Public Assessment Report

UKPAR

Valsartan-Hydrochlorothiazide 80 mg/12.5 mg Film-coated Tablets
Valsartan-Hydrochlorothiazide 160mg/12.5mg Film-coated tablets
Valsartan- Hydrochlorothiazide 160mg/25mg Film-coated tablets

(Valsartan and hydrochlorothiazide)

UK Licence Numbers: PL 43801/0031-0033

Sciecure Pharma Limited.
LAY SUMMARY

Valsartan-Hydrochlorothiazide 80mg/12.5mg, 160mg/12.5mg and 160mg/25mg film-coated Tablets
(valsartan and hydrochlorothiazide, film-coated tablet, 80mg/12.5mg, 160mg/12.5mg and 160mg/25mg).

This is a summary of the Public Assessment Report (PAR) for Valsartan-Hydrochlorothiazide 80mg/12.5mg, 160mg/12.5mg and 160mg/25mg film-coated Tablets (PL 43801/0031-0033). It explains how Valsartan-Hydrochlorothiazide 80mg/12.5mg, 160mg/12.5mg and 160mg/25mg film-coated Tablets were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use Valsartan-Hydrochlorothiazide 80mg/12.5mg, 160mg/12.5mg and 160mg/25mg film-coated Tablets.

The products will be collectively referred to as Valsartan-Hydrochlorothiazide Tablets throughout the remainder of this public assessment report (PAR).

For practical information about using Valsartan-Hydrochlorothiazide Tablets, patients should read the package leaflet or contact their doctor or pharmacist.

What are Valsartan-Hydrochlorothiazide Tablets and what are they used for?
Valsartan-Hydrochlorothiazide Tablets are ‘generic medicines’. This means that Valsartan-Hydrochlorothiazide Tablets are similar to ‘reference medicines’ already authorised in the European Union (EU) called Co-Diovan 80/12.5 mg, 160/12.5 mg and 160/25mg film-coated tablets (Novartis Pharmaceuticals UK Limited (trading as Ciba Laboratories), UK).

Valsartan-Hydrochlorothiazide Tablets are used to treat high blood pressure which is not adequately controlled by a single substance alone.

High blood pressure increases the workload of the heart and arteries. If not treated, it can damage the blood vessels of the brain, heart, and kidneys, and may result in a stroke, heart failure or kidney failure. High blood pressure increases the risk of heart attacks. Lowering the patient’s blood pressure to normal reduces the risk of developing these disorders.

How do Valsartan-Hydrochlorothiazide Tablets work?
Valsartan-Hydrochlorothiazide Tablets contain two active substances called valsartan and hydrochlorothiazide. Both of these substances help to control high blood pressure (hypertension).

- Valsartan belongs to a class of medicines known as “angiotensin II receptor antagonists”, which help to control high blood pressure. Angiotensin II is a substance in the body that causes vessels to tighten, thus causing the patient’s blood pressure to increase. Valsartan works by blocking the effect of angiotensin II. As a result, blood vessels relax and blood pressure is lowered.
- Hydrochlorothiazide belongs to a group of medicines called thiazide diuretics (also known as “water tablets”). Hydrochlorothiazide increases urine output, which also lowers blood pressure.

How are Valsartan-Hydrochlorothiazide Tablets used?
The pharmaceutical form of this medicine is a film-coated tablet and the route of administration is oral (by mouth).

The patient should always take this medicine exactly as their doctor or pharmacist has told them. This will help the patient to get the best results and lower the risk of side effects. The patient should check with their doctor or pharmacist if they are not sure.
People with high blood pressure often do not notice any signs of this problem. Many may feel quite normal. This makes it all the more important for the patient to keep their appointments with their doctor even if they are feeling well.

The patient’s doctor will tell them exactly how many tablets of Valsartan-Hydrochlorothiazide Tablets to take.

Depending on how the patient responds to the treatment, their doctor may suggest a higher or lower dose.

- The usual dose is one tablet per day.
- The patient SHOULD NOT change the dose or stop taking the tablets without consulting their doctor.
- The medicine should be taken at the same time each day, usually in the morning.
- This medicine can be taken with or without food.
- Swallow the tablet with a glass of water.

The Valsartan-Hydrochlorothiazide 160mg/25mg film-coated Tablet has a break line on one side. This means that the tablet can be divided into equal doses.

Please read section 3 of the package leaflet for detailed dosing recommendations, the route of administration, and the duration of treatment.

This medicine can only be obtained with a prescription.

**What benefits of Valsartan-Hydrochlorothiazide Tablets have been shown in studies?**

As Valsartan-Hydrochlorothiazide Tablets are generic medicines of Co-Diovan 80/12.5 mg, 160/12.5 mg and 160/25mg film-coated tablets (Novartis Pharmaceuticals UK Limited, UK), studies have been limited to tests to determine that Valsartan-Hydrochlorothiazide Tablets are bioequivalent equivalent to the reference medicines Co-Diovan 80/12.5 mg, 160/12.5 mg and 160/25mg film-coated tablets (Novartis Pharmaceuticals UK Limited, UK). Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

**What are the possible side effects of Valsartan-Hydrochlorothiazide Tablets?**

Because Valsartan-Hydrochlorothiazide Tablets are generic medicines that are considered bioequivalent to the reference medicines Co-Diovan 80/12.5 mg, 160/12.5 mg and 160/25mg film-coated tablets (Novartis Pharmaceuticals UK Limited, UK) the benefits and possible side effects are taken as being the same as the reference medicines.

For the full list of restrictions, see the package leaflet.

For the full list of all side effects reported with Valsartan-Hydrochlorothiazide Tablets, see section 4 of the package leaflet available on the MHRA website.

**Why was Valsartan-Hydrochlorothiazide Tablets approved?**

It was concluded that, in accordance with EU requirements, Valsartan-Hydrochlorothiazide Tablets have been shown to have comparable quality and to be bioequivalent to Co-Diovan 80/12.5 mg, 160/12.5 mg and 160/25mg film-coated tablets (Novartis Pharmaceuticals UK Limited, UK). Therefore, the MHRA decided that, as for Co-Diovan 80/12.5 mg, 160/12.5 mg and 160/25mg film-coated tablets (Novartis Pharmaceuticals UK Limited, UK); the benefits are greater than the risks and recommended that Valsartan-Hydrochlorothiazide Tablets can be approved for use.
What measures are being taken to ensure the safe and effective use of Valsartan-Hydrochlorothiazide Tablets

A risk management plan (RMP) has been developed to ensure that Valsartan-Hydrochlorothiazide Tablets are used as safely as possible. Based on this plan, safety information has been included in the Summaries of Product Characteristics (SmPCs) and the package leaflet for Valsartan-Hydrochlorothiazide Tablets including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously.

Other information about Valsartan-Hydrochlorothiazide Tablets

Marketing authorisations were granted in the UK on 26 July 2017.

The full PAR for Valsartan-Hydrochlorothiazide Tablets follows this summary.

For more information about use of Valsartan-Hydrochlorothiazide Tablets read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in September 2017.
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>I  Introduction</td>
<td>6</td>
</tr>
<tr>
<td>II Quality aspects</td>
<td>8</td>
</tr>
<tr>
<td>III Non-clinical aspects</td>
<td>10</td>
</tr>
<tr>
<td>IV Clinical aspects</td>
<td>10</td>
</tr>
<tr>
<td>V  User consultation</td>
<td>14</td>
</tr>
<tr>
<td>VI Overall conclusion, benefit/risk assessment and recommendation</td>
<td>14</td>
</tr>
<tr>
<td>Table of content of the PAR update</td>
<td>18</td>
</tr>
</tbody>
</table>
I  INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Sciecure Pharma Limited, marketing authorisations for the medicinal products Valsartan-Hydrochlorothiazide Tablets (PL 43801/0031-0033). The products are prescription only medicines (POM) indicated for the treatment of essential hypertension in adults. Valsartan-Hydrochlorothiazide Tablets are a fixed-dose combination indicated in patients whose blood pressure is not adequately controlled on valsartan or hydrochlorothiazide monotherapy.

The applications were submitted under Article 10(1) of Directive 2001/83/EC, as amended, as generic applications. For the purposes of establishing data exclusivity, the reference medicinal products for these applications are Co-Diovan 80/12.5mg, 160/12.5mg Filmtabletten and Co-Diovan Forte 160/25 mg Filmtabletten which were first licensed in Germany to Novartis Pharma GmbH on 11 March 1998, 28 August 2003 and 01 November 2004 respectively. The UK reference products are Co-Diovan 80/12.5mg, 160/12.5mg and 160/25mg Film-Coated Tablets (PL 00101/0480, PL 00101/0650, PL 00101/0651) which were first authorised to Novartis Pharmaceuticals UK Limited on 29 January 2003 (PL 00101/0480) and 23 June 2004 (PL 00101/0650-651). The reference products used in the bioequivalence studies were Co-Diovan Forte 160/25 mg and 320/25 mg Filmtabletten (Novartis Pharma GmbH, Germany). This is acceptable.

**Valsartan:**

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.

**Hydrochlorothiazide:**

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.

Two bioequivalence studies (conducted under fasting conditions) were submitted to support these applications. The applicant has stated that the bioequivalence studies were conducted in accordance with Good Clinical Practice (GCP). These were preceded by a pilot study and two earlier bioequivalence studies, neither showed bioequivalence for valsartan for both C\textsubscript{max} and AUC; the applicant notes that there were some concerns identified with the methodology, hence they were repeated. These 3 studies will not be considered further in this report.

With the exception of the bioequivalence studies, no new non-clinical or clinical data were submitted, which is acceptable given that these applications were based on being generic medicinal products of originator products that have been in clinical use for over 10 years.
The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place at all sites responsible for the manufacture, assembly and batch release of these products.

No new or unexpected safety concerns arose during the review of information provided by the Marketing Authorisation Holder and it was, therefore, judged that the benefits of taking Valsartan-Hydrochlorothiazide Tablets outweigh the risks and Marketing Authorisations were granted.
II QUALITY ASPECTS

II.1 Introduction
Each film-coated tablet contains 80mg/12.5mg, 160mg/12.5mg or 160mg/25mg of valsartan and hydrochlorothiazide, as the active ingredients. Other ingredients consist of the pharmaceutical excipients:

Film coating:
Polyvinyl alcohol, titanium dioxide (E171), talc (E553b), macrogol 3350, lecithin (derived from soya bean) (E322), iron oxide red (E172) and iron oxide yellow (E172).

The 80mg/12.5mg and 160mg/12.5mg tablet strengths also contain iron oxide black (E172).

All strengths of the finished product are packed in to polyvinyl chloride (PVC)/polyethylene (PE)/polyvinylidene chloride (PVDC)-aluminium blisters and are available in pack sizes of 28 tablets. Not all pack sizes may be marketed. Satisfactory specifications and Certificates of Analysis have been provided for all packaging components.

II.2 Drug Substance
1. Valsartan
INN: Valsartan
Chemical name: (2S)-3-Methyl-2-[pentanoyl][2′-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]amino]butanoic acid

Molecular formula: C24H29N5O3
Molecular weight: 435.5 g/mol
Description: White or almost white, hydroscopic powder.
Solubility: Practically insoluble in water, freely soluble in anhydrous ethanol, sparingly soluble in methylene chloride.

Valsartan is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, valsartan, are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

2. Hydrochlorothiazide
INN: Hydrochlorothiazide
Chemical name: 6-Chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide.
Structural formula:

![Structural formula](image)

Molecular formula: \( \text{C}_7\text{H}_8\text{ClIN}_3\text{O}_4\text{S}_2 \)
Molecular weight: 297.7 g/mol
Appearance: White or almost white, crystalline powder.
Solubility: Very slightly soluble in water, soluble in acetone, sparingly soluble in ethanol (96 per cent). It dissolves in dilute solutions of alkali hydroxides.

Hydrochlorothiazide is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, hydrochlorothiazide, are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

II.3. Medicinal Product

Pharmaceutical Development
The objective of the development programme was to formulate safe, efficacious tablets containing 80mg/12.5mg, 160mg/12.5mg and 160mg/25mg of the active ingredients valsartan/hydrochlorothiazide per tablet, that are generic versions of the reference products Co-Diovan 80/12.5 mg, 160/12.5 mg and 160/25mg film-coated tablets (Novartis Pharmaceuticals UK Limited, UK). A satisfactory account of the pharmaceutical development has been provided.

Comparative in-vitro dissolution and impurity profiles have been provided for the proposed and originator products.

All excipients comply with their respective European Pharmacopoeia monographs with the exception of iron oxide yellow (E172), iron oxide red (E172) and lecithin (soya) which are in compliance with the United States Pharmacopeia and National Formulary (USP-NF) and iron oxide black (E172) which is in compliance with the Japanese Pharmacopoeia. Satisfactory Certificates of Analysis have been provided for all excipients. Suitable batch analysis data have been provided for each excipient.

None of the excipients contain materials of animal or human origin.

No genetically modified organisms (GMO) have been used in the preparation of this product.

Manufacture of the product
Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at pilot scale batch size and has shown satisfactory results. The marketing authorisation holder (MAH) has provided a satisfactory process validation scheme for future production scale batches.

Finished Product Specification
The finished product specifications proposed are acceptable. Test methods have been described that have been adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for all working standards used.
Stability of the Product
Finished product stability studies were performed in accordance with current guidelines on batches of the finished product in the packaging proposed for marketing. The data from these studies support a shelf-life of 36 months with the storage conditions ‘Store in the original package in order to protect from light and moisture.’

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects
There are no objections to the approval of these applications from a pharmaceutical viewpoint.

III NON-CLINICAL ASPECTS

III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of valsartan and hydrochlorothiazide are well-known, no new non-clinical studies are required and none have been provided. An overview based on the literature review is, thus, appropriate.

The applicant’s non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

III.2 Pharmacology
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.3 Pharmacokinetics
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.4 Toxicology
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.5 Ecotoxicity/environmental risk assessment (ERA)
Since Valsartan-Hydrochlorothiazide Tablets are intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects
No new non-clinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years.

There are no objections to the approval of these applications from a non-clinical viewpoint.

IV CLINICAL ASPECTS

IV.1 Introduction
The clinical pharmacology of valsartan and hydrochlorothiazide is well-known. With the exception of data from the bioequivalence studies detailed below, no new pharmacodynamics or pharmacokinetic data are provided or are required for these applications.

No new efficacy or safety studies have been performed and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of valsartan and hydrochlorothiazide.
It is noteworthy that a 320/25mg tablet strength has been used for bioequivalence testing of the 160/25mg strength to which it is quantitatively proportional. All strengths are included in the applicant’s Module 3 and therefore may be referred to in this report. A biwaiver is requested for 80/12.5mg and 160mg/12.5 mg tablet strengths.

Based on the data provided, Valsartan-Hydrochlorothiazide 160mg/25mg and 320mg/25mg film-coated Tablets (Sciecure Pharma Limited, UK) can be considered bioequivalent to Co-Diovan Forte 160/25 mg and 320/25 mg Filmtabletten (Novartis Pharma GmbH, Germany).

IV.2 Pharmacokinetics

In support of these applications, the applicant submitted the following bioequivalence studies:

**STUDY 1**

A randomised, open label, two period, two sequence, controlled, single dose, crossover bioequivalence study of the applicant’s test product Valsartan-Hydrochlorothiazide 160mg/25mg film-coated tablets (Sciecure Pharma Limited, UK) versus the reference product Co-Diovan Forte 160/25 mg Filmtabletten (Novartis Pharma GmbH, Germany) in healthy, adult, subjects under fasting conditions.

Following an overnight fast of at least 10 hours, subjects were administered a single dose (1 x 160mg/25mg tablet) of the test or the reference product with 240 mL of water.

Blood samples were collected for plasma levels before dosing and up to and including 48 hours after each administration. The washout period between the treatment phases was 7 days.

Primary variables for the assessment of bioequivalence were $C_{\text{max}}$ and $\text{AUC}_{0-\infty}$, secondary variable was $T_{\text{max}}$ and $\text{AUC}_{0-\text{inf}}$, MRT, $T_{1/2}$, and % extrapolated AUC were obtained as additional parameters.

**Results**

Study 1 was designed as a 2-stage study; however, bioequivalence was shown at the first stage on the basis of standard confidence intervals.

The summary statistics for pharmacokinetic parameters are presented below:

<table>
<thead>
<tr>
<th>Parameter (unit)</th>
<th>Test</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Valsartan</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$C_{\text{max}}$ (ng/ml)</td>
<td>4472.702 ± 2187.186</td>
<td>4194.554 ± 1800.828</td>
</tr>
<tr>
<td>$T_{\text{max}}$ (h)*</td>
<td>2.643 ± 1.069</td>
<td>2.869 ± 1.696</td>
</tr>
<tr>
<td>$\text{AUC}_{0-\infty}$ (ng/ml x h)</td>
<td>31681.277 ± 17192.478</td>
<td>31869.359 ± 18773.693</td>
</tr>
<tr>
<td>$\text{AUC}_{0-\text{inf}}$ (ng/ml x h)</td>
<td>32793.880 ± 17461.974</td>
<td>32975.886 ± 19129.580</td>
</tr>
<tr>
<td>$T_{1/2}$ (h)</td>
<td>6.886 ± 2.829</td>
<td>7.210 ± 3.428</td>
</tr>
<tr>
<td>$\text{AUC% (extrapolated)}$</td>
<td>3.961 ± 2.210</td>
<td>3.908 ± 2.250</td>
</tr>
<tr>
<td>MRT (h)</td>
<td>8.138 ± 1.847</td>
<td>8.533 ± 2.034</td>
</tr>
<tr>
<td><strong>Hydrochlorothiazide</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$C_{\text{max}}$ (ng/ml)</td>
<td>129.837 ± 36.693</td>
<td>119.670 ± 32.204</td>
</tr>
<tr>
<td>$T_{\text{max}}$ (h)*</td>
<td>1.810 ± 0.631</td>
<td>2.298 ± 0.761</td>
</tr>
<tr>
<td>$\text{AUC}_{0-\infty}$ (ng/ml x h)</td>
<td>973.418 ± 325.370</td>
<td>957.356 ± 254.989</td>
</tr>
<tr>
<td>$\text{AUC}_{0-\text{inf}}$ (ng/ml x h)</td>
<td>998.421 ± 332.790</td>
<td>981.532 ± 261.604</td>
</tr>
<tr>
<td>$T_{1/2}$ (h)</td>
<td>9.107 ± 1.358</td>
<td>9.296 ± 1.430</td>
</tr>
<tr>
<td>$\text{AUC% (extrapolated)}$</td>
<td>2.656 ± 1.138</td>
<td>2.472 ± 0.934</td>
</tr>
<tr>
<td>MRT (h)</td>
<td>9.909 ± 1.349</td>
<td>10.318 ± 1.283</td>
</tr>
</tbody>
</table>
STUDY 2
A randomised, open label, two period, two sequence, controlled, single dose, crossover bioequivalence study of the applicant’s test product Valsartan-Hydrochlorothiazide 320mg/25mg film-coated tablets (Sciencure Pharma Limited, UK) versus the reference product Co-Diovan Forte 320/25 mg Filmtabletten (Novartis Pharma GmbH, Germany) in healthy, adult, subjects under fasting conditions.

Following an overnight fast of at least 10 hours, subjects were administered a single dose (1 x 320mg/25mg tablet) of the test or the reference product with 240 mL of water.

Blood samples were collected for plasma levels before dosing and up to and including 48 hours after each administration. The washout period between the treatment phases was 7 days.

Primary variables for the assessment of bioequivalence were \( C_{\text{max}} \) and \( \text{AUC}_{0-t} \), secondary variable was \( T_{\text{max}} \) and \( \text{AUC}_{0-\infty} \), MRT, \( T_{1/2} \), and % extrapolated \( \text{AUC} \) were obtained as additional parameters.

Results
Table: Summary of pharmacokinetic parameters for valsartan and hydrochloride:

<table>
<thead>
<tr>
<th>Parameter (unit)</th>
<th>Test</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Valsartan</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( C_{\text{max}} ) (ng/ml)</td>
<td>6165.221 ± 2839.547</td>
<td>6220.177 ± 2397.212</td>
</tr>
<tr>
<td>( T_{\text{max}} ) (h)*</td>
<td>3.012 ± 1.298</td>
<td>2.815 ± 1.250</td>
</tr>
<tr>
<td>( \text{AUC}_{0-t} ) (ng/ml x h)</td>
<td>49890.100 ± 26760.557</td>
<td>48684.635 ± 23126.616</td>
</tr>
<tr>
<td>( \text{AUC}_{0-\infty} ) (ng/ml x h)</td>
<td>51400.777 ± 26905.837</td>
<td>50537.256 ± 23595.303</td>
</tr>
<tr>
<td>( T_{1/2} ) (h)</td>
<td>8.915 ± 3.544</td>
<td>10.314 ± 4.468</td>
</tr>
<tr>
<td>MRT (h)</td>
<td>10.038 ± 2.852</td>
<td>10.305 ± 3.100</td>
</tr>
<tr>
<td>( K_{\text{el}} ) (h⁻¹)</td>
<td>0.090 ± 0.036</td>
<td>0.080 ± 0.033</td>
</tr>
<tr>
<td><strong>Hydrochlorothiazide</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( C_{\text{max}} ) (ng/ml)</td>
<td>130.950 ± 35.377</td>
<td>119594.30.894</td>
</tr>
<tr>
<td>( \text{AUC}_{0-t} ) (ng/ml x h)</td>
<td>1013.531 ± 261.833</td>
<td>948.219 ± 239.903</td>
</tr>
<tr>
<td>( \text{AUC}_{0-\infty} ) (ng/ml x h)</td>
<td>1043.184 ± 265.987</td>
<td>979.283 ± 245.500</td>
</tr>
<tr>
<td>( T_{1/2} ) (h)</td>
<td>10.086 ± 1.687</td>
<td>10.476 ± 1.789</td>
</tr>
<tr>
<td>MRT (h)</td>
<td>10.842 ± 1.356</td>
<td>11.149 ± 1.811</td>
</tr>
<tr>
<td>( K_{\text{el}} ) (h⁻¹)</td>
<td>0.071 ± 0.012</td>
<td>0.068 ± 0.012</td>
</tr>
</tbody>
</table>
Conclusion for both bioequivalence studies 1 and 2
The 94% confidence intervals of the test/reference ratio for AUC and $C_{\text{max}}$ values for valsartan and hydrochloride for the 160mg/25mg and 320mg/25mg test product strengths lie within the acceptable limits of 80.00% to 125.00%, in line with the ‘Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**). Thus, the data support the claim that the applicant’s test products Valsartan-Hydrochlorothiazide 160mg/25mg and 320mg/25mg film-coated tablets (Sciencure Pharma Limited, UK) are bioequivalent to the reference products Co-Diovan Forte 160/25mg and 320/25 mg Filmtabletten (Novartis Pharma GmbH, Germany).

As the 80mg/12.5mg, 160mg/12.5mg, 160mg/25mg and 320mg/25mg strength test products meet the biowaiver criteria specified in the current bioequivalence guidance, the results and conclusions of the bioequivalence studies with the 160mg/25mg and 320mg/25mg tablet strengths can be extrapolated to the 80mg/12.5mg and 160mg/12.5mg strength tablets.

### IV.3 Pharmacodynamics
No new pharmacodynamic data were submitted and none were required for applications of this type.

### IV.4 Clinical efficacy
No new efficacy data were submitted and none were required for applications of this type.

### IV.5 Clinical safety
No new safety data were submitted and none are required.

### IV.6 Risk Management Plan (RMP) and Pharmacovigilance System
The marketing authorisation holder (MAH) has submitted a risk management plan (RMP), in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Valsartan-Hydrochlorothiazide Tablets.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, are listed below:

<table>
<thead>
<tr>
<th></th>
<th>Ratio (T/R) (%)</th>
<th>94% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Lower limit</td>
</tr>
<tr>
<td><strong>Valsartan</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$C_{\text{max}}$ (ng/ml) &amp; AUC$_{0-\infty}$ (ng/ml x h)</td>
<td>97.019 &amp; 100.783</td>
<td>85.058 &amp; 90.826</td>
</tr>
<tr>
<td><strong>Hydrochlorothiazide</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$C_{\text{max}}$ (ng/ml) &amp; AUC$_{0-\infty}$ (ng/ml x h)</td>
<td>109.503 &amp; 106.554</td>
<td>102.697 &amp; 101.709</td>
</tr>
</tbody>
</table>
Summary table of safety concerns:

<table>
<thead>
<tr>
<th>Summary of safety concerns</th>
</tr>
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<tbody>
<tr>
<td><strong>Important identified risks</strong></td>
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<tr>
<td><strong>Important potential risks</strong></td>
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<tr>
<td><strong>Missing information</strong></td>
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</tbody>
</table>

Routine pharmacovigilance and routine risk minimisation are proposed for all safety concerns.

IV.7  Discussion on the clinical aspects
The grant of marketing authorisations is recommended for these applications.

V  User consultation
The package leaflet has been evaluated via a user consultation study, in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the package leaflet was English.

The results show that the package leaflet meets the criteria for readability, as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI  Overall conclusion, benefit/risk assessment and recommendation
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with valsartan and hydrochlorothiazide is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The approved labelling for this medicine is presented below:
PAR Valsartan-Hydrochlorothiazide 80mg/12.5mg, 160mg/12.5mg and 160mg/25mg film-coated Tablets

Marketing Authorisation Holder:
Scripune Pharma Limited
47 Bloomfield Close, Rainhill, Woking, Surrey, GU21 2BL, United Kingdom
PL 43801/0031

Each Valsartan/Hydrochlorothiazide 160mg/12.5mg film-coated tablet contains 160mg valsartan and 12.5mg hydrochlorothiazide. Also contains lactose (derived from soya bean (E322)). See leaflet for further information. For oral use. Keep out of the sight and reach of children. Read the package leaflet before use. Store in the original package in order to protect from light and moisture.

Batch No./EXP will be printed/embossed during production
Annex 1

Table of content of the PAR update

Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Product information affected</th>
<th>Date of start of the procedure</th>
<th>Date of end of procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached Y/N (version)</th>
</tr>
</thead>
<tbody>
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