PUBLIC ASSESSMENT REPORT
of the Medicines Evaluation Board
in the Netherlands

Valsartan/hydrochlorothiazide Apotex 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
Apotex Europe 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/2407/001-005/DC
Registration number in the Netherlands: RVG 110370-110374

1 October 2012

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: 1 August 2012
Concerned Member States: Decentralised procedure with BE, CZ, ES, LU, PL
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/hydrochlorothiazide Apotex 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 from Apotex Europe B.V. The date of authorisation was on 1 August 2012 in the Netherlands.

The product is indicated for treatment of essential hypertension in adults. Valsartan/Hydrochlorothiazide Apotex 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\textsubscript{1} receptor subtype, which is responsible for the known actions of angiotensin II. The increased plasma levels of Ang II following AT\textsubscript{1} receptor blockade with valsartan may stimulate the unblocked AT\textsubscript{2} receptor, which appears to counterbalance the effect of the AT\textsubscript{1} receptor. Valsartan does not exhibit any partial agonist activity at the AT\textsubscript{1} receptor and has much (about 20,000 fold) greater affinity for the AT\textsubscript{1} receptor than for the AT\textsubscript{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\textsuperscript{+}Cl\textsuperscript{−} symporter perhaps by competing for the Cl\textsuperscript{−} 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.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product CoDiovan 80 mg/12.5 mg film-coated tablets which has been registered in Germany by Novartis Pharma since 21 October 1997 (original product). CoDiovan 160 mg/12.5 mg and CoDiovan 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. CoDiovan has been approved via MRP SE/H/0565/001-005.

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 160/25 mg and 320/25 mg products is compared with the pharmacokinetic profile of the reference products CoDiovan\textsuperscript{®} Forte 160/25 mg tablets and CoDiovan\textsuperscript{®} Forte 320/25 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 freely soluble in methanol and ethanol. There are fourteen different polymorphic forms: 13 crystalline forms and an almost amorphous form. The almost amorphous form is used.

The Active Substance Master File (ASMF) procedure is used for valsartan. 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/EMA 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 synthesis of valsartan comprises three steps. Sufficient information has been provided on the starting materials and solvents.

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

Stability of drug substance
Stability data on the active substance have been provided during storage at 25°C/60% RH and 40°C/75% RH. Based on the data provided, a retest period of 48 months stored at controlled room temperature between 15°C and 30°C was granted.

* 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. It is a white or practically white crystalline powder, which is slightly soluble in dilute aqueous sodium hydroxide and less soluble in water. Hydrochlorothiazide exhibits polymorphism.

The CEP procedure is used for hydrochlorothiazide. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of
Transmissible Spongiform Encephalopathy (TSE) risk, according to the new general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

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

Quality control of drug substance
The active substance specification is compliant with the Ph.Eur. monograph and general ICH requirements for specifications. Batch analytical data demonstrating compliance with this specification have been provided for two batches.

Stability of drug substance
Stability data on the active substance have been provided for 6 batches stored at 25°C/60% RH (up to 48 months) and 40°C/75% RH (6 months). At accelerated and long term conditions no changes in any of the parameters were observed. Based on the data submitted, a retest period of 1 year was granted without any special storage conditions.

Medicinal Product

Composition
Valsartan/hydrochlorothiazide Apotex 80 mg/12.5 mg is an orange, modified, capsule shaped, film-coated tablet, engraved ‘APO’ on one side and ‘80/12.5’ on the other side.
Valsartan/hydrochlorothiazide Apotex 160 mg/12.5 mg is a dark red, modified, capsule shaped, film-coated tablet, engraved ‘APO’ on one side and ‘160/12.5’ on the other side.
Valsartan/hydrochlorothiazide Apotex 160 mg/25 mg is a brown, modified, capsule shaped, film-coated tablet, engraved ‘APO’ on one side and ‘160/25’ on the other side.
Valsartan/hydrochlorothiazide Apotex 320 mg/12.5 mg is a pink, oval shaped film-coated tablet, engraved ‘APO’ on one side and ‘320/12.5’ on the other side.
Valsartan/hydrochlorothiazide Apotex 320 mg/25 mg is a yellow, oval shaped film-coated tablet, engraved ‘APO’ on one side and ‘320/25’ on the other side.

The film-coated tablets are packed in ALU-PVC/PE/PVDC blister packs.

The excipients are:

Tablet Core
Cellulose powdered
Calcium hydrogen phosphate dihydrate
Colloidal anhydrous silica
Crocsmelllose sodium
Magnesium stearate

Tablet Coat
Hypromellose
Hydroxypropyl cellulose
Titanium dioxide (E171)
Yellow iron oxide (E172): 320/ 25 mg, 160/ 25 mg, 80/12.5 mg
Euroxide iron oxide red (E7016): 160/ 12.5 mg, 160/25 mg, 80/ 12.5 mg, 320/ 12.5mg
Black iron oxide (E172): 160/ 25 mg, 320/ 12.5 mg

The 160/25 mg tablet is dose proportional to the 80/12.5 mg tablet, and the 320/25 mg strength is proportional to the 160/12.5 mg. Valsartan/hydrochlorothiazide Apotex 320/12.5 mg and 320/25 mg are look-alike formulations where the amount of hydrochlorothiazide is less than 5 % of the tablet core weight and proportions of the core tablet excipients are the same except the diluent anhydrous dibasic calcium phosphate, which is changed to account for the change in amount of hydrochlorothiazide. The 160/25 mg...
tablet and the 160/12.5 mg tablet differ only in the amount of the diluent anhydrous dibasic calcium to compensate for the difference in hydrochlorothiazide. The formulations differ in colorants (Titanium dioxide, Yellow Iron Oxide and Black iron oxide, Euroxide red iron oxide) which is considered a minor issue.

**Pharmaceutical development**

The product composition is adequately described. The development of the product has been satisfactorily performed and explained. The excipients used are commonly employed. The packaging materials are standard and shown suitable by the presented stability studies. Comparative dissolution profiles of all strengths versus the dissolution profile of the innovator using pH 6.8 phosphate buffer, pH 4.5 phosphate buffer and 0.1N HCL demonstrated that the profiles were similar except for hydrochlorothiazide in the 160/25 mg tablet. HCTZ was released faster than in Co-Diovan forte 160/25 mg tablets. Although *in vitro* dissolution of HCTZ was faster than in the reference product, the test and reference product are considered to be essentially similar, as bioequivalence has been demonstrated. The pharmaceutical development has been sufficiently explained.

**Manufacturing process**

The manufacturing process for all strengths except the 320/12.5 mg strength is a standard process. The process consists of preblending, granulation, lubrication, compression and coating. Validation has been performed on three batches per strength. Manufacturing process validation data for full production-scale batches for the 320/12.5 mg tablets have been provided, as the amount of HCTZ in the 320/12.5 mg strength is below 2% of the tablet weight and the process is therefore considered to be a non-standard.

**Control of excipients**

The excipients are in line with the Ph.Eur or National Formulary, with the exception of iron oxide black, red and purified water. Adequate specifications for red and black iron oxide have been provided. The specifications for purified water are in line with Ph.Eur. standards. 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 analytical methods have been adequately described and validated. Batch analysis data of 3 batches of each tablet strength have been provided, showing compliance with the release requirements.

**Stability of drug product**

Stability data have been provided for the same 3 batches of each strength stored in the proposed market packagings. At accelerated conditions (6 months) out of specification results for impurities were observed. Furthermore an increase in water content was observed. This was not seen in the long term and intermediate stability studies (12 months). A photostability study was performed in line with the ICH guideline. It was adequately demonstrated that the drug product is photostable. A shelf-life of 24 months with the storage conditions: “Store below 25°C. Keep in the original package in order to protect from moisture” packed in coldform Al-PVC/PE/PVdC blisters was granted based on the presented data.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded. Magnesium stearate is of vegetable origin.

**II.2 Non-clinical aspects**

This product is a generic formulation of CoDiovan, 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/hydrochlorothiazide Apotex 160 mg/25 mg and 320/25 mg (Apotex Europe B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference products CoDiovan® Forte 160/25 mg and 320/25 mg tablets (Novartis Pharma GmbH, Germany).

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

**Bioequivalence study I – 160/25 mg**
*Design*
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 57 healthy male subjects, aged 20-42 years. Each subject received a single dose (160/25 mg) of one of the 2 valsartan/hydrochlorothiazide formulations. The tablet was orally administered after an overnight fast of at least 10 hours. There were 2 dosing periods, separated by a washout period of two weeks.

Blood samples were collected pre-dose and at 0.5, 0.75, 1, 1.33, 1.67, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 10, 14, 18, 24, 32, 40 and 48 hours after administration of the products. This design is considered acceptable. The wash-out period is long enough and sampling scheme and sampling period are adequate.

*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*
A total of 55 subjects completed both study periods and were included in pharmacokinetic and statistical analysis. One subject was withdrawn from the study due to the adverse event of vomiting during the first period and one subject did not report for check-in of the second period.

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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>(\text{AUC}_{0-t})</th>
<th>(\text{AUC}_{0-\infty})</th>
<th>(\text{C}_{\text{max}})</th>
<th>(t_{\text{max}})</th>
<th>(t_{1/2})</th>
</tr>
</thead>
</table>

|          |                |                |                |               |            |
### Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, *(median, range)*) of hydrochlorothiazide under fasted conditions.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N=55</th>
<th><strong>AUC(_{0-\infty})</strong> (ng.h/ml)</th>
<th><strong>AUC(_{0,t})</strong> (ng.h/ml)</th>
<th><strong>C(_{\text{max}})</strong> (ng/ml)</th>
<th><strong>t(_{\text{max}})</strong> (h)</th>
<th><strong>t(_{1/2})</strong> (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>35121 ± 11876</td>
<td>35484 ± 11946</td>
<td>5167 ± 1771</td>
<td>3.5 (0.75-5.5)</td>
<td>8.6 ± 1.9</td>
<td></td>
</tr>
<tr>
<td>Reference</td>
<td>31676 ± 11768</td>
<td>32022 ± 11865</td>
<td>4731 ± 1797</td>
<td>3.0 (1.0-6.0)</td>
<td>8.7 ± 1.9</td>
<td></td>
</tr>
<tr>
<td><em>Ratio (90% CI)</em></td>
<td>1.11 (1.03-1.21)</td>
<td>1.11 (1.03-1.21)</td>
<td>1.10 (1.01-1.21)</td>
<td>--</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>CV (%)</td>
<td>25.1</td>
<td>24.9</td>
<td>29.0</td>
<td>--</td>
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<td></td>
</tr>
</tbody>
</table>

**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\(_{\text{max}}\)** maximum plasma concentration

**t\(_{\text{max}}\)** time for maximum concentration

**t\(_{1/2}\)** half-life

*In-transformed values*

The 90% confidence intervals calculated for AUC\(_{0,t}\), AUC\(_{0-\infty}\) and C\(_{\text{max}}\) 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/hydrochlorothiazide Apotex 160 mg/25 mg and CoDiovan® Forte 160/25 mg tablets are bioequivalent with respect to rate and extent of absorption, and fulfill the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

**Bioequivalence study II – 320/25 mg**

**Design**

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 58 healthy male subjects, aged 18-39 years. Each subject received a single dose (320/25 mg) of one of the 2 valsartan/hydrochlorothiazide formulations. The tablet was orally administered after an overnight fast of at least 10 hours. There were 2 dosing periods, separated by a washout period of two weeks.

Blood samples were collected pre-dose and at 0.5, 0.75, 1, 1.33, 1.67, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 10, 14, 18, 24, 32, 40 and 48 hours after administration of the products.
This design is considered acceptable. The wash-out period is long enough and sampling scheme and sampling period are adequate.

**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**
A total of 57 subjects completed both study periods and were included in pharmacokinetic and statistical analysis. One subject was excluded from the study as he did not report for the second study period.

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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N=57</th>
<th>AUC$_{0-t}$ ng.h/ml</th>
<th>AUC$_{0-\infty}$ ng.h/ml</th>
<th>C$_{\text{max}}$ ng/ml</th>
<th>$t_{\text{max}}$ h</th>
<th>$t_{1/2}$ h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>64244 ± 22655</td>
<td>64911 ± 22837</td>
<td>8972 ± 2950</td>
<td>3.0 (1.0-7.0)</td>
<td>8.5 ± 1.8</td>
<td></td>
</tr>
<tr>
<td>Reference</td>
<td>60727 ± 23541</td>
<td>61396 ± 23687</td>
<td>8522 ± 3416</td>
<td>3.0 (1.0-6.0)</td>
<td>8.6 ± 1.8</td>
<td></td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td>1.06 (0.96-1.16)</td>
<td>1.05 (0.96-1.16)</td>
<td>1.06 (0.95-1.18)</td>
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<td></td>
</tr>
<tr>
<td>CV (%)</td>
<td>30.8</td>
<td>30.6</td>
<td>35.7</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$_{\text{max}}$ maximum plasma concentration
$t_{\text{max}}$ time for maximum concentration
$t_{1/2}$ half-life

*ln-transformed values

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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N=57</th>
<th>AUC$_{0-t}$ ng.h/ml</th>
<th>AUC$_{0-\infty}$ ng.h/ml</th>
<th>C$_{\text{max}}$ ng/ml</th>
<th>$t_{\text{max}}$ h</th>
<th>$t_{1/2}$ h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>1022 ± 255</td>
<td>1064 ± 257</td>
<td>136 ± 37</td>
<td>2.0 (1.0-5.0)</td>
<td>10.1 ± 1.2</td>
<td></td>
</tr>
<tr>
<td>Reference</td>
<td>1036 ± 272</td>
<td>1077 ± 276</td>
<td>144 ± 42</td>
<td>1.7 (1.0-3.5)</td>
<td>10.2 ± 1.2</td>
<td></td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td>0.99 (0.94-1.04)</td>
<td>0.99 (0.94-1.04)</td>
<td>0.95 (0.90-1.00)</td>
<td>--</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>CV (%)</td>
<td>16.5</td>
<td>15.3</td>
<td>17.8</td>
<td>--</td>
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<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$_{\text{max}}$ maximum plasma concentration
$t_{\text{max}}$ 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\(_{\text{max}}\) 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/hydrochlorothiazide Apotex 320 mg/25 mg and CoDiovan\textsuperscript{®} Forte 320/25 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.

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.

Extrapolation to different strengths
A bio waiver has been granted for the 80/12.5, 160/12.5 and 320/12.5 strengths, based on the following conditions:

- The pharmaceutical products are manufactured by the same manufacturer and process.
- The pharmacokinetics has been shown to be linear over the therapeutic range, for both substances.
- The qualitative composition of the different strengths is the same, with the exception of the colorant.
- The ratio between amounts of active substance and excipients is the same, with respect to the 320/25 mg compared to the 160/12.5 mg tablets and also the 160/25 mg with the 80/12.5 mg tablets.
- The 320/12.5 mg differs from the 320/25 mg strength in hydrochlorothiazide content and the amount of diluent anhydrous dibasic calcium phosphate which is changed to account for the change in amount of hydrochlorothiazide. This is acceptable since the amount of active substance is less than 5\% of the tablet core weight.
- The dissolution profile should be similar under identical conditions for the additional strengths and the strength of the biobatch, 320/12.5 mg and 160/12.5 mg compared to 320/25 mg and 80/12.5 mg compared to 160/25 mg.

The results of the study with the 160/25 mg formulation can be extrapolated to the 80/12.5 mg strength, according to conditions in the Note for Guidance on the Investigation of Bioavailability and Bioequivalence CPMP/EWP/QWP/1401/98, section 5.4. The results of the study with the 320/25 mg formulation can be extrapolated to the 160/12.5 mg and 320/12.5 mg strengths, according to conditions in the Note for Guidance.

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. 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 content of the SPC approved during the decentralised procedure is in accordance with that accepted for the reference product CoDiovan.
Readability test
The package leaflet has not been evaluated via a user consultation study. In their justification for not submitting a user test, the MAH states that the package leaflet of the product is identical to the package leaflet of CoDiovan (SE/H/565) with the exception of the product specific information. Furthermore, as the CoDiovan leaflet has undergone a referral under Article 30, no word deviations from the harmonised text are accepted. The member states agree with the reasoning of the MAH and with the submitted justification stated above that it is not necessary to test the content of the leaflet. The MAH submitted a bridging statement explaining that the design and layout of the package leaflet of Valsartan/Hydrochlorothiazide Apotex are comparable to the design and layout of the PL of Valsartan Apotex, which has successfully been user tested in the finalized procedure NL/H/1914/001-004/DC. Therefore it is not necessary to perform a user test on the design and layout of the PL. The member states agree with the reasoning of the MAH and with the submitted justification stated above that it is not necessary to test the design and layout of the leaflet.
III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Valsartan/hydrochlorothiazide Apotex 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 have a proven chemical-pharmaceutical quality and are generic forms of CoDiovan 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. CoDiovan 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 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/hydrochlorothiazide Apotex 80 mg/12.5 mg, 160 mg/12.5 mg, 160 mg/25 mg, 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 8 June 2012. Valsartan/hydrochlorothiazide Apotex 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 were authorised in the Netherlands on 1 August 2012.

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

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

Quality - medicinal product
- The MAH committed to place the first three production batches per strength on long term and accelerated stability studies.
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\text{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\frac{1}{2} Half-life
t_{\text{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

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