to update the product information in line with the originator Co-Diovan.

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 (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 PIL is common to that on the parent PIL, the results from the readability testing study of the parent PIL can be extrapolated to that of the daughter PIL. Separate user testing is not required.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Valsartan/Hydrochloorhiazide Mylan 320 mg/12.5 mg and 320 mg/25 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Co-Diovan 320/12.5 mg and 320/25 mg tablets. This decentralised procedure concerns a line extension to the already approved products Valsartan/Hydrochloorthiazide Mylan 80 mg/12.5 mg, 160 mg/12.5 mg and 160 mg/25 mg, film-coated tablets (NL/H/2360/001-003/DC). Co-Diovan 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 valsartan/HCTZ 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 Valsartan/Hydrochloorhiazide Mylan 320 mg/12.5 mg and 320 mg/25 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 28 April 2013. Valsartan/Hydrochloorhiazide Mylan 320 mg/12.5 mg and 320 mg/25 mg film-coated tablets were authorised in the Netherlands on 22 May 2013.

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

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

<u>Quality - medicinal product</u>

- 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).

<u>Product information</u>

- The MAH committed to submit a variation to update the product information of all 5 strengths of Valsartan/Hydrochlorothiazide in line with the innovator.

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_{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
$t_{½}$	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