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

PL 24668/0069-77

UKPAR

TABLE OF CONTENTS

Lay Summary Page 2
Scientific discussion Page 3
Steps taken for assessment Page 15
Steps taken after authorisation – summary
Summary of Product Characteristics Page 16
Product Information Leaflet Page 59
Labelling Page 61
VALSARTAN/HYDROCHLOROTHIAZIDE 80 MG/12.5 MG, 160 MG/12.5 MG AND 160 MG/25 MG FILM-COATED TABLETS
PL 24668/0069-77

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Caduceus Pharma Limited Marketing Authorisations for the medicinal products Valsartan/Hydrochlorothiazide 80 mg/12.5 mg, 160 mg/12.5 mg and 160 mg/25 mg Film-coated Tablets (PL 24668/0069-77) on 17 December 2010. These medicines are only available on prescription from your doctor.

Valsartan/Hydrochlorothiazide film-coated tablets contain two active substances called valsartan and hydrochlorothiazide. Both of these substances help to control high blood pressure (hypertension). Valsartan/Hydrochlorothiazide Film-coated Tablets are used to treat high blood pressure that is not adequately controlled by either valsartan or hydrochlorothiazide treatment alone.

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 your 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 and this also leads to a reduction in the blood pressure.

High blood pressure increases the workload of the heart and arteries. If not treated, high blood pressure can damage the blood vessels of the brain, heart and kidneys, and may result in stroke, heart failure or kidney failure. High blood pressure increases the risks of heart attacks. Lowering your blood pressure to normal reduces the risks of developing these disorders.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Valsartan/Hydrochlorothiazide 80 mg/12.5 mg, 160 mg/12.5 mg and 160 mg/25 mg Film-coated Tablets outweigh the risks; hence Marketing Authorisations have been granted.
SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

Introduction Page 4
Pharmaceutical assessment Page 5
Non-clinical assessment Page 9
Clinical assessment Page 10
Overall conclusions and risk assessment Page 14
INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Caduceus Pharma Limited Marketing Authorisations for the medicinal products Valsartan/Hydrochlorothiazide 80 mg/12.5 mg, 160 mg/12.5 mg and 160 mg/25 mg Film-coated Tablets (PL 24668/0069-77) on 17 December 2010. The products are prescription-only medicines for the treatment of essential hypertension (high blood pressure) in adults whose blood pressure is not adequately controlled by valsartan or hydrochlorothiazide monotherapy.

Valsartan/Hydrochlorothiazide Film-coated Tablets contain the active ingredients valsartan and hydrochlorothiazide. Valsartan is an angiotensin-II (AT1) receptor blocker. It blocks all the physiologically relevant actions of angiotensin II and through inhibition of aldosterone could tend to attenuate the potassium loss associated with the diuretic hydrochlorothiazide. Angiotensin II is a potent vasoconstrictor and is the primary active hormone in the renin-angiotensin system, and an important determinant of the pathophysiology of hypertension. Angiotensin binds to the AT1 receptor found in many tissues and illicits several important biological actions, including vasoconstriction and the release of aldosterone. Hydrocholorthiazide is a thiazide diuretic. It increases plasma-renin activity, increases aldosterone secretion, decreases serum potassium, and increases the levels of angiotensin II.

These applications were submitted under Article 10.1 and 10.3 of Directive 2001/83/EC, as amended, claiming to be generic (80 mg/12.5 mg tablet strength) and hybrid (160 mg/12.5 mg and 160 mg/25 mg tablet strengths) medicinal products of Cotareg 80 mg/12.5 mg comprimé pelliculé (Novartis Pharma SAS, France), which was licensed on 25 September 1997.

No new non-clinical data have been submitted, which is acceptable given that the applications were based on being generic/hybrid medicinal products of an originator product that has been in clinical use for over 10 years.

With the exception of the bioequivalence studies, no new clinical data were submitted, which is acceptable given that the applications were based on being generic/hybrid medicinal products of an originator product that has been in clinical use for over 10 years. The bioequivalence studies were carried out in accordance with Good Clinical Practice (GCP).

No new or unexpected safety concerns arose during review of information provided by the Marketing Authorisation Holder and it was, therefore, judged that the benefits of taking Valsartan /Hydrochlorothiazide 80 mg/12.5 mg, 160 mg/12.5 mg and 160 mg/25 mg Film-coated Tablets outweigh the risks; hence Marketing Authorisations have been granted.
PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE - VALSARTAN

INN: Valsartan
Chemical Name: N-(1-oxopentyl)-N-[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-L valine;
N-[p-(o-1H-tetrazol-5-ylphenyl)benzyl]-n-valeryl-L-valine;
(S)-N-(1-carboxy-2-methylprop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)]-biphenyl-4-methyl]amine
Molecular Formula: C_{24}H_{29}N_{5}O_{3}

Structure:

\[ \text{Structure Image} \]

Molecular weight: 435.52 g/mol
Appearance: A white or almost white hygroscopic and ‘essentially amorphous’ powder. Freely soluble in methanol and ethanol, sparingly soluble ethyl acetate, slightly soluble in dichloromethane and practically insoluble in water.

At the time of the assessment of these applications, valsartan was not the subject of a European Pharmacopoeia monograph.

Synthesis of the active substance from the designated starting materials has been adequately described, and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant certificates of analysis.

Appropriate proof-of-structure data have been supplied. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the specification limits. Batch analysis data are provided and comply with the proposed specification.

Satisfactory certificates of analysis have been provided for all working standards.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with foodstuff.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.
ACTIVE SUBSTANCE - HYDROCHLOROTHIAZIDE

INN: Hydrochlorothiazide
Chemical Name: 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulphonamido 1,1-dioxide;
6-chloro-3,4-dihydro-1,2-dioxide-2H-1,2,4-benzothiazine-7-sulphonamido
Molecular Formula: C_{7}H_{8}ClN_{3}O_{4}S_{2}

Structure:

Molecular weight: 297.7 g/mol
Appearance: A white to almost white, crystalline powder. Soluble in acetone and 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 (EDQM) Certificate of Suitability.

DRUG PRODUCT

Other Ingredients

Other ingredients consist of the pharmaceutical excipients, namely microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, povidone K29-K32, talc, magnesium stearate, colloidal anhydrous silica and either Opadry II Pink (80 mg/12.5 mg tablet), Opadry II Red (160 mg/12.5 mg) or Opadry II Orange (160 mg/25 mg).

Opadry II Pink (80 mg/12.5 mg tablet), Opadry II Red (160 mg/12.5 mg) or Opadry II Orange (160 mg/25 mg) are made up of the excipients polyvinyl alcohol, talc, titanium dioxide (E171), macrogol 3350, lecithin (E322), iron oxide red (E172), iron oxide black (E172 - 80 mg/12.5 mg and 160/25 mg tablets only), sunset yellow FCF aluminium lake (E110 - 160 mg/12.5 mg tablet only) and iron oxide yellow (E172 - 160 mg/25 mg tablets only).

Appropriate justifications for the inclusion of each excipient have been provided.

All excipients comply with their respective European Pharmacopoeia monograph, with the exception of iron oxide red (E172), iron oxide yellow (E172), iron oxide black (E172), sunset yellow FCF aluminium lake (E110) and lecithin (E322) – these comply either with suitable National Formulary specifications or suitable in-house specifications. In addition, the specifications for iron oxide red (E172), iron oxide yellow (E172), iron oxide black (E172), sunset yellow FCF aluminium lake (E110) and titanium oxide (E171) are in compliance with current European Directives concerning use of colouring agents in foodstuffs. Satisfactory Certificates of Analysis have been provided for all excipients.
With the exception of lactose monohydrate, none of the excipients contain materials of animal or human origin. The supplier of lactose monohydrate has confirmed that the lactose is sourced from healthy animals under the same conditions as milk for human consumption and prepared without the use of other ruminant materials, except calf rennet.

No genetically modified organisms (GMO) have been used in the preparation of these excipients.

**Pharmaceutical Development**
The objective of the development programme was to formulate safe, efficacious, stable products that could be considered generic/hybrid medicinal products of the reference product Cotareg 80 mg/12.5 mg comprimé pelliculé (Novartis Pharma SAS, France).

Suitable pharmaceutical development data have been provided for these applications.

Comparative *in-vitro* dissolution and impurity profiles have been provided for these products and their respective reference products.

**Manufacturing Process**
Satisfactory batch formulae have been provided for the manufacture of all strengths of the product, along with an appropriate account of the manufacturing process. Based on pilot-scale batches, the manufacturing process has been validated and has shown satisfactory results. The Marketing Authorisation Holder has committed to submitting validation data performed on full-scale batches as soon as they are available.

**Finished Product Specification**
The finished product specifications are satisfactory. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specifications. Certificates of analysis have been provided for any working standards used.

**Container Closure System**
The tablets are packaged in either:
1. polyvinylchloride/polyethylene/polyvinylidene chloride/aluminium (PVC/PE/PVDC/Al) blisters strips in pack sizes of 7, 14, 28, 30, 56, 98 and 280 film-coated tablets.
2. high-density polyethylene (HDPE) tablet containers with tamper-evident snap-off polyethylene caps in pack sizes of 7, 14, 28, 30, 56, 98 and 280 film-coated tablets.

Not all pack sizes may be marketed. However, the Marketing Authorisation Holder has committed to submitting mock-ups to the relevant regulatory authorities for approval before marketing any pack size.

Satisfactory specifications and certificates of analysis have been provided for all packaging components. All primary packaging complies with the current European regulations (Directive 2002/72/EC, as amended) concerning materials in contact with foodstuff.
Stability
Finished product stability studies were performed in accordance with current guidelines on batches of finished product packed in the packaging proposed for marketing. Based on the results, the following shelf-lives/storage conditions have been accepted:

- 4 years for products packaged in blister packs, with the storage conditions “Do not store above 30°C.”
- 5 years for product packaged in the HPDE bottles, with no special storage conditions

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

Bioequivalence/Bioavailability
Satisfactory certificates of analysis have been provided for the test and reference batches used in the bioequivalence studies.

Summaries of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and Labelling
The SmPCs, PIL and labelling are pharmaceutically satisfactory.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

MAA Forms
All aspects of the MAA forms are pharmaceutically satisfactory.

Expert Report
The pharmaceutical expert report is written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossiers.

Conclusion
It is recommended that Marketing Authorisations are granted for these applications.
NON-CLINICAL ASSESSMENT

PHarmacodynamics, Pharmacokinetics and Toxicology
As the pharmacodynamic, pharmacokinetic and toxicological properties of valsartan and hydrochlorothiazide are well-known, no further non-clinical studies are required and none have been provided.

NON-CLINICAL EXPERT REPORT
The non-clinical expert report has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

ENVIRONMENTAL RISK ASSESSMENT
A suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the product is intended for generic substitution with products that are already marketed, no increase in environmental burden is anticipated. Thus, the justification for non-submission of an Environmental Risk Assessment is accepted.

CONCLUSION
The grant of Marketing Authorisations is recommended.
CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY
The clinical pharmacology of valsartan and hydrochlorothiazide is well-known. With the exception of the below bioequivalence studies, no new pharmacodynamic or pharmacokinetic data are provided or required for these applications.

In support of the applications, the Marketing Authorisation Holder submitted the following bioequivalence studies:

Study 1
A randomised, single-dose, open-label, two-treatment, two-sequence, two-period, two-way crossover study comparing the pharmacokinetics of the test product Valparan/Hydrochlorothiazide 160 mg/25 mg Film-coated Tablets (Caduceus Pharma Limited, UK) and the reference product Co-Diovan Forte 160 mg/25 mg tablets (Novartis Pharma GmbH, Germany) in healthy male and female adult subjects under fasting conditions.

The subjects were given a single dose of either treatment with 240 ml of water after at least a 10-hour overnight fast. Blood samples were collected before and up to 48 hours after each administration. The washout period between the treatment arms was 14 days. The pharmacokinetic results (presented as geometric means, ratios and 90% confidence intervals) are presented below:

| Pharmacokinetic parameters (geometric mean, ratio and confidence intervals [CI]) of valsartan |
|-----------------------------------|-----------------------------------|-----------------------|-----------------------|
|                                   | Valsartan/hydrochlorothiazide 160 mg/25 mg (Test) | Co-Diovan Forte 160 mg/25 mg (Reference) | Test/Ref Ratio (%) | 90% CI |
| AUC_0-t (ng h/mL)                 | 21648.29                              | 21854.23              | 99.1                  | 90.8-108.1 |
| AUC_0-inf (ng.h/mL)              | 22557.48                              | 22575.70              | 99.9                  | 91.8-108.7 |
| C_max (ng/mL)                    | 3712.66                                | 3609.72               | 102.9                 | 93.1-113.6 |

AUC_0-t: area under the plasma concentration-time curve from time zero to t hours
AUC_0-inf: area under the plasma concentration-time curve from time zero to infinity
C_max: maximum plasma concentration
Ratios and 90% geometric CI calculated from ln-transformed data

| Pharmacokinetic parameters (geometric mean, ratio and confidence intervals [CI]) of hydrochlorothiazide |
|---------------------------------------------------------------|---------------------------------------------------------------|-----------------------|-----------------------|
|                                                               | Valsartan/hydrochlorothiazide 160 mg/25 mg (Test)             | Co-Diovan Forte 160 mg/25 mg (Reference) | Test/Ref Ratio (%) | 90% CI |
| AUC_0-t (ng h/mL)                                             | 958.23                                                        | 973.96                | 98.4                  | 95.3-101.5 |
| AUC_0-inf (ng.h/mL)                                          | 981.29                                                        | 998.79                | 98.2                  | 95.3-101.3 |
| C_max (ng/mL)                                                 | 135.50                                                        | 134.12                | 101.0                 | 95.8-106.5 |

AUC_0-t: area under the plasma concentration-time curve from time zero to t hours
AUC_0-inf: area under the plasma concentration-time curve from time zero to infinity
C_max: maximum plasma concentration
Ratios and 90% geometric CI calculated from ln-transformed data
The current *Notes for Guidance on the Investigation of Bioavailability and Bioequivalence* (CPMP/EWP/QWP/1401/98) defines the confidence limits as 80% to 125% for $C_{\text{max}}$ and AUC values. The 90% confidence intervals of the test/reference ratio of geometric means for $\text{AUC}_{0-t}$, $\text{AUC}_{0-\text{inf}}$, and $C_{\text{max}}$ lie within the acceptable limits. Thus, the data support the claim that the test product Valsartan/Hydrochlorothiazide 160 mg/25 mg film coated tablets (Caduceus Pharma Limited, UK) is bioequivalent to the reference product Co-Diovan Forte 160 mg/25 mg tablets (Novartis Pharma GmbH, Germany).

As the 160 mg/25 mg and 80 mg/12.5 mg strength products meet all the criteria specified in the *Notes for Guidance on the Investigation of Bioavailability and Bioequivalence* (CPMP/EWP/QWP/1401/98), the results and conclusions from the bioequivalence study with the 160 mg/25 mg tablet strength can be extrapolated to the 80 mg/12.5 mg tablet strength.

As the German product used in the bioequivalence study is considered identical to the UK brand leader (Co-Diovan 160 mg/25 mg), bioequivalence has also been shown between the test products and the respective UK brand leaders.

**Study 2**

A randomised, single-dose, open-label, two-treatment, four-period, two-sequence, crossover study comparing the pharmacokinetics of the test product Valsartan/Hydrochlorothiazide 160 mg/12.5 mg Film coated Tablets (Caduceus Pharma Limited, UK) and the reference product Co-Diovan 160 mg/12.5 mg Film-coated Tablets (Novartis Pharma GmbH, Germany) in healthy male and female adult subjects under fasting conditions.

The subjects were given a single dose of either treatment with 240 ml of water after at least a 10-hour overnight fast. Blood samples were collected before and up to 48 hours after each administration. The washout period between the treatment arms was 8 days. The pharmacokinetic results (presented as ratios and 90% confidence intervals) are presented below:

### Pharmacokinetic parameters (geometric mean, ratio and confidence intervals [CI]) of valsartan

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Valsartan/hydrochlorothiazide 160 mg/12.5 mg (Test)</th>
<th>Co-Diovan 160 mg/12.5 mg (Reference)</th>
<th>Test/Ref Ratio (%)</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{AUC}_{0-t}$ (ug.h/mL)</td>
<td>25.5148</td>
<td>23.6575</td>
<td>107.85</td>
<td>99.50-116.90</td>
</tr>
<tr>
<td>$\text{AUC}_{0-\text{inf}}$ (ug.h/mL)</td>
<td>26.3103</td>
<td>24.4388</td>
<td>107.66</td>
<td>99.60-116.36</td>
</tr>
<tr>
<td>$C_{\text{max}}$ (ug/mL)</td>
<td>3.8097</td>
<td>3.3978</td>
<td>112.12</td>
<td>102.15-123.07</td>
</tr>
</tbody>
</table>

$\text{AUC}_{0-t}$ area under the plasma concentration-time curve from time zero to t hours
$\text{AUC}_{0-\text{inf}}$ area under the plasma concentration-time curve from time zero to infinity
$C_{\text{max}}$ maximum plasma concentration
Ratios and 90% geometric CI calculated from ln-transformed data
Pharmacokinetic parameters (geometric mean, ratio and confidence intervals [CI]) of hydrochlorothiazide

<table>
<thead>
<tr>
<th></th>
<th>Valsartan/hydrochlorothiazide 160 mg/12.5 mg (Test)</th>
<th>Co-Diovan 160 mg/12.5 mg (Reference)</th>
<th>Test/Ref Ratio (%)</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC_{0-t} (ng.h/mL)</td>
<td>504.474</td>
<td>507.635</td>
<td>99.38</td>
<td>95.91-102.97</td>
</tr>
<tr>
<td>AUC_{0-inf} (ng.h/mL)</td>
<td>528.328</td>
<td>531.390</td>
<td>99.42</td>
<td>96.14-102.82</td>
</tr>
<tr>
<td>C_{max} (ng/mL)</td>
<td>64.109</td>
<td>63.064</td>
<td>101.66</td>
<td>97.84-105.62</td>
</tr>
</tbody>
</table>

AUC_{0-inf} area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
Ratios and 90% geometric CI calculated from ln-transformed data

The current Notes for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98) defines the confidence limits as 80% to 125% for C_{max} and AUC values. The 90% confidence intervals of the test/reference ratio of geometric means for AUC_{0-t}, AUC_{0-inf} and C_{max} lie within the acceptable limits. Thus, the data support the claim that the test product Valsartan/Hydrochlorothiazide 160 mg/12.5 mg film coated tablets (Caduceus Pharma Limited, UK) is bioequivalent to the reference product Co-Diovan Forte 160 mg/12.5 mg tablets (Novartis Pharma GmbH, Germany).

As the German product used in the bioequivalence study is considered identical to the UK brand leader (Co-Diovan 160 mg/12.5 mg), bioequivalence has also been shown between the test product and the respective UK brand leader.

Efficacy
The efficacy of valsartan and hydrochlorothiazide is well-known. No new efficacy data have been submitted and none are required for applications of these types.

Safety
With the exception of the data generated during the bioequivalence studies, no new safety data were submitted and none are required for these types of applications. No new or unexpected safety issues were raised by the bioequivalence data.

Pharmacovigilance System and Risk Management Plan
The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

A suitable justification has been provided for not submitting a risk management plan for these products.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling
The SmPCs, PIL and labelling are clinically acceptable. The SmPCs are consistent with those for the UK brand leaders. The PIL is consistent with the details in the
SmPCs and in-line with the current guidelines. The labelling is in-line with the current guidelines.

CLINICAL EXPERT REPORT
The clinical expert report is written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossiers.

CONCLUSION
The grant of Marketing Authorisations is recommended.
OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY
The important quality characteristics of Valsartan/Hydrochlorothiazide 80 mg/12.5 mg, 160 mg/12.5 mg and 160 mg/25 mg Film-coated Tablets are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL
No new non-clinical data were submitted. As the pharmacokinetics, pharmacodynamics and toxicology of valsartan and hydrochlorothiazide are well-known, no additional data were required.

EFFICACY
With the exception of the bioequivalence studies, no new data were submitted and none are required for these types of applications.

Bioequivalence has been demonstrated between the applicant’s 160 mg/25 mg and 160 mg/12.5 mg strength tablets and their respective reference products. As the 80 mg/12.5 mg and 160 mg/25 mg strengths of the product meet all the criteria specified in the Notes for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions from the bioequivalence study with the 160 mg/25 mg tablet strength can be extrapolated to the 80 mg/12.5 mg tablet strength.

SAFETY
With the exception of the safety data from the bioequivalence studies, no new data were submitted and none are required for these types of applications. As the safety profile of valsartan and hydrochlorothiazide are well-known, no additional data were required. No new or unexpected safety concerns were raised from the bioequivalence studies.

PRODUCT LITERATURE
The SmPCs, PIL and labelling are satisfactory, and consistent with those for the reference products, where appropriate, along with current guidelines.

BENEFIT/RISK ASSESSMENT
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 products. The benefit/risk is, therefore, considered to be positive.
VALSARTAN/HYDROCHLOROTHIAZIDE 80 MG/12.5 MG, 160 MG/12.5 MG AND 160 MG/25 MG FILM-COATED TABLETS
PL 24668/0069-77

STEPS TAKEN FOR ASSESSMENT

1. The MHRA received the marketing authorisation applications on 23 October 2007.

2. Following standard checks and communication with the applicant the MHRA considered the applications valid on 02 November 2007.

3. Following assessment of the applications the MHRA requested further information relating to the quality dossiers on 03 March 2008, 21 August 2009, 02 February 2010 and 09 September 2010 and to the clinical dossiers on 28 June 2010, 28 September 2010 and 06 December 2010.


5. The applications were determined on 16 December 2010 and granted on 17 December 2010.
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Valsartan/Hydrochlorothiazide 80 mg/12.5 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains 80 mg valsartan and 12.5 mg hydrochlorothiazide.

Excipients: Each Valsartan/Hydrochlorothiazide 80 mg/12.5 mg Film-coated Tablet contains 29.75 mg lactose monohydrate and 0.25 mg lecithin soya (contains soya oil).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet

Pink, biconvex, oval, 11 mm x 5.8 mm. Marked ‘V’ on one side and ‘H’ on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Treatment of essential hypertension in adults.

Valsartan/Hydrochlorothiazide film-coated tablet fixed dose combination is indicated in patients whose blood pressure is not adequately controlled on valsartan or hydrochlorothiazide monotherapy.

4.2 Posology and method of administration
The recommended dose of Valsartan/Hydrochlorothiazide 80 mg/12.5 mg Film-coated Tablets is one film-coated tablet once daily.

Dose titration with the individual components is recommended. In each case, up-titration of individual components to the next dose should be followed in order to reduce the risk of hypotension and other adverse events.

When clinically appropriate direct change from monotherapy to the fixed combination may be considered in patients whose blood pressure is not adequately controlled on valsartan or hydrochlorothiazide monotherapy, provided the recommended dose titration sequence for the individual components is followed.

The clinical response to Valsartan/Hydrochlorothiazide film-coated tablets should be evaluated after initiating therapy and if blood pressure remains uncontrolled, the dose may be increased by increasing either one of the components to a maximum dose of Valsartan/Hydrochlorothiazide 320 mg/25 mg.

The antihypertensive effect is substantially present within 2 weeks.

In most patients, maximal effects are observed within 4 weeks. However, in some patients, 4-8 weeks treatment may be required. This should be taken into account during dose-titration.

Method of administration
Valsartan/Hydrochlorothiazide film-coated tablets can be taken with or without food and should be administered with water.

Special populations
Renal Impairment
No dose adjustment is required for patients with mild to moderate renal impairment (creatinine clearance ≥ 30 ml/min). Due to the hydrochlorothiazide component, Valsartan/Hydrochlorothiazide Film-coated Tablets are contraindicated in patients with severe renal impairment (see sections 4.3, 4.4 and 5.2).
Hepatic Impairment
In patients with mild to moderate hepatic impairment without cholestasis the dose of valsartan should not exceed 80 mg (see section 4.4). Valsartan/Hydrochlorothiazide film-coated tablets are contraindicated in patients with severe hepatic impairment (see sections 4.3, 4.4 and 5.2).

Elderly
No dose adjustment is required in elderly patients.

Paediatric patients
Valsartan/Hydrochlorothiazide Film-coated Tablets are not recommended for use in children below the age of 18 years due to a lack of data on safety and efficacy.

4.3 Contraindications
- Hypersensitivity to valsartan, hydrochlorothiazide, other sulphonamide-derived medicinal products, soya oil, peanut oil or to any of the excipients.
- Second and third trimester of pregnancy (section 4.4 and 4.6).
- Severe hepatic impairment, biliary cirrhosis and cholestasis.
- Severe renal impairment (creatinine clearance < 30 ml/min), anuria
- Refractory hypokalaemia, hyponatraemia, hypercalcaemia, and symptomatic hyperuricaemia.

4.4 Special warnings and precautions for use
Serum electrolyte changes
Valsartan
Concomitant use with potassium supplements, potassium sparing diuretics, salt substitutes containing potassium, or other agents that may increase potassium levels (heparin, etc.) is not recommended. Monitoring of potassium should be undertaken as appropriate.

Hydrochlorothiazide
Hypokalaemia has been reported under treatment with thiazide diuretics, including hydrochlorothiazide. Frequent monitoring of serum potassium is recommended.

Treatment with thiazide diuretics, including hydrochlorothiazide, has been associated with hyponatraemia and hypochloraemic alkalosis. Thiazides, including hydrochlorothiazide, increase the urinary excretion of magnesium, which may result in hypomagnesaemia. Calcium excretion is decreased by thiazide diuretics. This may result in hypercalcaemia.

As for any patient receiving diuretic therapy, periodic determination of serum electrolytes should be performed at appropriate intervals.

Sodium, and/or volume-depleted patients:
Patients receiving thiazide diuretics, including hydrochlorothiazide, should be observed for clinical signs of fluid or electrolyte imbalance. In severely sodium-depleted and/or volume-depleted patients, such as those receiving high doses of diuretics, symptomatic hypotension may occur in rare cases after initiation of therapy with valsartan/hydrochlorothiazide. Sodium and/or volume depletion should be corrected before starting treatment with Valsartan/Hydrochlorothiazide Film-coated Tablets.

Patients with severe chronic heart failure or other conditions with stimulation of the renin-angiotensin-aldosterone-system
In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (e.g. patients with severe congestive heart failure), treatment with angiotensin converting enzyme inhibitors has been associated with oliguria and/or progressive azotaemia, and in rare cases with acute renal failure. The use of valsartan/hydrochlorothiazide in patients with severe chronic heart failure has not been established.

Hence it cannot be excluded that because of the inhibition of the renin-angiotensin-aldosterone system the application of valsartan/hydrochlorothiazide as well may be associated with impairment of the renal function. Valsartan/Hydrochlorothiazide Film-coated Tablets should not be used in these patients.
Renal artery stenosis
Valsartan/Hydrochlorothiazide Film-coated Tablets should not be used to treat hypertension in patients with unilateral or bilateral renal artery stenosis or stenosis of the artery to a solitary kidney, since blood urea and serum creatinine may increase in such patients.

Primary hyperaldosteronism
Patients with primary hyperaldosteronism should not be treated with Valsartan/Hydrochlorothiazide Film-coated Tablets as their renin-angiotensin system is not activated.

Aortic and mitral valve stenosis, hypertrophic obstructive cardiomyopathy
As with all other vasodilators, special caution is indicated in patients suffering from aortic or mitral stenosis, or hypertrophic obstructive cardiomyopathy (HOCM).

Renal impairment
No dosage adjustment is required for patients with renal impairment with a creatinine clearance $\geq 30$ml/min (see section 4.2). Periodic monitoring of serum potassium, creatinine and uric acid levels is recommended when Valsartan/Hydrochlorothiazide Film-coated Tablets is used in patients with renal impairment.

Kidney transplantation
There is currently no experience on the safe use of valsartan/hydrochlorothiazide in patients who have recently undergone kidney transplantation.

Hepatic impairment
In patients with mild to moderate hepatic impairment without cholestasis, Valsartan/Hydrochlorothiazide Film-coated Tablets should be used with caution (see sections 4.2 and 5.2).

Systemic Lupus Erythematosus
Thiazide diuretics, including hydrochlorothiazide, have been reported to exacerbate or activate systemic lupus erythematosus.

Other metabolic disturbances
Thiazide diuretics, including hydrochlorothiazide, may alter glucose tolerance and raise serum levels of cholesterol, triglycerides and uric acid. In diabetic patients dosage adjustments of insulin or oral hypoglycaemic agents may be required.

Thiazides may reduce urinary calcium excretion and cause an intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcaemia may be evidence of underlying hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Photosensitivity
Cases of photosensitivity reactions have been reported with thiazide diuretics (see section 4.8). If a photosensitivity reaction occurs during treatment, it is recommended to stop the treatment. If re-administration of the diuretic is deemed necessary, it is recommended to protect exposed areas to the sun or to artificial UVA.

Pregnancy
Angiotensin II Receptor Antagonists (AIIRAs) should not be initiated during pregnancy. Unless continued AIIRAs therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with AIIRAs should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).
General
Caution should be exercised in patients who have shown prior hypersensitivity to other angiotensin II receptor antagonists. Hypersensitivity reactions to hydrochlorothiazide are more likely in patients with allergy and asthma.

Galactose intolerance, Lapp lactase deficiency, glucose-galactose malabsorption
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Lecithin soya
If a patient is hypersensitive to peanut or soya, this medicine should not be used.

4.5 Interaction with other medicinal products and other forms of interaction
Interactions related to both valsartan and hydrochlorothiazide
Concomitant use not recommended
Lithium
Reversible increases in serum lithium concentrations and toxicity have been reported during concurrent use of ACE inhibitors and thiazide, including hydrochlorothiazide. Due to the lack of experience with concomitant use of valsartan and lithium, this combination is not recommended. If the combination proves necessary, careful monitoring of serum lithium levels is recommended.

Concomitant use requiring caution
Other antihypertensive agents
Valsartan/Hydrochlorothiazide Film-coated Tablets may increase the effects of other agents with antihypertensive properties (e.g. ACEI, beta-blockers, calcium channel blockers).

Pressor amines (e.g. noradrenaline, adrenaline)
Possible decreased response to pressor amines but not sufficient to preclude their use.

Non-steroidal anti-inflammatory medicines (NSAIDs), including selective COX-2 inhibitors, acetylsalicylic acid >3 g/day), and non-selective NSAIDs
NSAIDs can attenuate the antihypertensive effect of both angiotensin II antagonists and hydrochlorothiazide when administered simultaneously. Furthermore, concomitant use of valsartan/hydrochlorothiazide and NSAIDs may lead to worsening of renal function and an increase in serum potassium. Therefore, monitoring of renal function at the beginning of the treatment is recommended, as well as adequate hydration of the patient.

Interactions related to valsartan
Concomitant use not recommended
Potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium and other substances that may increase potassium levels
If a medicinal product that affects potassium levels is considered necessary in combination with valsartan, monitoring of potassium plasma levels is advised.

No interaction
In drug interaction studies with valsartan, no interactions of clinical significance have been found with valsartan or any of the following substances: cimetidine, warfarin, furosemide, digoxin, atenolol, indometacin, hydrochlorothiazide, amiodipine, glibenclamide. Digoxin and indometacin could interact with the hydrochlorothiazide component of Valsartan/Hydrochlorothiazide Film-coated Tablets (see interactions related to hydrochlorothiazide).

Interactions related to hydrochlorothiazide
Concomitant use requiring caution
Medicinal products associated with potassium loss and hypokalaemia (e.g. kaliuretic diuretics, corticosteroids, laxatives, ACTH, amphotericin, carbenoxolone, penicillin G, salicylic acid and derivatives).
If these medicinal products are to be prescribed with the hydrochlorothiazide-valsartan combination, monitoring of potassium plasma levels is advised. These medicinal products may potentiate the effect of hydrochlorothiazide on serum potassium (see section 4.4).

**Medicinal products that could induce torsades de pointes**

- Class Ia antiarrhythmics (e.g. quinidine, hydroquinidine, disopyramide)
- Class III antiarrhythmics (e.g. amiodarone, sotalol, dofetilide, ibutilide)
- Some antipsychotics (e.g. thioridazine, chlorpromazine, levomepromazine, trifluoperazine, cyamemazine, sulpiride, sultopride, amisulpride, tiapride, pimozide, haloperidol, droperidol)
- Others (e.g. bepridil, cisapride, diphenamid, erythromycin i.v., halofantrin, ketanserin, mizolastin, pentamidine, sparfl Roxacine, terfenadine, vincamine i.v.)

Due to the risk of hypokalemia, hydrochlorothiazide should be administered with caution when associated with medicinal products that could induce torsades de pointes.

**Digitalis glycosides**

Thiazide-induced hypokalaemia or hypomagnesaemia may occur as unwanted effects favouring the onset of digitalis-induced cardiac arrhythmias.

**Calcium salts and vitamin D**

Administration of thiazide diuretics, including hydrochlorothiazide, with vitamin D or with calcium salts may potentiate the rise in serum calcium.

**Antidiabetic agents** (oral agents and insulin)

The treatment with a thiazide may influence the glucose tolerance. Dose adjustment of the antidiabetic medicinal product may be necessary.

Metformin should be used with caution because of the risk of lactic acidosis induced by possible functional renal failure linked to hydrochlorothiazide.

**Beta blockers and diazoxide**

Concomitant use of thiazide diuretics, including hydrochlorothiazide, with beta blockers may increase the risk of hyperglycaemia. Thiazide diuretics, including hydrochlorothiazide, may enhance the hyperglycaemic effect of diazoxide.

**Medicinal products used in the treatment of gout** (probenecid, sulfinpyrazone and allopurinol)

Dose adjustment of uricosuric medications may be necessary as hydrochlorothiazide may raise the level of serum uric acid. Increase of dosage of probenecid or sulfinpyrazone may be necessary. Co-administration of thiazide diuretics, including hydrochlorothiazide, may increase the incidence of hypersensitivity reactions to allopurinol.

**Anticholinergic agents** (e.g. atropine, biperiden)

The bioavailability of thiazide-type diuretics may be increased by anticholinergic agents, apparently due to a decrease in gastrointestinal motility and the stomach emptying rate.

**Amantadine**

Thiazides, including hydrochlorothiazide, may increase the risk of adverse effects caused by amantadine.

**Cholestyramine and cholestipol resins**

Absorption of thiazide diuretics, including hydrochlorothiazide, is impaired in the presence of anionic exchange resins.

**Cytotoxic agents** (e.g. cyclophosphamide, methotrexate)

Thiazides, including hydrochlorothiazide, may reduce renal excretion of cytotoxic agents and potentiate their myelosuppressive effects.

**Non-depolarising skeletal muscle relaxants** (e.g. tubocurarine)

Thiazides, including hydrochlorothiazide, potentiate the action of curare derivatives.
Concomitant treatment with ciclosporin may increase the risk of hyperuricaemia and gout-type complications.

**Alcohol, anaesthetics and sedatives**

Potentiation of orthostatic hypotension may occur.

**Methyldopa**

There have been isolated reports of haemolytic anaemia in patients receiving concomitant treatment with methyldopa and hydrochlorothiazide.

**Carbamazepine**

Patients receiving hydrochlorothiazide concomitantly with carbamazepine may develop hyponatraemia. Such patients should therefore be advised about the possibility of hyponatraemic reactions, and should be monitored accordingly.

**Iodine contrast media**

In case of diuretic-induced dehydration, there is an increased risk of acute renal failure, especially with high doses of the iodine product. Patients should be rehydrated before the administration.

### 4.6 Pregnancy and lactation

**Pregnancy**

**Valsartan**

The use of Angiotensin II Receptor Antagonists (AIIRAs) is not recommended during first trimester of pregnancy (see section 4.4). The use of AIIRAs is contra-indicated during the second and third trimester of pregnancy (see sections 4.3 and 4.4).

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Whilst there is no controlled epidemiological data on the risk with Angiotensin II Receptor Inhibitors (AIIRAs), similar risks may exist for this class of drugs. Unless continued AIIRAs therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with AIIRAs should be stopped immediately and, if appropriate, alternative therapy should be started.

AIIRAs therapy exposure during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (see also section 5.3).

Should exposure to AIIRAs have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.

Infants whose mothers have taken AIIRAs should be closely observed for hypotension (see also section 4.3 and 4.4).

**Hydrochlorothiazide**

There is limited experience with hydrochlorothiazide during pregnancy, especially during the first trimester. Animal studies are insufficient. Hydrochlorothiazide crosses the placenta. Based on the pharmacological mechanism of action of hydrochlorothiazide its use during the second and third trimester may compromise foeto-placental perfusion and may cause foetal and neonatal effects like icterus, disturbance of electrolyte balance and thrombocytopenia.

**Lactation**

No information is available regarding the use of valsartan during breastfeeding. Hydrochlorothiazide is excreted in human milk. Therefore the use of Valsartan/Hydrochlorothiazide Film-coated Tablets during breast feeding is not
recommended. Alternative treatments with better established safety profiles during breastfeeding are preferable, especially while nursing a newborn or preterm infant.

4.7 Effects on ability to drive and use machines
No studies on the effect of valsartan/hydrochlorothiazide, on the ability to drive and use machines have been performed. When driving vehicles or operating machines it should be taken into account that occasionally dizziness or weariness may occur.

4.8 Undesirable effects
Adverse reactions reported in clinical trials and laboratory findings occurring more frequently with valsartan plus hydrochlorothiazide versus placebo and individual postmarketing reports are presented below according to system organ class. Adverse reactions known to occur with each component given individually but which have not been seen in clinical trials may occur during treatment with valsartan/hydrochlorothiazide.

Adverse drug reactions are ranked by frequency, the most frequent first, using the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.

Table 1. Frequency of adverse reactions with valsartan/hydrochlorothiazide

<table>
<thead>
<tr>
<th>Metabolism and nutrition disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon</td>
<td>Dehydration</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
</tr>
<tr>
<td>Very rare</td>
<td>Dizziness</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Paraesthesia</td>
</tr>
<tr>
<td>Not known</td>
<td>Syncope</td>
</tr>
<tr>
<td>Eye disorders</td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td>Vision blurred</td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td>Tinnitus</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td>Hypotension</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td>Cough</td>
</tr>
<tr>
<td>Not known</td>
<td>Non cardiogenic pulmonary oedema</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
</tr>
<tr>
<td>Very rare</td>
<td>Diarrhoea</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td>Myalgia</td>
</tr>
<tr>
<td>Very rare</td>
<td>Arthralgia</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td></td>
</tr>
<tr>
<td>Not known</td>
<td>Impaired renal function</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td>Fatigue</td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
</tr>
<tr>
<td>Not known</td>
<td>Serum uric acid increased, Serum bilirubin and Serum creatinine increased, Hypokalaemia, Hyponatraemia, Elevation of Blood Urea Nitrogen, Neutropenia</td>
</tr>
</tbody>
</table>
Additional information on the individual components
Adverse reactions previously reported with one of the individual components may be potential undesirable effects with Valsartan/Hydrochlorothiazide Film-coated Tablets as well, even if not observed in clinical trials or during postmarketing period.

Table 2. Frequency of adverse reactions with valsartan

**Blood and lymphatic system disorders**
- Not known
  - Decrease in haemoglobin,
  - decrease in haematocrit,
  - thrombocytopenia

**Immune system disorders**
- Not known
  - Other hypersensitivity/allergic reactions including serum sickness

**Metabolism and nutrition disorders**
- Not known
  - Increase of serum potassium

**Ear and labyrinth disorders**
- Uncommon
  - Vertigo

**Vascular disorders**
- Not known
  - Vasculitis

**Gastrointestinal disorders**
- Uncommon
  - Abdominal pain

**Hepatobiliary disorders**
- Not known
  - Elevation of liver function values

**Skin and subcutaneous tissue disorders**
- Not known
  - Angioedema, rash, pruritus

**Renal and urinary disorders**
- Not known
  - Renal failure

Table 3. Frequency of adverse reactions with hydrochlorothiazide

Hydrochlorothiazide has been extensively prescribed for many years, frequently in higher doses than those administered with Valsartan/Hydrochlorothiazide Film-coated Tablets. The following adverse reactions have been reported in patients treated with monotherapy of thiazide diuretics, including hydrochlorothiazide:

**Blood and lymphatic system disorders**
- Rare
  - Thrombocytopenia sometimes with purpura
- Very rare
  - Agranulocytosis, leucopenia, haemolytic anaemia, bone marrow depression

**Immune system disorders**
- Very rare
  - Hypersensitivity reactions

**Psychiatric disorders**
- Rare
  - Depression, sleep disturbances

**Nervous system disorders**
- Rare
  - Headache

**Cardiac disorders**
- Rare
  - Cardiac arrhythmias

**Vascular disorders**
- Common
  - Postural hypotension

**Respiratory, thoracic and mediastinal disorders**
- Very rare
  - Respiratory distress including pneumonitis and pulmonary oedema

**Gastrointestinal disorders**
- Common
  - Loss of appetite, mild nausea and vomiting
- Rare
  - Constipation, gastrointestinal discomfort
- Very rare
  - Pancreatitis
### Hepatobiliary disorders
- **Rare**
  - Intrahepatic cholestasis or jaundice

### Skin and subcutaneous tissue disorders
- **Common**
  - Urticaria and other forms of rash

- **Rare**
  - Photosensitisation

- **Very rare**
  - Necrotising vasculitis and toxic epidermal necrolysis, cutaneous lupus erythematosus-like reactions, reactivation of cutaneous lupus erythematosus

### Reproductive system and breast disorders
- **Common**
  - Impotence

### 4.9 Overdose

#### Symptoms
Overdose with valsartan may result in marked hypotension, which could lead to depressed level of consciousness, circulatory collapse and/or shock. In addition, the following signs and symptoms may occur due to an overdose of the hydrochlorothiazide component: nausea, somnolence, hypovolaemia, and electrolyte disturbances associated with cardiac arrhythmias and muscle spasms.

#### Treatment
The therapeutic measures depend on the time of ingestion and the type and severity of the symptoms, stabilisation of the circulatory condition being of prime importance.

If hypotension occurs, the patient should be placed in the supine position and salt and volume supplementation should be given rapidly. Valsartan cannot be eliminated by means of haemodialysis because of its strong plasma binding behaviour whereas clearance of hydrochlorothiazide will be achieved by dialysis.

### 5 PHARMACOLOGICAL PROPERTIES

#### 5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Angiotensin II antagonists and diuretics, valsartan and diuretics; ATC code: C09D A03.

Dose-dependent decreases in serum potassium occurred in controlled clinical studies with valsartan + hydrochlorothiazide. Reduction in serum potassium occurred more frequently in patients given 25 mg hydrochlorothiazide than in those given 12.5 mg hydrochlorothiazide. In controlled clinical trials with valsartan/hydrochlorothiazide the potassium lowering effect of hydrochlorothiazide was attenuated by the potassium-sparing effect of valsartan.

Beneficial effects of valsartan in combination with hydrochlorothiazide on cardiovascular mortality and morbidity are currently unknown.

Epidemiological studies have shown that long-term treatment with hydrochlorothiazide reduces the risk of cardiovascular mortality and morbidity.

**Valsartan**
Valsartan is an orally active and specific angiotensin II (Ang II) receptor antagonist. It acts selectively on the AT₁ receptor subtype, which is responsible for the known actions of angiotensin II. The increased plasma levels of Ang II following AT₁ receptor blockade with valsartan may stimulate the unblocked AT₂ receptor, which appears to counterbalance the effect of the AT₁ receptor. Valsartan does not exhibit any partial agonist activity at the AT₁ receptor and has much (about 20,000 fold) greater affinity for the AT₁ receptor than for the AT₂ receptor. Valsartan is not known to bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.
Valsartan does not inhibit ACE, also known as kininase II, which converts Ang I to Ang II and degrades bradykinin. Since there is no effect on ACE and no potentiation of bradykinin or substance P, angiotensin II antagonists are unlikely to be associated with coughing. In clinical trials where valsartan was compared with an ACE inhibitor, the incidence of dry cough was significantly (P <0.05) lower in patients treated with valsartan than in those treated with an ACE inhibitor (2.6% versus 7.9% respectively). In a clinical trial of patients with a history of dry cough during ACE inhibitor therapy, 19.5% of trial subjects receiving valsartan and 19.0% of those receiving a thiazide diuretic experienced cough compared to 68.5% of those treated with an ACE inhibitor (P <0.05).

Administration of valsartan to patients with hypertension results in reduction of blood pressure without affecting pulse rate. In most patients, after administration of a single oral dose, onset of antihypertensive activity occurs within 2 hours, and the peak reduction of blood pressure is achieved within 4-6 hours. The antihypertensive effect persists over 24 hours after dosing. During repeated dosing, the maximum reduction in blood pressure with any dose is generally attained within 2-4 weeks and is sustained during long-term therapy. Combined with hydrochlorothiazide, a significant additional reduction in blood pressure is achieved.

Abrupt withdrawal of valsartan has not been associated with rebound hypertension or other adverse clinical events.

In hypertensive patients with type 2 diabetes and microalbuminuria, valsartan has been shown to reduce the urinary excretion of albumin. The MARVAL (Micro Albuminuria Reduction with Valsartan) study assessed the reduction in urinary albumin excretion (UAE) with valsartan (80-160 mg/od) versus amlopidine (5-10 mg/od), in 332 type 2 diabetic patients (mean age: 58 years; 265 men) with microalbuminuria (valsartan: 58 µg/min; amlopidine: 55.4 µg/min), normal or high blood pressure and with preserved renal function (blood creatinine <120 µmol/l). At 24 weeks, UAE was reduced (p <0.001) by 42% (–24.2 µg/min; 95% CI: –40.4 to –19.1) with valsartan and approximately 3% (–1.7 µg/min; 95% CI: –5.6 to 14.9) with amlopidine despite similar rates of blood pressure reduction in both groups. The Diovan Reduction of Proteinuria (DROP) study further examined the efficacy of valsartan in reducing UAE in 391 hypertensive patients (BP=150/88 mmHg) with type 2 diabetes, albuminuria (mean=102 µg/min; 20–700 µg/min) and preserved renal function (mean serum creatinine = 80 µmol/l). Patients were randomised to one of 3 doses of valsartan (160, 320 and 640 mg/od) and treated for 30 weeks. The purpose of the study was to determine the optimal dose of valsartan for reducing UAE in hypertensive patients with type 2 diabetes. At 30 weeks, the percentage change in UAE was significantly reduced by 36% from baseline with valsartan 160 mg (95%CI: 22 to 47%), and by 44% with valsartan 320 mg (95%CI: 31 to 54%). It was concluded that 160-320 mg of valsartan produced clinically relevant reductions in UAE in hypertensive patients with type 2 diabetes.

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.

Valsartan/hydrochlorothiazide

In a double-blind, randomised, active-controlled trial in patients not adequately controlled on hydrochlorothiazide 12.5 mg, significantly greater mean systolic/diastolic BP reductions were observed with the combination of valsartan/hydrochlorothiazide 80/12.5 mg (14.9/11.3 mmHg) compared to hydrochlorothiazide 12.5 mg (5.2/2.9 mmHg) and hydrochlorothiazide 25 mg (6.8/5.7 mmHg). In addition, a significantly greater percentage of patients responded
(diastolic BP <90 mmHg or reduction ≥10 mmHg) with valsartan/hydrochlorothiazide 80/12.5 mg (60 %) compared to hydrochlorothiazide 12.5 mg (25 %) and hydrochlorothiazide 25 mg (27 %).

In a double-blind, randomised, active-controlled trial in patients not adequately controlled on valsartan 80 mg, significantly greater mean systolic/diastolic BP reductions were observed with the combination of valsartan/hydrochlorothiazide 80/12.5 mg (9.8/8.2 mmHg) compared to valsartan 80 mg (3.9/5.1 mmHg) and valsartan 160 mg (6.5/6.2 mmHg). In addition, a significantly greater percentage of patients responded (diastolic BP <90 mmHg or reduction ≥10 mmHg) with valsartan/hydrochlorothiazide 80/12.5 mg (51 %) compared to valsartan 80 mg (36 %) and valsartan 160 mg (37 %).

In a double-blind, randomised, placebo-controlled, factorial design trial comparing various dose combinations of valsartan/hydrochlorothiazide to their respective components, significantly greater mean systolic/diastolic BP reductions were observed with the combination of valsartan/hydrochlorothiazide 80/12.5 mg (16.5/11.8 mmHg) compared to placebo (1.9/4.1 mmHg) and both hydrochlorothiazide 12.5 mg (7.3/7.2 mmHg) and valsartan 80 mg (8.8/8.6 mmHg). In addition, a significantly greater percentage of patients responded (diastolic BP <90 mmHg or reduction ≥10 mmHg) with valsartan/hydrochlorothiazide 80/12.5 mg (64 %) compared to placebo (29 %) and hydrochlorothiazide (41 %).

5.2 Pharmacokinetic properties

Valsartan/hydrochlorothiazide

The systemic availability of hydrochlorothiazide is reduced by about 30 % when co-administered with valsartan. The kinetics of valsartan are not markedly affected by the co-administration of hydrochlorothiazide. This observed interaction has no impact on the combined use of valsartan and hydrochlorothiazide, since controlled clinical trials have shown a clear anti-hypertensive effect, greater than that obtained with either active substance given alone, or placebo.

Valsartan

Absorption

Following oral administration of valsartan alone, peak plasma concentrations of valsartan are reached in 2–4 hours. Mean absolute bioavailability is 23 %. Food decreases exposure (as measured by AUC) to valsartan by about 40 % and peak plasma concentration (C_{max}) by about 50 %, although from about 8 h post dosing plasma valsartan concentrations are similar for the fed and fasted groups. This reduction in AUC is not, however, accompanied by a clinically significant reduction in the therapeutic effect, and valsartan can therefore be given either with or without food.

Distribution

The steady-state volume of distribution of valsartan after intravenous administration is about 17 litres, indicating that valsartan does not distribute into tissues extensively. Valsartan is highly bound to serum proteins (94–97 %), mainly serum albumin.

Biotransformation

Valsartan is not biotransformed to a high extent as only about 20 % of dose is recovered as metabolites. A hydroxy metabolite has been identified in plasma at low concentrations (less than 10 % of the valsartan AUC). This metabolite is pharmacologically inactive.

Elimination

Valsartan shows multiexponential decay kinetics (t_{1/2α} <1 h and t_{1/β} about 9 h). Valsartan is primarily eliminated in faeces (about 83% of dose) and urine (about 13% of dose), mainly as unchanged drug. Following intravenous administration, plasma clearance of valsartan is about 2 l/h and its renal clearance is 0.62 l/h (about 30% of total clearance). The half-life of valsartan is 6 hours.
**Hydrochlorothiazide**

**Absorption**
The absorption of hydrochlorothiazide, after an oral dose, is rapid ($t_{max}$ about 2 h), with similar absorption characteristics for both suspension and tablet formulations. Absolute bioavailability of hydrochlorothiazide is 60–80 % after oral administration. Concomitant administration with food has been reported to both increase and decrease the systemic availability of hydrochlorothiazide compared with the fasted state. The magnitude of these effects is small and has minimal clinical importance. The increase in mean AUC is linear and dose proportional in the therapeutic range. There is no change in the kinetics of hydrochlorothiazide on repeated dosing, and accumulation is minimal when dosed once daily.

**Distribution**
The distribution and elimination kinetics have generally been described by a bi-exponential decay function. The apparent volume of distribution is 4–8 l/kg. Circulating hydrochlorothiazide is bound to serum proteins (40–70 %), mainly serum albumin. Hydrochlorothiazide also accumulates in erythrocytes at approximately 1.8 times the level in plasma.

**Elimination**
For hydrochlorothiazide, >95 % of the absorbed dose being excreted as unchanged compound in the urine. The renal clearance is composed of passive filtration and active secretion into the renal tubule. The terminal half-life is 6-15 h.

**Special populations**

**Elderly**
A somewhat higher systemic exposure to valsartan was observed in some elderly subjects than in young subjects; however, this has not been shown to have any clinical significance. Limited data suggest that the systemic clearance of hydrochlorothiazide is reduced in both healthy and hypertensive elderly subjects compared to young healthy volunteers.

**Renal impairment**
At the recommended dose of Valsartan/Hydrochlorothiazide Film-coated tablets no dose adjustment is required for patients with a creatinine clearance of 30-70mL/min.

In patients with severe renal impairment (creatinine clearance <30mL/min) and patients undergoing dialysis, no data are available for Valsartan/Hydrochlorothiazide Film-coated Tablets. Valsartan is highly bound to plasma protein and is not to be removed by dialysis, whereas clearance of hydrochlorothiazide will be achieved by dialysis.

Renal clearance of hydrochlorothiazide is composed of passive filtration and active secretion into the renal tubule. As expected for a compound which is cleared almost exclusively via the kidneys, renal function has a marked effect on the kinetics of hydrochlorothiazide (see Section 4.3).

**Hepatic impairment**
In a pharmacokinetics trial in patients with mild (n=6) to moderate (n=5) hepatic dysfunction, exposure to valsartan was increased approximately twofold compared with healthy volunteers. There are no data available on the use of valsartan in patients with severe hepatic dysfunction (see section 4.3). Hepatic disease does not significantly affect the pharmacokinetics of hydrochlorothiazide.

5.3 Preclinical safety data
The potential toxicity of the valsartan - hydrochlorothiazide combination after oral administration was investigated in rats and marmosets in studies lasting up to six months. No findings emerged that would exclude the use of therapeutic doses in man.

The changes produced by the combination in the chronic toxicity studies are most likely to have been caused by the valsartan component. The toxicological target organ was the kidney, the reaction being more marked in the marmoset than the rat. The combination led to kidney damage (nephropathy with tubular basophilia, rises in plasma urea, plasma creatinine and
serum potassium, increases in urine volume and urinary electrolytes from 30 mg/kg/day valsartan + 9 mg/kg/day hydrochlorothiazide in rats and 10 + 3 mg/kg/d in marmosets), probably by way of altered renal haemodynamics. These doses in rat, respectively, represent 0.9 and 3.5–times the maximum recommended human dose (MRHD) of valsartan and hydrochlorothiazide on a mg/m² basis. These doses in marmoset, respectively, represent 0.3 and 1.2–times the maximum recommended human dose (MRHD) of valsartan and hydrochlorothiazide on a mg/m² basis. (Calculations assume an oral dose of 320 mg/day valsartan in combination with 25 mg/day hydrochlorothiazide and a 60-kg patient.)

High doses of the valsartan - hydrochlorothiazide combination caused falls in red blood cell indices (red cell count, haemoglobin, haematocrit, from 100 + 31 mg/kg/d in rats and 30 + 9 mg/kg/d in marmosets). These doses in rat, respectively, represent 3.0 and 12 times the maximum recommended human dose (MRHD) of valsartan and hydrochlorothiazide on a mg/m² basis. These doses in marmoset, respectively, represent 0.9 and 3.5 times the maximum recommended human dose (MRHD) of valsartan and hydrochlorothiazide on a mg/m² basis. (Calculations assume an oral dose of 320 mg/day valsartan in combination with 25 mg/day hydrochlorothiazide and a 60-kg patient).

In marmosets, damage was observed in the gastric mucosa (from 30 + 9 mg/kg/d). The combination also led in the kidney to hyperplasia of the afferent arterioles (at 600 + 188 mg/kg/d in rats and from 30 + 9 mg/kg/d in marmosets). These doses in marmoset, respectively, represent 0.9 and 3.5 times the maximum recommended human dose (MRHD) of valsartan and hydrochlorothiazide on a mg/m² basis. These doses in rat, respectively, represent 18 and 73 times the maximum recommended human dose (MRHD) of valsartan and hydrochlorothiazide on a mg/m² basis. (Calculations assume an oral dose of 320 mg/day valsartan in combination with 25 mg/day hydrochlorothiazide and a 60-kg patient).

The above mentioned effects appear to be due to the pharmacological effects of high valsartan doses (blockade of angiotensin II-induced inhibition of renin release, with stimulation of the renin-producing cells) and also occur with ACE inhibitors. These findings appear to have no relevance to the use of therapeutic doses of valsartan in humans.

The valsartan - hydrochlorothiazide combination was not tested for mutagenicity, chromosomal breakage or carcinogenicity, since there is no evidence of interaction between the two substances. However, these tests were performed separately with valsartan and hydrochlorothiazide, and produced no evidence of mutagenicity, chromosomal breakage or carcinogenicity.

In rats, maternally toxic doses of valsartan (600 mg/kg/day) during the last days of gestation and lactation led to lower survival, lower weight gain and delayed development (pinna detachment and ear-canal opening) in the offspring (see section 4.6). These doses in rats (600 mg/kg/day) are approximately 18 times the maximum recommended human dose on a mg/m² basis (calculations assume an oral dose of 320 mg/day and a 60-kg patient). Similar findings were seen with valsartan/hydrochlorothiazide in rats and rabbits. In embryo-fetal development (Segment II) studies with valsartan/hydrochlorothiazide in rat and rabbit, there was no evidence of teratogenicity; however, fetotoxicity associated with maternal toxicity was observed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
- Microcrystalline Cellulose
- Lactose Monohydrate
- Croscarmellose Sodium
- Povidone K29-K32
- Talc
- Magnesium Stearate
- Colloidal Anhydrous Silica
Coating
Opadry II 85G34642 Pink:
Polyvinyl Alcohol
Talc
Titanium Dioxide (E171)
Macrogol 3350
Lecithin soya (E322)
Iron Oxide Red (E172)
Iron Oxide Yellow (E172)
Iron Oxide Black (E172)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
4 years for tablets packed in PVC/PE/PVDC-Al blisters
5 years for tablets packed in polyethylene tablet containers

6.4 Special precautions for storage
Tablets packed in PVC/PE/PVDC-Al blisters: Do not store above 30°C.
Tablets packed in polyethylene tablet containers: This medicinal product does not require any special storage conditions

6.5 Nature and contents of container
PVC/PE/PVDC-Al blisters and HDPE containers with PE closure.
Pack sizes of 7, 14, 28, 30, 56, 98 and 280 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements
Any unused or waste material should be disposed of in accordance to local requirements.

7 MARKETING AUTHORISATION HOLDER
Caduceus Pharma Limited
6th Floor
94 Wigmore Street
London
W1U 3RF
UK

8 MARKETING AUTHORISATION NUMBER(S)
PL 24668/0069
PL 24668/0072
PL 24668/0075

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
17/12/2010

10 DATE OF REVISION OF THE TEXT
17/12/2010
1 NAME OF THE MEDICINAL PRODUCT
Valsartan/Hydrochlorothiazide 160 mg/12.5 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains 160 mg valsartan and 12.5 mg hydrochlorothiazide.
Excipients: Each Valsartan/Hydrochlorothiazide 160 mg/12.5 mg Film-coated Tablet contains 29.75 mg lactose monohydrate 0.25 mg lecithin (contains soya oil) and Sunset yellow FCF (E110).
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet
Red, biconvex, oval, 15 mm x 6 mm. Marked ‘V’ on one side and ‘H’ on the other.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Treatment of essential hypertension in adults.
Valsartan/Hydrochlorothiazide film-coated tablet fixed dose combination is indicated in patients whose blood pressure is not adequately controlled on valsartan or hydrochlorothiazide monotherapy.

4.2 Posology and method of administration
The recommended dose of Valsartan/Hydrochlorothiazide 160 mg/12.5 mg Film-coated Tablets is one film-coated tablet once daily.
Dose titration with the individual components is recommended. In each case, up-titration of individual components to the next dose should be followed in order to reduce the risk of hypotension and other adverse events.

When clinically appropriate direct change from monotherapy to the fixed combination may be considered in patients whose blood pressure is not adequately controlled on valsartan or hydrochlorothiazide monotherapy, provided the recommended dose titration sequence for the individual components is followed.

The clinical response to Valsartan/Hydrochlorothiazide film-coated tablets should be evaluated after initiating therapy and if blood pressure remains uncontrolled, the dose may be increased by increasing either one of the components to a maximum dose of Valsartan/Hydrochlorothiazide 320 mg/25 mg.

The antihypertensive effect is substantially present within 2 weeks.

In most patients, maximal effects are observed within 4 weeks. However, in some patients, 4-8 weeks treatment may be required. This should be taken into account during dose-titration.

Method of administration
Valsartan/Hydrochlorothiazide film-coated tablets can be taken with or without food and should be administered with water.

Special populations
Renal Impairment
No dose adjustment is required for patients with mild to moderate renal impairment (creatinine clearance ≥ 30 ml/min). Due to the hydrochlorothiazide component, Valsartan/Hydrochlorothiazide Film-coated Tablets are contraindicated in patients with severe renal impairment (see sections 4.3, 4.4 and 5.2).
Hepatic Impairment
In patients with mild to moderate hepatic impairment without cholestasis the dose of valsartan should not exceed 80 mg (see section 4.4). Valsartan/Hydrochlorothiazide film-coated tablets are contraindicated in patients with severe hepatic impairment (see sections 4.3, 4.4 and 5.2).

Elderly
No dose adjustment is required in elderly patients.

Paediatric patients
Valsartan/Hydrochlorothiazide Film-coated Tablets are not recommended for use in children below the age of 18 years due to a lack of data on safety and efficacy.

4.3 Contraindications
- Hypersensitivity to valsartan, hydrochlorothiazide, other sulphonamide-derived medicinal products, soya oil, peanut oil or to any of the excipients.
- Second and third trimester of pregnancy (section 4.4 and 4.6).
- Severe hepatic impairment, biliary cirrhosis and cholestasis.
- Severe renal impairment (creatinine clearance < 30 ml/min), anuria
- Refractory hypokalaemia, hyponatraemia, hypercalcaemia, and symptomatic hyperuricaemia.

4.4 Special warnings and precautions for use

Serum electrolyte changes

Valsartan
Concomitant use with potassium supplements, potassium sparing diuretics, salt substitutes containing potassium, or other agents that may increase potassium levels (heparin, etc.) is not recommended. Monitoring of potassium should be undertaken as appropriate.

Hydrochlorothiazide
Hypokalaemia has been reported under treatment with thiazide diuretics, including hydrochlorothiazide. Frequent monitoring of serum potassium is recommended.

Treatment with thiazide diuretics, including hydrochlorothiazide, has been associated with hyponatraemia and hypochloraemic alkalosis. Thiazides, including hydrochlorothiazide, increase the urinary excretion of magnesium, which may result in hypomagnesaemia. Calcium excretion is decreased by thiazide diuretics. This may result in hypercalcaemia.

As for any patient receiving diuretic therapy, periodic determination of serum electrolytes should be performed at appropriate intervals.

Sodium, and/or volume-depleted patients:
Patients receiving thiazide diuretics, including hydrochlorothiazide, should be observed for clinical signs of fluid or electrolyte imbalance. In severely sodium-depleted and/or volume-depleted patients, such as those receiving high doses of diuretics, symptomatic hypotension may occur in rare cases after initiation of therapy with valsartan/hydrochlorothiazide. Sodium and/or volume depletion should be corrected before starting treatment with Valsartan/Hydrochlorothiazide Film-coated Tablets.

Patients with severe chronic heart failure or other conditions with stimulation of the renin-angiotensin-aldosterone-system
In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (e.g. patients with severe congestive heart failure), treatment with angiotensin converting enzyme inhibitors has been associated with oliguria and/or progressive azotaemia, and in rare cases with acute renal failure. The use of valsartan/hydrochlorothiazide in patients with severe chronic heart failure has not been established.

Hence it cannot be excluded that because of the inhibition of the renin-angiotensin-aldosterone system the application of valsartan/hydrochlorothiazide as well may be associated with impairment of the renal function. Valsartan/Hydrochlorothiazide Film-coated Tablets should not be used in these patients.
Renal artery stenosis
Valsartan/Hydrochlorothiazide Film-coated Tablets should not be used to treat hypertension in patients with unilateral or bilateral renal artery stenosis or stenosis of the artery to a solitary kidney, since blood urea and serum creatinine may increase in such patients.

Primary hyperaldosteronism
Patients with primary hyperaldosteronism should not be treated with Valsartan/Hydrochlorothiazide Film-coated Tablets as their renin-angiotensin system is not activated.

Aortic and mitral valve stenosis, hypertrophic obstructive cardiomyopathy
As with all other vasodilators, special caution is indicated in patients suffering from aortic or mitral stenosis, or hypertrophic obstructive cardiomyopathy (HOCM).

Renal impairment
No dosage adjustment is required for patients with renal impairment with a creatinine clearance $\geq 30\text{ml/min}$ (see section 4.2). Periodic monitoring of serum potassium, creatinine and uric acid levels is recommended when Valsartan/Hydrochlorothiazide Film-coated Tablets is used in patients with renal impairment.

Kidney transplantation
There is currently no experience on the safe use of valsartan/hydrochlorothiazide in patients who have recently undergone kidney transplantation.

Hepatic impairment
In patients with mild to moderate hepatic impairment without cholestasis, Valsartan/Hydrochlorothiazide Film-coated Tablets should be used with caution (see sections 4.2 and 5.2).

Systemic Lupus Erythematosus
Thiazide diuretics, including hydrochlorothiazide, have been reported to exacerbate or activate systemic lupus erythematosus.

Other metabolic disturbances
Thiazide diuretics, including hydrochlorothiazide, may alter glucose tolerance and raise serum levels of cholesterol, triglycerides and uric acid. In diabetic patients dosage adjustments of insulin or oral hypoglycaemic agents may be required.

Thiazides may reduce urinary calcium excretion and cause an intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcaemia may be evidence of underlying hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Photosensitivity
Cases of photosensitivity reactions have been reported with thiazide diuretics (see section 4.8). If a photosensitivity reaction occurs during treatment, it is recommended to stop the treatment. If a re-administration of the diuretic is deemed necessary, it is recommended to protect exposed areas to the sun or to artificial UVA.

Pregnancy
Angiotensin II Receptor Antagonists (AIIRAs) should not be initiated during pregnancy. Unless continued AIIRAs therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with AIIRAs should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).
General
Caution should be exercised in patients who have shown prior hypersensitivity to other angiotensin II receptor antagonists. Hypersensitivity reactions to hydrochlorothiazide are more likely in patients with allergy and asthma.

Galactose intolerance, Lapp lactase deficiency, glucose-galactose malabsorption
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Lecithin
If a patient is hypersensitive to peanut or soya, this medicine should not be used.

Sunset yellow FCF (E110)
This medicine contains Sunset Yellow which may cause allergic reactions

4.5 Interaction with other medicinal products and other forms of interaction

Interactions related to both valsartan and hydrochlorothiazide

Concomitant use not recommended

Lithium
Reversible increases in serum lithium concentrations and toxicity have been reported during concurrent use of ACE inhibitors and thiazide, including hydrochlorothiazide. Due to the lack of experience with concomitant use of valsartan and lithium, this combination is not recommended. If the combination proves necessary, careful monitoring of serum lithium levels is recommended.

Concomitant use requiring caution

Other antihypertensive agents
Valsartan/Hydrochlorothiazide Film-coated Tablets may increase the effects of other agents with antihypertensive properties (e.g. ACEI, beta-blockers, calcium channel blockers).

Pressor amines (e.g. noradrenaline, adrenaline)
Possible decreased response to pressor amines but not sufficient to preclude their use.

Non-steroidal anti-inflammatory medicines (NSAIDs), including selective COX-2 inhibitors, acetylsalicylic acid >3 g/day), and non-selective NSAIDs

NSAIDS can attenuate the antihypertensive effect of both angiotensin II antagonists and hydrochlorothiazide when administered simultaneously. Furthermore, concomitant use of valsartan/hydrochlorothiazide and NSAIDs may lead to worsening of renal function and an increase in serum potassium. Therefore, monitoring of renal function at the beginning of the treatment is recommended, as well as adequate hydration of the patient.

Interactions related to valsartan

Concomitant use not recommended

Potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium and other substances that may increase potassium levels
If a medicinal product that affects potassium levels is considered necessary in combination with valsartan, monitoring of potassium plasma levels is advised.

No interaction

In drug interaction studies with valsartan, no interactions of clinical significance have been found with valsartan or any of the following substances: cimetidine, warfarin, furosemide, digoxin, atenolol, indometacin, hydrochlorothiazide, amlodipine, glibenclamide. Digoxin and indometacin could interact with the hydrochlorothiazide component of Valsartan/Hydrochlorothiazide Film-coated Tablets (see interactions related to hydrochlorothiazide).
Interactions related to hydrochlorothiazide

Concomitant use requiring caution

Medicinal products associated with potassium loss and hypokalaemia (e.g. kaliuretic diuretics, corticosteroids, laxatives, ACTH, amphotericin, carbemoxolone, penicillin G, salicylic acid and derivatives).

If these medicinal products are to be prescribed with the hydrochlorothiazide-valsartan combination, monitoring of potassium plasma levels is advised. These medicinal products may potentiate the effect of hydrochlorothiazide on serum potassium (see section 4.4).

Medicinal products that could induce torsades de pointes

- Class Ia antiarrhythmics (e.g. quinidine, hydroquinidine, disopyramide)
- Class III antiarrhythmics (e.g. amiodarone, sotalol, dofetilide, ibutilide)
- Some antipsychotics (e.g. thioridazine, chlorpromazine, levomepromazine, trifluoperazine, cyamemazine, sulpiride, sulotropride, amisulpride, tiapride, pimozide, haloperidol, droperidol)
- Others (e.g. bepridil, cisapride, diphemanil, erythromycin i.v., halofantrin, ketanserin, mizolastin, pentamidine, sparfloxacin, terfenadine, vincamine i.v.)

Due to the risk of hypokalemia, hydrochlorothiazide should be administered with caution when associated with medicinal products that could induce torsades de pointes.

Digitalis glycosides

Thiazide-induced hypokalaemia or hypomagnesaemia may occur as unwanted effects favouring the onset of digitalis-induced cardiac arrhythmias.

Calcium salts and vitamin D

Administration of thiazide diuretics, including hydrochlorothiazide, with vitamin D or with calcium salts may potentiate the rise in serum calcium.

Antidiabetic agents (oral agents and insulin)

The treatment with a thiazide may influence the glucose tolerance. Dose adjustment of the antidiabetic medicinal product may be necessary. Metformin should be used with caution because of the risk of lactic acidosis induced by possible functional renal failure linked to hydrochlorothiazide.

Beta blockers and diazoxide

Concomitant use of thiazide diuretics, including hydrochlorothiazide, with beta blockers may increase the risk of hyperglycaemia. Thiazide diuretics, including hydrochlorothiazide, may enhance the hyperglycaemic effect of diazoxide.

Medicinal products used in the treatment of gout (probenecid, sulfinpyrazone and allopurinol)

Dose adjustment of uricosuric medications may be necessary as hydrochlorothiazide may raise the level of serum uric acid. Increase of dosage of probenecid or sulfinpyrazone may be necessary. Co-administration of thiazide diuretics, including hydrochlorothiazide, may increase the incidence of hypersensitivity reactions to allopurinol.

Anticholinergic agents (e.g. atropine, biperiden)

The bioavailability of thiazide-type diuretics may be increased by anticholinergic agents, apparently due to a decrease in gastrointestinal motility and the stomach emptying rate.

Amantadine

Thiazides, including hydrochlorothiazide, may increase the risk of adverse effects caused by amantadine.

Cholestyramine and cholestipol resins

Absorption of thiazide diuretics, including hydrochlorothiazide, is impaired in the presence of anionic exchange resins.

Cytotoxic agents (e.g. cyclophosphamide, methotrexate)
Thiazides, including hydrochlorothiazide, may reduce renal excretion of cytotoxic agents and potentiate their myelosuppressive effects.

Non-depolarising skeletal muscle relaxants (e.g. tubocurarine) Thiazides, including hydrochlorothiazide, potentiate the action of curare derivatives.

Ciclosporin
Concomitant treatment with ciclosporin may increase the risk of hyperuricaemia and gout-type complications.

Alcohol, anaesthetics and sedatives
Potentiation of orthostatic hypotension may occur.

Methyldopa
There have been isolated reports of haemolytic anaemia in patients receiving concomitant treatment with methyldopa and hydrochlorothiazide.

Carbamazepine
Patients receiving hydrochlorothiazide concomitantly with carbamazepine may develop hyponatraemia. Such patients should therefore be advised about the possibility of hyponatraemic reactions, and should be monitored accordingly.

Iodine contrast media
In case of diuretic-induced dehydration, there is an increased risk of acute renal failure, especially with high doses of the iodine product. Patients should be rehydrated before the administration.

4.6 Pregnancy and lactation
Pregnancy
Valsartan
The use of Angiotensin II Receptor Antagonists (AIIRAs) is not recommended during first trimester of pregnancy (see section 4.4). The use of AIIRAs is contra-indicated during the second and third trimester of pregnancy (see sections 4.3 and 4.4).

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Whilst there is no controlled epidemiological data on the risk with Angiotensin II Receptor Inhibitors (AIIRAs), similar risks may exist for this class of drugs. Unless continued AIIRAs therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with AIIRAs should be stopped immediately and, if appropriate, alternative therapy should be started.

AIIRAs therapy exposure during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (see also section 5.3 ‘Preclinical safety data’).

Should exposure to AIIRAs have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.

Infants whose mothers have taken AIIRAs should be closely observed for hypotension (see also section 4.3 and 4.4).

Hydrochlorothiazide
There is limited experience with hydrochlorothiazide during pregnancy, especially during the first trimester. Animal studies are insufficient. Hydrochlorothiazide crosses the placenta. Based on the pharmacological mechanism of action of hydrochlorothiazide its use during the second and third trimester may compromise foeto-placental perfusion and may cause foetal and neonatal effects like icterus, disturbance of electrolyte balance and thrombocytopenia.
**Lactation**
No information is available regarding the use of valsartan during breastfeeding. Hydrochlorothiazide is excreted in human milk. Therefore the use of Valsartan/Hydrochlorothiazide Film-coated Tablets during breastfeeding is not recommended. Alternative treatments with better established safety profiles during breastfeeding are preferable, especially while nursing a newborn or preterm infant.

4.7 **Effects on ability to drive and use machines**
No studies on the effect of valsartan/hydrochlorothiazide, on the ability to drive and use machines have been performed. When driving vehicles or operating machines it should be taken into account that occasionally dizziness or weariness may occur.

4.8 **Undesirable effects**
Adverse reactions reported in clinical trials and laboratory findings occurring more frequently with valsartan plus hydrochlorothiazide versus placebo and individual postmarketing reports are presented below according to system organ class. Adverse reactions known to occur with each component given individually but which have not been seen in clinical trials may occur during treatment with valsartan/ hydrochlorothiazide.

Adverse drug reactions are ranked by frequency, the most frequent first, using the following convention: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.

**Table 1. Frequency of adverse reactions with valsartan/hydrochlorothiazide**

<table>
<thead>
<tr>
<th>Metabolism and nutrition disorders</th>
<th>Dehydration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervous system disorders</td>
<td>Dizziness</td>
</tr>
<tr>
<td>Very rare</td>
<td>Paraesthesia</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Syncope</td>
</tr>
<tr>
<td>Not known</td>
<td>Vision blurred</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Tinnitus</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Hypotension</td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td>Cough</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Non cardiogenic pulmonary oedema</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Diarrhoea</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Myalgia</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Arthralgia</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Cough</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Impaired renal function</td>
</tr>
<tr>
<td>Not known</td>
<td>Fatigue</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Serum uric acid increased,</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Serum bilirubin and Serum creatinine increased,</td>
</tr>
<tr>
<td>Investigations</td>
<td>Hypokalaemia,</td>
</tr>
<tr>
<td>Not known</td>
<td>Hyponatraemia, Elevation of</td>
</tr>
<tr>
<td></td>
<td>Blood Urea Nitrogen,</td>
</tr>
<tr>
<td></td>
<td>Neutropenia</td>
</tr>
</tbody>
</table>
Additional information on the individual components
Adverse reactions previously reported with one of the individual components may be potential undesirable effects with Valsartan/Hydrochlorothiazide Film-coated Tablets as well, even if not observed in clinical trials or during postmarketing period.

Table 2. Frequency of adverse reactions with valsartan

<table>
<thead>
<tr>
<th>Blood and lymphatic system disorders</th>
<th>Not known</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Decrease in haemoglobin, decrease in haematocrit, thrombocytopenia</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Not known</td>
</tr>
<tr>
<td></td>
<td>Other hypersensitivity/allergic reactions including serum sickness</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Not known</td>
</tr>
<tr>
<td></td>
<td>Increase of serum potassium</td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Vertigo</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Not known</td>
</tr>
<tr>
<td></td>
<td>Vasculitis</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Abdominal pain</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>Not known</td>
</tr>
<tr>
<td></td>
<td>Elevation of liver function values</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Not known</td>
</tr>
<tr>
<td></td>
<td>Angioedema, rash, pruritus</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Not known</td>
</tr>
<tr>
<td></td>
<td>Renal failure</td>
</tr>
</tbody>
</table>

Table 3. Frequency of adverse reactions with hydrochlorothiazide
Hydrochlorothiazide has been extensively prescribed for many years, frequently in higher doses than those administered with Valsartan/Hydrochlorothiazide Film-coated Tablets. The following adverse reactions have been reported in patients treated with monotherapy of thiazide diuretics, including hydrochlorothiazide:

<table>
<thead>
<tr>
<th>Blood and lymphatic system disorders</th>
<th>Rare</th>
<th>Very rare</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Thrombocytopenia sometimes with purpura</td>
<td>Agranulocytosis, leucopenia, haemolytic anaemia, bone marrow depression</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Very rare</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hypersensitivity reactions</td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Rare</td>
<td>Very rare</td>
</tr>
<tr>
<td></td>
<td>Depression, sleep disturbances</td>
<td>Headache</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Headache</td>
<td>Cardiac arrhythmias</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Cardiac arrhythmias</td>
<td>Postural hypotension</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Common</td>
<td>Very rare</td>
</tr>
<tr>
<td></td>
<td>Respiratory distress including pneumonitis and pulmonary oedema</td>
<td></td>
</tr>
</tbody>
</table>

37
**Gastrointestinal disorders**

- **Common**
  - Loss of appetite, mild nausea and vomiting

- **Rare**
  - Constipation, gastrointestinal discomfort

- **Very rare**
  - Pancreatitis

**Hepatobiliary disorders**

- **Rare**
  - Intrahepatic cholestasis or jaundice

**Skin and subcutaneous tissue disorders**

- **Common**
  - Urticaria and other forms of rash

- **Rare**
  - Photosensitisation

- **Very rare**
  - Necrotising vasculitis and toxic epidermal necrolysis, cutaneous lupus erythematosus-like reactions, reactivation of cutaneous lupus erythematosus

**Reproductive system and breast disorders**

- **Common**
  - Impotence

### 4.9 Overdose

**Symptoms**

Overdose with valsartan may result in marked hypotension, which could lead to depressed level of consciousness, circulatory collapse and/or shock. In addition, the following signs and symptoms may occur due to an overdose of the hydrochlorothiazide component: nausea, somnolence, hypovolaemia, and electrolyte disturbances associated with cardiac arrhythmias and muscle spasms.

**Treatment**

The therapeutic measures depend on the time of ingestion and the type and severity of the symptoms, stabilisation of the circulatory condition being of prime importance.

If hypotension occurs, the patient should be placed in the supine position and salt and volume supplementation should be given rapidly. Valsartan cannot be eliminated by means of haemodialysis because of its strong plasma binding behaviour whereas clearance of hydrochlorothiazide will be achieved by dialysis.

### 5 PHARMACOLOGICAL PROPERTIES

#### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Angiotensin II antagonists and diuretics, valsartan and diuretics; ATC code: C09DA03

Dose-dependent decreases in serum potassium occurred in controlled clinical studies with valsartan + hydrochlorothiazide. Reduction in serum potassium occurred more frequently in patients given 25 mg hydrochlorothiazide than in those given 12.5 mg hydrochlorothiazide. In controlled clinical trials with valsartan/hydrochlorothiazide the potassium lowering effect of hydrochlorothiazide was attenuated by the potassium-sparing effect of valsartan.

Beneficial effects of valsartan in combination with hydrochlorothiazide on cardiovascular mortality and morbidity are currently unknown.

Epidemiological studies have shown that long-term treatment with hydrochlorothiazide reduces the risk of cardiovascular mortality and morbidity.

**Valsartan**

Valsartan is an orally active and specific angiotensin II (Ang II) receptor antagonist. It acts selectively on the AT₁ receptor subtype, which is responsible for the known actions of angiotensin II. The increased plasma levels of Ang II following AT₁ receptor blockade with
valsartan may stimulate the unblocked AT₂ receptor, which appears to counterbalance the effect of the AT₁ receptor. Valsartan does not exhibit any partial agonist activity at the AT₁ receptor and has much (about 20,000 fold) greater affinity for the AT₁ receptor than for the AT₂ receptor. Valsartan is not known to bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

Valsartan does not inhibit ACE, also known as kininase II, which converts Ang I to Ang II and degrades bradykinin. Since there is no effect on ACE and no potentiation of bradykinin or substance P, angiotensin II antagonists are unlikely to be associated with coughing. In clinical trials where valsartan was compared with an ACE inhibitor, the incidence of dry cough was significantly (P <0.05) lower in patients treated with valsartan than in those treated with an ACE inhibitor (2.6% versus 7.9% respectively). In a clinical trial of patients with a history of dry cough during ACE inhibitor therapy, 19.5% of trial subjects receiving valsartan and 19.0% of those receiving a thiazide diuretic experienced cough compared to 68.5% of those treated with an ACE inhibitor (P <0.05).

Administration of valsartan to patients with hypertension results in reduction of blood pressure without affecting pulse rate. In most patients, after administration of a single oral dose, onset of antihypertensive activity occurs within 2 hours, and the peak reduction of blood pressure is achieved within 4–6 hours. The antihypertensive effect persists over 24 hours after dosing. During repeated dosing, the maximum reduction in blood pressure with any dose is generally attained within 2–4 weeks and is sustained during long-term therapy. Combined with hydrochlorothiazide, a significant additional reduction in blood pressure is achieved.

Abrupt withdrawal of valsartan has not been associated with rebound hypertension or other adverse clinical events.

In hypertensive patients with type 2 diabetes and microalbuminuria, valsartan has been shown to reduce the urinary excretion of albumin. The MARVAL (Micro Albuminuria Reduction with Valsartan) study assessed the reduction in urinary albumin excretion (UAE) with valsartan (80-160 mg/od) versus amlodipine (5-10 mg/od), in 332 type 2 diabetic patients (mean age: 58 years; 265 men) with microalbuminuria (valsartan: 58 µg/min; amlodipine: 55.4 µg/min), normal or high blood pressure and with preserved renal function (blood creatinine <120 µmol/l). At 24 weeks, UAE was reduced (p <0.001) by 42% (−24.2 µg/min; 95% CI: −40.4 to −19.1) with valsartan and approximately 3% (−1.7 µg/min; 95% CI: −5.6 to 14.9) with amlodipine despite similar rates of blood pressure reduction in both groups. The Diovan Reduction of Proteinuria (DROP) study further examined the efficacy of valsartan in reducing UAE in 391 hypertensive patients (BP=150/88 mmHg) with type 2 diabetes, albuminuria (mean=102 µg/min; 20– 700 µg/min) and preserved renal function (mean serum creatinine = 80 µmol/l). Patients were randomised to one of 3 doses of valsartan (160, 320 and 640 mg/od) and treated for 30 weeks. The purpose of the study was to determine the optimal dose of valsartan for reducing UAE in hypertensive patients with type 2 diabetes. At 30 weeks, the percentage change in UAE was significantly reduced by 36% from baseline with valsartan 160 mg (95%CI: 22 to 47%), and by 44% with valsartan 320 mg (95%CI: 31 to 54%). It was concluded that 160-320 mg of valsartan produced clinically relevant reductions in UAE in hypertensive patients with type 2 diabetes.

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.
Valsartan/hydrochlorothiazide
In a double-blind, randomised, active-controlled trial in patients not adequately controlled on hydrochlorothiazide 12.5 mg, significantly greater mean systolic/diastolic BP reductions were observed with the combination of valsartan/hydrochlorothiazide 160/12.5 mg (12.4/7.5 mmHg) compared to hydrochlorothiazide 25 mg (5.6/2.1 mmHg). In addition, a significantly greater percentage of patients responded (BP <140/90 mmHg or SBP reduction ≥20 mmHg or DBP reduction ≥10 mmHg) with valsartan/hydrochlorothiazide 160/12.5 mg (50 %) compared to hydrochlorothiazide (25 %).

In a double-blind, randomised, active-controlled trial in patients not adequately controlled on valsartan 160 mg, significantly greater mean systolic/diastolic BP reductions were observed with both the combination of valsartan/hydrochlorothiazide 160/25 mg (14.6/11.9 mmHg) and valsartan/hydrochlorothiazide 160/12.5 mg (12.4/10.4 mmHg) compared to valsartan 160 mg (8.7/8.8 mmHg). The difference in BP reductions between the 160/25 mg and 160/12.5 mg doses also reached statistical significance. In addition, a significantly greater percentage of patients responded (diastolic BP <90 mmHg or reduction ≥10 mmHg) with valsartan/hydrochlorothiazide 160/25 mg (68%) and 160/12.5 mg (62 %) compared to valsartan 160 mg (49 %).

In a double-blind, randomised, placebo-controlled, factorial design trial comparing various dose combinations of valsartan/hydrochlorothiazide to their respective components, significantly greater mean systolic/diastolic BP reductions were observed with the combination of valsartan/hydrochlorothiazide 160/12.5 mg (17.8/13.5 mmHg) and 160/25 mg (22.5/15.3 mmHg) compared to placebo (1.9/4.1 mmHg) and the respective monotherapies, i.e., hydrochlorothiazide 12.5 mg (7.3/7.2 mmHg), hydrochlorothiazide 25 mg (12.7/9.3 mmHg) and valsartan 160 mg (12.1/9.4 mmHg). In addition, a significantly greater percentage of patients responded (diastolic BP <90 mmHg or reduction ≥10 mmHg) with valsartan/hydrochlorothiazide 160/25 mg (81%) and valsartan/hydrochlorothiazide 160/12.5 mg (76 %) compared to placebo (29 %) and the respective monotherapies, i.e., hydrochlorothiazide 12.5 mg (41 %), hydrochlorothiazide 25 mg (54%) and valsartan 160 mg (59%).

5.2 Pharmacokinetic properties

Valsartan/hydrochlorothiazide
The systemic availability of hydrochlorothiazide is reduced by about 30 % when co-administered with valsartan. The kinetics of valsartan are not markedly affected by the co-administration of hydrochlorothiazide. This observed interaction has no impact on the combined use of valsartan and hydrochlorothiazide, since controlled clinical trials have shown a clear anti-hypertensive effect, greater than that obtained with either active substance given alone, or placebo.

Valsartan

Absorption
Following oral administration of valsartan alone, peak plasma concentrations of valsartan are reached in 2–4 hours. Mean absolute bioavailability is 23 %. Food decreases exposure (as measured by AUC) to valsartan by about 40 % and peak plasma concentration (Cmax) by about 50 %, although from about 8 h post dosing plasma valsartan concentrations are similar for the fed and fasted groups. This reduction in AUC is not, however, accompanied by a clinically significant reduction in the therapeutic effect, and valsartan can therefore be given either with or without food.

Distribution
The steady-state volume of distribution of valsartan after intravenous administration is about 17 litres, indicating that valsartan does not distribute into tissues extensively. Valsartan is highly bound to serum proteins (94–97 %), mainly serum albumin.

Biotransformation
Valsartan is not biotransformed to a high extent as only about 20 % of dose is recovered as metabolites. A hydroxy metabolite has been identified in plasma at low concentrations (less than 10 % of the valsartan AUC). This metabolite is pharmacologically inactive.
Elimination
Valsartan shows multiexponential decay kinetics ($t_{1/2a} < 1$ h and $t_{1/2b}$ about 9 h). Valsartan is primarily eliminated in faeces (about 83% of dose) and urine (about 13% of dose), mainly as unchanged drug. Following intravenous administration, plasma clearance of valsartan is about 2 l/h and its renal clearance is 0.62 l/h (about 30% of total clearance). The half-life of valsartan is 6 hours.

Hydrochlorothiazide
Absorption
The absorption of hydrochlorothiazide, after an oral dose, is rapid ($t_{max}$ about 2 h), with similar absorption characteristics for both suspension and tablet formulations. Absolute bioavailability of hydrochlorothiazide is 60–80% after oral administration. Concomitant administration with food has been reported to both increase and decrease the systemic availability of hydrochlorothiazide compared with the fasted state. The magnitude of these effects is small and has minimal clinical importance. The increase in mean AUC is linear and dose proportional in the therapeutic range. There is no change in the kinetics of hydrochlorothiazide on repeated dosing, and accumulation is minimal when dosed once daily.

Distribution
The distribution and elimination kinetics have generally been described by a bi-exponential decay function. The apparent volume of distribution is 4–8 l/kg. Circulating hydrochlorothiazide is bound to serum proteins (40–70%), mainly serum albumin. Hydrochlorothiazide also accumulates in erythrocytes at approximately 1.8 times the level in plasma.

Elimination
For hydrochlorothiazide, >95% of the absorbed dose being excreted as unchanged compound in the urine. The renal clearance is composed of passive filtration and active secretion into the renal tubule. The terminal half-life is 6–15 h.

Special populations
Elderly
A somewhat higher systemic exposure to valsartan was observed in some elderly subjects than in young subjects; however, this has not been shown to have any clinical significance. Limited data suggest that the systemic clearance of hydrochlorothiazide is reduced in both healthy and hypertensive elderly subjects compared to young healthy volunteers.

Renal impairment
At the recommended dose of Valsartan/Hydrochlorothiazide Film-coated tablets no dose adjustment is required for patients with a creatinine clearance of 30-70mL/min.

In patients with severe renal impairment (creatinine clearance <30mL/min) and patients undergoing dialysis, no data are available for Valsartan/Hydrochlorothiazide Film-coated Tablets. Valsartan is highly bound to plasma protein and is not to be removed by dialysis, whereas clearance of hydrochlorothiazide will be achieved by dialysis.

Renal clearance of hydrochlorothiazide is composed of passive filtration and active secretion into the renal tubule. As expected for a compound which is cleared almost exclusively via the kidneys, renal function has a marked effect on the kinetics of hydrochlorothiazide (see Section 4.3).

Hepatic impairment
In a pharmacokinetics trial in patients with mild ($n=6$) to moderate ($n=5$) hepatic dysfunction, exposure to valsartan was increased approximately twofold compared with healthy volunteers. There are no data available on the use of valsartan in patients with severe hepatic dysfunction (see section 4.3). Hepatic disease does not significantly affect the pharmacokinetics of hydrochlorothiazide.
5.3 Preclinical safety data

The potential toxicity of the valsartan - hydrochlorothiazide combination after oral administration was investigated in rats and marmosets in studies lasting up to six months. No findings emerged that would exclude the use of therapeutic doses in man.

The changes produced by the combination in the chronic toxicity studies are most likely to have been caused by the valsartan component. The toxicological target organ was the kidney, the reaction being more marked in the marmoset than the rat. The combination led to kidney damage (nephropathy with tubular basophilia, rises in plasma urea, plasma creatinine and serum potassium, increases in urine volume and urinary electrolytes from 30 mg/kg/day valsartan + 9 mg/kg/day hydrochlorothiazide in rats and 10 + 3 mg/kg/d in marmosets), probably by way of altered renal haemodynamics. These doses in rat, respectively, represent 0.9 and 3.5–times the maximum recommended human dose (MRHD) of valsartan and hydrochlorothiazide on a mg/m² basis. These doses in marmoset, respectively, represent 0.3 and 1.2–times the maximum recommended human dose (MRHD) of valsartan and hydrochlorothiazide on a mg/m² basis. (Calculations assume an oral dose of 320 mg/day valsartan in combination with 25 mg/day hydrochlorothiazide and a 60-kg patient.)

High doses of the valsartan - hydrochlorothiazide combination caused falls in red blood cell indices (red cell count, haemoglobin, haematocrit, from 100 + 31 mg/kg/d in rats and 30 + 9mg/kg/d in marmosets). These doses in rat, respectively, represent 3.0 and 12 times the maximum recommended human dose (MRHD) of valsartan and hydrochlorothiazide on a mg/m² basis. These doses in marmoset, respectively, represent 0.9 and 3.5 times the maximum recommended human dose (MRHD) of valsartan and hydrochlorothiazide on a mg/m² basis. (Calculations assume an oral dose of 320 mg/day valsartan in combination with 25 mg/day hydrochlorothiazide and a 60-kg patient).

In marmosets, damage was observed in the gastric mucosa (from 30 + 9 mg/kg/d). The combination also led in the kidney to hyperplasia of the afferent aterioles (at 600 + 188 mg/kg/d in rats and from 30 + 9 mg/kg/d in marmosets). These doses in marmoset, respectively, represent 0.9 and 3.5 times the maximum recommended human dose (MRHD) of valsartan and hydrochlorothiazide on a mg/m² basis. These doses in rat, respectively, represent 18 and 73 times the maximum recommended human dose (MRHD) of valsartan and hydrochlorothiazide on a mg/m² basis. (Calculations assume an oral dose of 320 mg/day valsartan in combination with 25 mg/day hydrochlorothiazide and a 60-kg patient).

The above mentioned effects appear to be due to the pharmacological effects of high valsartan doses (blockade of angiotensin II-induced inhibition of renin release, with stimulation of the renin-producing cells) and also occur with ACE inhibitors. These findings appear to have no relevance to the use of therapeutic doses of valsartan in humans.

The valsartan - hydrochlorothiazide combination was not tested for mutagenicity, chromosomal breakage or carcinogenicity, since there is no evidence of interaction between the two substances. However, these tests were performed separately with valsartan and hydrochlorothiazide, and produced no evidence of mutagenicity, chromosomal breakage or carcinogenicity.

In rats, maternally toxic doses of valsartan (600 mg/kg/day) during the last days of gestation and lactation led to lower survival, lower weight gain and delayed development (pinna detachment and ear-canal opening) in the offspring (see section 4.6). These doses in rats (600 mg/kg/day) are approximately 18 times the maximum recommended human dose on a mg/m² basis (calculations assume an oral dose of 320 mg/day and a 60-kg patient). Similar findings were seen with valsartan/hydrochlorothiazide in rats and rabbits. In embryo-fetal development (Segment II) studies with valsartan/hydrochlorothiazide in rat and rabbit, there was no evidence of teratogenicity; however, fetotoxicity associated with maternal toxicity was observed.
6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Tablet core
Microcrystalline Cellulose
Lactose Monohydrate
Crocarmellose Sodium
Povidone K29-K32
Talc
Magnesium Stearate
Colloidal Anhydrous Silica

Coating
Opadry II 85G25455 Red:
Polyvinyl Alcohol
Talc
Titanium Dioxide (E171)
Macrogol 3350
Lecithin soya (E322)
Iron Oxide Red (E172)
Sunset Yellow FCF Aluminium Lake (E110)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
4 years for tablets packed in PVC/PE/PVDC-Al blisters
5 years for tablets packed in polyethylene tablet containers

6.4 Special precautions for storage
Tablets packed in PVC/PE/PVDC-Al blisters: Do not store above 30°C.
Tablets packed in polyethylene tablet containers: This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container
PVC/PE/PVDC-Al blisters, and HDPE containers with PE closure.
Pack sizes of 7, 14, 28, 30, 56, 98 and 280 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements
Any unused or waste material should be disposed of in accordance to local requirements.

7 MARKETING AUTHORISATION HOLDER
Caduceus Pharma Limited
6th Floor
94 Wigmore Street
London
W1U 3RF
UK

8 MARKETING AUTHORISATION NUMBER(S)
PL 24668/0070
PL 24668/0073
PL 24668/0076

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
17/12/2010
DATE OF REVISION OF THE TEXT
17/12/2010
NAME OF THE MEDICINAL PRODUCT
Valsartan/Hydrochlorothiazide 160 mg/25 mg Film-coated Tablets

QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains 160 mg valsartan and 25 mg hydrochlorothiazide.

Excipients: Each Valsartan/Hydrochlorothiazide 160 mg/25 mg Film-coated Tablet contains 29.75 mg lactose monohydrate and 0.25 mg lecithin (contains soya oil).

For a full list of excipients, see section 6.1.

PHARMACEUTICAL FORM
Film-coated tablet
Orange, biconvex, oval, 15 mm x 6 mm. Marked ‘V’ on one side and ‘H’ on the other.

CLINICAL PARTICULARS
4.1 Therapeutic indications
Treatment of essential hypertension in adults.

Valsartan/Hydrochlorothiazide film-coated tablet fixed dose combination is indicated in patients whose blood pressure is not adequately controlled on valsartan or hydrochlorothiazide monotherapy.

4.2 Posology and method of administration
The recommended dose of Valsartan/Hydrochlorothiazide 160 mg/25 mg Film-coated Tablets is one film-coated tablet once daily.

Dose titration with the individual components is recommended. In each case, up-titration of individual components to the next dose should be followed in order to reduce the risk of hypotension and other adverse events.

When clinically appropriate direct change from monotherapy to the fixed combination may be considered in patients whose blood pressure is not adequately controlled on valsartan or hydrochlorothiazide monotherapy, provided the recommended dose titration sequence for the individual components is followed.

The clinical response to Valsartan/Hydrochlorothiazide film-coated tablets should be evaluated after initiating therapy and if blood pressure remains uncontrolled, the dose may be increased by increasing either one of the components to a maximum dose of Valsartan/Hydrochlorothiazide 320 mg/25 mg.

The antihypertensive effect is substantially present within 2 weeks.

In most patients, maximal effects are observed within 4 weeks. However, in some patients, 4-8 weeks treatment may be required. This should be taken into account during dose-titration.

Method of administration
Valsartan/Hydrochlorothiazide film-coated tablets can be taken with or without food and should be administered with water.

Special populations
Renal Impairment
No dose adjustment is required for patients with mild to moderate renal impairment (creatinine clearance ≥ 30 ml/min). Due to the hydrochlorothiazide component, Valsartan/Hydrochlorothiazide Film-coated Tablets are contraindicated in patients with severe renal impairment (see sections 4.3, 4.4 and 5.2).
**Hepatic Impairment**
In patients with mild to moderate hepatic impairment without cholestasis the dose of valsartan should not exceed 80 mg (see section 4.4). Valsartan/Hydrochlorothiazide film-coated tablets are contraindicated in patients with severe hepatic impairment (see sections 4.3, 4.4 and 5.2).

**Elderly**
No dose adjustment is required in elderly patients.

**Paediatric patients**
Valsartan/Hydrochlorothiazide Film-coated Tablets are not recommended for use in children below the age of 18 years due to a lack of data on safety and efficacy.

### 4.3 Contraindications
- Hypersensitivity to valsartan, hydrochlorothiazide, other sulphonamide-derived medicinal products, soya oil, peanut oil or to any of the excipients.
- Second and third trimester of pregnancy (section 4.4 and 4.6).
- Severe hepatic impairment, biliary cirrhosis and cholestasis.
- Severe renal impairment (creatinine clearance < 30 ml/min), anuria
- Refractory hypokalaemia, hyponatraemia, hypercalcaemia, and symptomatic hyperuricaemia.

### 4.4 Special warnings and precautions for use

**Serum electrolyte changes**

**Valsartan**
Concomitant use with potassium supplements, potassium sparing diuretics, salt substitutes containing potassium, or other agents that may increase potassium levels (heparin, etc.) is not recommended. Monitoring of potassium should be undertaken as appropriate.

**Hydrochlorothiazide**
Hypokalaemia has been reported under treatment with thiazide diuretics, including hydrochlorothiazide. Frequent monitoring of serum potassium is recommended.

Treatment with thiazide diuretics, including hydrochlorothiazide, has been associated with hyponatraemia and hypochloraeamic alkalosis. Thiazides, including hydrochlorothiazide, increase the urinary excretion of magnesium, which may result in hypomagnesaemia. Calcium excretion is decreased by thiazide diuretics. This may result in hypercalcaemia.

As for any patient receiving diuretic therapy, periodic determination of serum electrolytes should be performed at appropriate intervals.

**Sodium, and/or volume-depleted patients:**
Patients receiving thiazide diuretics, including hydrochlorothiazide, should be observed for clinical signs of fluid or electrolyte imbalance. In severely sodium-depleted and/or volume-depleted patients, such as those receiving high doses of diuretics, symptomatic hypotension may occur in rare cases after initiation of therapy with valsartan/hydrochlorothiazide. Sodium and/or volume depletion should be corrected before starting treatment with Valsartan/Hydrochlorothiazide Film-coated Tablets.

**Patients with severe chronic heart failure or other conditions with stimulation of the renin-angiotensin-aldosterone-system**
In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (e.g. patients with severe congestive heart failure), treatment with angiotensin converting enzyme inhibitors has been associated with oliguria and/or progressive azotaemia, and in rare cases with acute renal failure. The use of valsartan/hydrochlorothiazide in patients with severe chronic heart failure has not been established.

Hence it cannot be excluded that because of the inhibition of the renin-angiotensin-aldosterone system the application of valsartan/hydrochlorothiazide as well may be associated with impairment of the renal function. Valsartan/Hydrochlorothiazide Film-coated Tablets should not be used in these patients.
Renal artery stenosis
Valsartan/Hydrochlorothiazide Film-coated Tablets should not be used to treat hypertension in patients with unilateral or bilateral renal artery stenosis or stenosis of the artery to a solitary kidney, since blood urea and serum creatinine may increase in such patients.

Primary hyperaldosteronism
Patients with primary hyperaldosteronism should not be treated with Valsartan/Hydrochlorothiazide Film-coated Tablets as their renin-angiotensin system is not activated.

Aortic and mitral valve stenosis, hypertrophic obstructive cardiomyopathy
As with all other vasodilators, special caution is indicated in patients suffering from aortic or mitral stenosis, or hypertrophic obstructive cardiomyopathy (HOCM).

Renal impairment
No dosage adjustment is required for patients with renal impairment with a creatinine clearance 30ml/min (see section 4.2). Periodic monitoring of serum potassium, creatinine and uric acid levels is recommended when Valsartan/Hydrochlorothiazide Film-coated Tablets is used in patients with renal impairment.

Kidney transplantation
There is currently no experience on the safe use of valsartan/hydrochlorothiazide in patients who have recently undergone kidney transplantation.

Hepatic impairment
In patients with mild to moderate hepatic impairment without cholestasis, Valsartan/Hydrochlorothiazide Film-coated Tablets should be used with caution (see sections 4.2 and 5.2).

Systemic Lupus Erythematosus
Thiazide diuretics, including hydrochlorothiazide, have been reported to exacerbate or activate systemic lupus erythematosus.

Other metabolic disturbances
Thiazide diuretics, including hydrochlorothiazide, may alter glucose tolerance and raise serum levels of cholesterol, triglycerides and uric acid. In diabetic patients dosage adjustments of insulin or oral hypoglycaemic agents may be required. Thiazides may reduce urinary calcium excretion and cause an intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcaemia may be evidence of underlying hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Photosensitivity
Cases of photosensitivity reactions have been reported with thiazides diuretics (see section 4.8). If photosensitivity reaction occurs during treatment, it is recommended to stop the treatment. If a re-administration of the diuretic is deemed necessary, it is recommended to protect exposed areas to the sun or to artificial UVA.

Pregnancy
Angiotensin II Receptor Antagonists (AIIRAs) should not be initiated during pregnancy. Unless continued AIIRAs therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with AIIRAs should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

General
Caution should be exercised in patients who have shown prior hypersensitivity to other angiotensin II receptor antagonists. Hypersensitivity reactions to hydrochlorothiazide are more likely in patients with allergy and asthma.
Galactose intolerance, Lapp lactase deficiency, glucose-galactose malabsorption
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Lecithin
If a patient is hypersensitive to peanut or soya, this medicine should not be used.

4.5 Interaction with other medicinal products and other forms of interaction
Interactions related to both valsartan and hydrochlorothiazide

Concomitant use not recommended
Lithium
Reversible increases in serum lithium concentrations and toxicity have been reported during concurrent use of ACE inhibitors and thiazide, including hydrochlorothiazide. Due to the lack of experience with concomitant use of valsartan and lithium, this combination is not recommended. If the combination proves necessary, careful monitoring of serum lithium levels is recommended.

Concomitant use requiring caution
Other antihypertensive agents
Valsartan/Hydrochlorothiazide Film-coated Tablets may increase the effects of other agents with antihypertensive properties (e.g. ACEI, beta-blockers, calcium channel blockers).

Pressor amines (e.g. noradrenaline, adrenaline)
Possible decreased response to pressor amines but not sufficient to preclude their use.

Non-steroidal anti-inflammatory medicines (NSAIDs), including selective COX-2 inhibitors, acetylsalicylic acid >3 g/day), and non-selective NSAIDs
NSAIDs can attenuate the antihypertensive effect of both angiotensin II antagonists and hydrochlorothiazide when administered simultaneously. Furthermore, concomitant use of valsartan/hydrochlorothiazide and NSAIDs may lead to worsening of renal function and an increase in serum potassium. Therefore, monitoring of renal function at the beginning of the treatment is recommended, as well as adequate hydration of the patient.

Interactions related to valsartan

Concomitant use not recommended
Potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium and other substances that may increase potassium levels
If a medicinal product that affects potassium levels is considered necessary in combination with valsartan, monitoring of potassium plasma levels is advised.

No interaction
In drug interaction studies with valsartan, no interactions of clinical significance have been found with valsartan or any of the following substances: cimetidine, warfarin, furosemide, digoxin, atenolol, indometacin, hydrochlorothiazide, amlodipine, glibenclamide. Digoxin and indometacin could interact with the hydrochlorothiazide component of Valsartan/Hydrochlorothiazide Film-coated Tablets (see interactions related to hydrochlorothiazide).

Interactions related to hydrochlorothiazide

Concomitant use requiring caution
Medicinal products associated with potassium loss and hypokalaemia (e.g. kaliuretic diuretics, corticosteroids, laxatives, ACTH, amphotericin, carbenoxolone, penicillin G, salicylic acid and derivatives).
If these medicinal products are to be prescribed with the hydrochlorothiazide-valsartan combination, monitoring of potassium plasma levels is advised. These medicinal products may potentiate the effect of hydrochlorothiazide on serum potassium (see section 4.4).

**Medicinal products that could induce torsades de pointes**

- Class Ia antiarrhythmics (e.g. quinidine, hydroquinidine, disopyramide)
- Class III antiarrhythmics (e.g. amiodarone, sotalol, dofetilide, ibutilide)
- Some antipsychotics (e.g. thioridazine, chlorpromazine, levomepromazine, trifluoperazine, cyamemazine, sulpiride, sulpoxide, amisulpride, tiapride, pimozide, haloperidol, droperidol)
- Others (e.g. bepridil, cisapride, diphemanil, erythromycin i.v., halofantrin, ketanserin, mizolastin, pentamidine, sparfloxacin, terfenadine, vincamine i.v.)

Due to the risk of hypokalemia, hydrochlorothiazide should be administered with caution when associated with medicinal products that could induce torsades de pointes.

**Digitalis glycosides**

Thiazide-induced hypokalaemia or hypomagnesaemia may occur as unwanted effects favouring the onset of digitalis-induced cardiac arrhythmias.

**Calcium salts and vitamin D**

Administration of thiazide diuretics, including hydrochlorothiazide, with vitamin D or with calcium salts may potentiate the rise in serum calcium.

**Antidiabetic agents (oral agents and insulin)**

The treatment with a thiazide may influence the glucose tolerance. Dose adjustment of the antidiabetic medicinal product may be necessary.

Metformin should be used with caution because of the risk of lactic acidosis induced by possible functional renal failure linked to hydrochlorothiazide.

**Beta blockers and diazoxide**

Concomitant use of thiazide diuretics, including hydrochlorothiazide, with beta blockers may increase the risk of hyperglycaemia. Thiazide diuretics, including hydrochlorothiazide, may enhance the hyperglycaemic effect of diazoxide.

**Medicinal products used in the treatment of gout (probenecid, sulfinpyrazone and allopurinol)**

Dose adjustment of uricosuric medications may be necessary as hydrochlorothiazide may raise the level of serum uric acid. Increase of dosage of probenecid or sulfinpyrazone may be necessary. Co-administration of thiazide diuretics, including hydrochlorothiazide, may increase the incidence of hypersensitivity reactions to allopurinol.

**Anticholinergic agents (e.g. atropine, biperiden)**

The bioavailability of thiazide-type diuretics may be increased by anticholinergic agents, apparently due to a decrease in gastrointestinal motility and the stomach emptying rate.

**Amantadine**

Thiazides, including hydrochlorothiazide, may increase the risk of adverse effects caused by amantadine

**Cholestyramine and cholestipol resins**

Absorption of thiazide diuretics, including hydrochlorothiazide, is impaired in the presence of anionic exchange resins.

**Cytotoxic agents (e.g. cyclophosphamide, methotrexate)**

Thiazides, including hydrochlorothiazide, may reduce renal excretion of cytotoxic agents and potentiate their myelosuppressive effects.

**Non-depolarising skeletal muscle relaxants (e.g. tubocurarine)**

Thiazides, including hydrochlorothiazide, potentiate the action of curare derivatives.
**Ciclosporin**
Concomitant treatment with ciclosporin may increase the risk of hyperuricaemia and gout-type complications.

**Alcohol, anaesthetics and sedatives**
Potentiation of orthostatic hypotension may occur.

**Methyldopa**
There have been isolated reports of haemolytic anaemia in patients receiving concomitant treatment with methyldopa and hydrochlorothiazide.

**Carbamazepine**
Patients receiving hydrochlorothiazide concomitantly with carbamazepine may develop hyponatraemia. Such patients should therefore be advised about the possibility of hyponatraemic reactions, and should be monitored accordingly.

**Iodine contrast media**
In case of diuretic-induced dehydration, there is an increased risk of acute renal failure, especially with high doses of the iodine product. Patients should be rehydrated before the administration.

### 4.6 Pregnancy and lactation

**Pregnancy**

<table>
<thead>
<tr>
<th><strong>Valsartan</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>The use of Angiotensin II Receptor Antagonists (AIIRAs) is not recommended during first trimester of pregnancy (see section 4.4). The use of AIIRAs is contra-indicated during the second and third trimester of pregnancy (see sections 4.3 and 4.4).</td>
<td></td>
</tr>
</tbody>
</table>

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Whilst there is no controlled epidemiological data on the risk with Angiotensin II Receptor Inhibitors (AIIRAs), similar risks may exist for this class of drugs. Unless continued AIIRAs therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with AIIRAs should be stopped immediately and, if appropriate, alternative therapy should be started.

AIIRAs therapy exposure during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (see also section 5.3 ‘Preclinical safety data’).

Should exposure to AIIRAs have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.

Infants whose mothers have taken AIIRAs should be closely observed for hypotension (see also section 4.3 and 4.4).

**Hydrochlorothiazide**

There is limited experience with hydrochlorothiazide during pregnancy, especially during the first trimester. Animal studies are insufficient. Hydrochlorothiazide crosses the placenta.

Based on the pharmacological mechanism of action of hydrochlorothiazide its use during the second and third trimester may compromise foeto-placental perfusion and may cause foetal and neonatal effects like icterus, disturbance of electrolyte balance and thrombocytopenia.

**Lactation**

No information is available regarding the use of valsartan during breastfeeding.

Hydrochlorothiazide is excreted in human milk. Therefore the use of Valsartan/Hydrochlorothiazide Film-coated Tablets during breast feeding is not recommended. Alternative treatments with better established safety profiles during breastfeeding are preferable, especially while nursing a newborn or preterm infant.
4.7 Effects on ability to drive and use machines
No studies on the effect of valsartan/hydrochlorothiazide, on the ability to drive and use machines have been performed. When driving vehicles or operating machines it should be taken into account that occasionally dizziness or weariness may occur.

4.8 Undesirable effects
Adverse reactions reported in clinical trials and laboratory findings occurring more frequently with valsartan plus hydrochlorothiazide versus placebo and individual postmarketing reports are presented below according to system organ class. Adverse reactions known to occur with each component given individually but which have not been seen in clinical trials may occur during treatment with valsartan/ hydrochlorothiazide.

Adverse drug reactions are ranked by frequency, the most frequent first, using the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.

Table 1. Frequency of adverse reactions with valsartan/hydrochlorothiazide

<table>
<thead>
<tr>
<th>Metabolism and nutrition disorders</th>
<th>Uncommon</th>
<th>Very rare</th>
<th>Common</th>
<th>Rare</th>
<th>Very rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dehydration</td>
<td></td>
<td>Dizziness</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Nervous system disorders              |          |           |        |      |           |
| Dehydration                            |          |           |        |      |           |
| Dizziness                              |          |           |        |      |           |
| Paraesthesia                           |          |           |        |      |           |
| Syncope                                |          |           |        |      |           |

| Eye disorders                          |          |           |        |      |           |
| Vision blurred                         |          |           |        |      |           |
| Paraesthesia                            |          |           |        |      |           |
| Syncope                                |          |           |        |      |           |

| Ear and labyrinth disorders           |          |           |        |      |           |
| Tinnitus                              |          |           |        |      |           |

| Vascular disorders                    |          |           |        |      |           |
| Hypotension                            |          |           |        |      |           |

| Respiratory, thoracic and mediastinal disorders |          |           |        |      |           |
| Cough                                   |          |           |        |      |           |
| Non cardiogenic pulmonary oedema       |          |           |        |      |           |

| Gastrointestinal disorders             |          |           |        |      |           |
| Diarrhoea                              |          |           |        |      |           |

| Musculoskeletal and connective tissue disorders |          |           |        |      |           |
| Myalgia                                 |          |           |        |      |           |
| Arthralgia                              |          |           |        |      |           |

| Renal and urinary disorders            |          |           |        |      |           |
| Impaired renal function                |          |           |        |      |           |

| General disorders and administration site conditions |          |           |        |      |           |
| Fatigue                                 |          |           |        |      |           |

| Investigations                         |          |           |        |      |           |
| Serum uric acid increased,             |          |           |        |      |           |
| Serum bilirubin and Serum creatinine increased, |          |           |        |      |           |
| Hypokalaemia                           |          |           |        |      |           |
| Hyponatraemia                           |          |           |        |      |           |
| Elevation of Blood Urea Nitrogen,      |          |           |        |      |           |
| Neutropenia                             |          |           |        |      |           |

Additional information on the individual components
Adverse reactions previously reported with one of the individual components may be potential undesirable effects with Valsartan/Hydrochlorothiazide Film-coated Tablets as well, even if not observed in clinical trials or during postmarketing period.
Table 2. Frequency of adverse reactions with valsartan

<table>
<thead>
<tr>
<th>Blood and lymphatic system disorders</th>
<th>Decrease in haemoglobin, decrease in haematocrit, thrombocytopenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune system disorders</td>
<td>Other hypersensitivity/allergic reactions including serum sickness</td>
</tr>
<tr>
<td>Not known</td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Increase of serum potassium</td>
</tr>
<tr>
<td>Not known</td>
<td></td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td>Vertigo</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
</tr>
<tr>
<td>Not known</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td></td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td></td>
</tr>
<tr>
<td>Not known</td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Angioedema, rash, pruritus</td>
</tr>
<tr>
<td>Not known</td>
<td></td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td></td>
</tr>
<tr>
<td>Not known</td>
<td>Renal failure</td>
</tr>
</tbody>
</table>

Table 3. Frequency of adverse reactions with hydrochlorothiazide

Hydrochlorothiazide has been extensively prescribed for many years, frequently in higher doses than those administered with Valsartan/hydrochlorothiazide Tablets. The following adverse reactions have been reported in patients treated with monotherapy of thiazide diuretics, including hydrochlorothiazide:

<table>
<thead>
<tr>
<th>Blood and lymphatic system disorders</th>
<th>Thrombocytopenia sometimes with purpura</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune system disorders</td>
<td>Hypersensitivity reactions</td>
</tr>
<tr>
<td>Very rare</td>
<td>Depression, sleep disturbances</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Headache</td>
</tr>
<tr>
<td>Rare</td>
<td>Cardiac arrhythmias</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Postural hypotension</td>
</tr>
<tr>
<td>Rare</td>
<td>Respiratory distress including pneumonitis and pulmonary oedema</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Intrahepatic cholestasis or jaundice</td>
</tr>
<tr>
<td>Rare</td>
<td>Loss of appetite, mild nausea and vomiting</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Constipation, gastrointestinal discomfort</td>
</tr>
<tr>
<td>Common</td>
<td>Pancreatitis</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
</tr>
<tr>
<td>Very rare</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td></td>
</tr>
<tr>
<td>Rare</td>
<td></td>
</tr>
<tr>
<td>Very rare</td>
<td></td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td></td>
</tr>
</tbody>
</table>
Skin and subcutaneous tissue disorders
Common
Urticaria and other forms of rash
Rare
Photosensitisation
Very rare
Necrotising vasculitis and toxic epidermal necrolysis, cutaneous lupus erythematosus-like reactions, reactivation of cutaneous lupus erythematosus

Reproductive system and breast disorders
Common
Impotence

4.9 Overdose

Symptoms
Overdose with valsartan may result in marked hypotension, which could lead to depressed level of consciousness, circulatory collapse and/or shock. In addition, the following signs and symptoms may occur due to an overdose of the hydrochlorothiazide component: nausea, somnolence, hypovolaemia, and electrolyte disturbances associated with cardiac arrhythmias and muscle spasms.

Treatment
The therapeutic measures depend on the time of ingestion and the type and severity of the symptoms, stabilisation of the circulatory condition being of prime importance. If hypotension occurs, the patient should be placed in the supine position and salt and volume supplementation should be given rapidly. Valsartan cannot be eliminated by means of haemodialysis because of its strong plasma binding behaviour whereas clearance of hydrochlorothiazide will be achieved by dialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Angiotensin II antagonists and diuretics, valsartan and diuretics; ATC code: C09D A03

Dose-dependent decreases in serum potassium occurred in controlled clinical studies with valsartan + hydrochlorothiazide. Reduction in serum potassium occurred more frequently in patients given 25 mg hydrochlorothiazide than in those given 12.5 mg hydrochlorothiazide. In controlled clinical trials with valsartan/hydrochlorothiazide the potassium lowering effect of hydrochlorothiazide was attenuated by the potassium-sparing effect of valsartan.

Beneficial effects of valsartan in combination with hydrochlorothiazide on cardiovascular mortality and morbidity are currently unknown.

Epidemiological studies have shown that long-term treatment with hydrochlorothiazide reduces the risk of cardiovascular mortality and morbidity.

Valsartan
Valsartan is an orally active and specific angiotensin II (Ang II) receptor antagonist. It acts selectively on the AT1 receptor subtype, which is responsible for the known actions of angiotensin II. The increased plasma levels of Ang II following AT1 receptor blockade with valsartan may stimulate the unblocked AT2 receptor, which appears to counterbalance the effect of the AT1 receptor. Valsartan does not exhibit any partial agonist activity at the AT1 receptor and has much (about 20,000 fold) greater affinity for the AT1 receptor than for the AT2 receptor. Valsartan is not known to bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

Valsartan does not inhibit ACE, also known as kininase II, which converts Ang I to Ang II and degrades bradykinin. Since there is no effect on ACE and no potentiation of bradykinin or substance P, angiotensin II antagonists are unlikely to be associated with coughing. In clinical trials where valsartan was compared with an ACE inhibitor, the incidence of dry cough was
significantly (P <0.05) lower in patients treated with valsartan than in those treated with an ACE inhibitor (2.6% versus 7.9% respectively). In a clinical trial of patients with a history of dry cough during ACE inhibitor therapy, 19.5% of trial subjects receiving valsartan and 19.0% of those receiving a thiazide diuretic experienced cough compared to 68.5% of those treated with an ACE inhibitor (P <0.05).

Administration of valsartan to patients with hypertension results in reduction of blood pressure without affecting pulse rate. In most patients, after administration of a single oral dose, onset of antihypertensive activity occurs within 2 hours, and the peak reduction of blood pressure is achieved within 4-6 hours. The antihypertensive effect persists over 24 hours after dosing. During repeated dosing, the maximum reduction in blood pressure with any dose is generally attained within 2-4 weeks and is sustained during long-term therapy. Combined with hydrochlorothiazide, a significant additional reduction in blood pressure is achieved.

Abrupt withdrawal of valsartan has not been associated with rebound hypertension or other adverse clinical events.

In hypertensive patients with type 2 diabetes and microalbuminuria, valsartan has been shown to reduce the urinary excretion of albumin. The MARVAL (Micro Albuminuria Reduction with Valsartan) study assessed the reduction in urinary albumin excretion (UAE) with valsartan (80-160 mg/od) versus amlodipine (5-10 mg/od), in 332 type 2 diabetic patients (mean age: 58 years; 265 men) with microalbuminuria (valsartan: 58 µg/min; amlodipine: 55.4 µg/min), normal or high blood pressure and with preserved renal function (blood creatinine <120 µmol/l). At 24 weeks, UAE was reduced (p <0.001) by 42% (−24.2 µg/min; 95% CI: −40.4 to −19.1) with valsartan and approximately 3% (−1.7 µg/min; 95% CI: −5.6 to 14.9) with amlodipine despite similar rates of blood pressure reduction in both groups. The Diovan Reduction of Proteinuria (DROP) study further examined the efficacy of valsartan in reducing UAE in 391 hypertensive patients (BP=150/88 mmHg) with type 2 diabetes, albuminuria (mean=102 µg/min; 20–700 µg/min) and preserved renal function (mean serum creatinine = 80 µmol/l). Patients were randomised to one of 3 doses of valsartan (160, 320 and 640 mg/od) and treated for 30 weeks. The purpose of the study was to determine the optimal dose of valsartan for reducing UAE in hypertensive patients with type 2 diabetes. At 30 weeks, the percentage change in UAE was significantly reduced by 36% from baseline with valsartan 160 mg (95%CI: 22 to 47%), and by 44% with valsartan 320 mg (95%CI: 31 to 54%). It was concluded that 160-320 mg of valsartan produced clinically relevant reductions in UAE in hypertensive patients with type 2 diabetes.

**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.

**Valsartan/hydrochlorothiazide**

In a double-blind, randomised, active-controlled trial in patients not adequately controlled on hydrochlorothiazide 12.5 mg, significantly greater mean systolic/diastolic BP reductions were observed with the combination of valsartan/hydrochlorothiazide 160/12.5 mg (12.4/7.5 mmHg) compared to hydrochlorothiazide 25 mg (5.6/2.1 mmHg). In addition, a significantly greater percentage of patients responded (BP <140/90 mmHg or SBP reduction ≥ 20 mmHg or DBP reduction ≥10 mmHg) with valsartan/hydrochlorothiazide 160/12.5 mg (50 %) compared to hydrochlorothiazide 25 mg (25 %).
In a double-blind, randomised, active-controlled trial in patients not adequately controlled on valsartan 160 mg, significantly greater mean systolic/diastolic BP reductions were observed with both the combination of valsartan/hydrochlorothiazide 160/25 mg (14.6/11.9 mmHg) and valsartan/hydrochlorothiazide 160/12.5 mg (12.4/10.4 mmHg) compared to valsartan 160 mg (8.7/8.8 mmHg). The difference in BP reductions between the 160/25 mg and the 160/12.5 mg doses also reached statistical significance. In addition, a significantly greater percentage of patients responded (diastolic BP <90 mmHg or reduction ≥10 mmHg) with valsartan/hydrochlorothiazide 160/25 mg (68%) and 160/12.5 mg (62%) compared to valsartan 160 mg (49%).

In a double-blind, randomised, placebo-controlled, factorial design trial comparing various dose combinations of valsartan/hydrochlorothiazide to their respective components, significantly greater mean systolic/diastolic BP reductions were observed with the combination of valsartan/hydrochlorothiazide 160/12.5 mg (17.8/13.5 mmHg) and 160/25 mg (22.5/15.3 mmHg) compared to placebo (1.9/4.1 mmHg) and the respective monotherapies, i.e., hydrochlorothiazide 12.5 mg (7.3/7.2 mmHg), hydrochlorothiazide 25 mg (12.7/9.3 mmHg) and valsartan 160 mg (12.1/9.4 mmHg). In addition, a significantly greater percentage of patients responded (diastolic BP <90 mmHg or reduction ≥10 mmHg) with valsartan/hydrochlorothiazide 160/25 mg (81%) and valsartan/hydrochlorothiazide 160/12.5 mg (76%) compared to placebo (29%) and the respective monotherapies, i.e., hydrochlorothiazide 12.5 mg (41%), hydrochlorothiazide 25 mg (54%) and valsartan 160 mg (59%).

5.2 Pharmacokinetic properties

Valsartan/hydrochlorothiazide

The systemic availability of hydrochlorothiazide is reduced by about 30% when co-administered with valsartan. The kinetics of valsartan are not markedly affected by the co-administration of hydrochlorothiazide. This observed interaction has no impact on the combined use of valsartan and hydrochlorothiazide, since controlled clinical trials have shown a clear anti-hypertensive effect, greater than that obtained with either active substance given alone, or placebo.

Valsartan

Absorption

Following oral administration of valsartan alone, peak plasma concentrations of valsartan are reached in 2–4 hours. Mean absolute bioavailability is 23%. Food decreases exposure (as measured by AUC) to valsartan by about 40% and peak plasma concentration (C_{max}) by about 50%, although from about 8 h post dosing plasma valsartan concentrations are similar for the fed and fasted groups. This reduction in AUC is not, however, accompanied by a clinically significant reduction in the therapeutic effect, and valsartan can therefore be given either with or without food.

Distribution

The steady-state volume of distribution of valsartan after intravenous administration is about 17 litres, indicating that valsartan does not distribute into tissues extensively. Valsartan is highly bound to serum proteins (94–97%), mainly serum albumin.

Biotransformation

Valsartan is not biotransformed to a high extent as only about 20% of dose is recovered as metabolites. A hydroxy metabolite has been identified in plasma at low concentrations (less than 10% of the valsartan AUC). This metabolite is pharmacologically inactive.

Elimination

Valsartan shows multiexponential decay kinetics (t_{1/2a} <1 h and t_{1/2b} about 9 h). Valsartan is primarily eliminated in faeces (about 83% of dose) and urine (about 13% of dose), mainly as unchanged drug. Following intravenous administration, plasma clearance of valsartan is about 2 l/h and its renal clearance is 0.62 l/h (about 30% of total clearance). The half-life of valsartan is 6 hours.
**Hydrochlorothiazide**

**Absorption**
The absorption of hydrochlorothiazide, after an oral dose, is rapid ($t_{max}$ about 2 h), with similar absorption characteristics for both suspension and tablet formulations. Absolute bioavailability of hydrochlorothiazide is 60–80 % after oral administration. Concomitant administration with food has been reported to both increase and decrease the systemic availability of hydrochlorothiazide compared with the fasted state. The magnitude of these effects is small and has minimal clinical importance. The increase in mean AUC is linear and dose proportional in the therapeutic range. There is no change in the kinetics of hydrochlorothiazide on repeated dosing, and accumulation is minimal when dosed once daily.

**Distribution**
The distribution and elimination kinetics have generally been described by a bi-exponential decay function. The apparent volume of distribution is 4–8 l/kg. Circulating hydrochlorothiazide is bound to serum proteins (40–70 %), mainly serum albumin. Hydrochlorothiazide also accumulates in erythrocytes at approximately 1.8 times the level in plasma.

**Elimination**
For hydrochlorothiazide, >95 % of the absorbed dose being excreted as unchanged compound in the urine. The renal clearance is composed of passive filtration and active secretion into the renal tubule. The terminal half-life is 6-15 h.

**Special populations**

**Elderly**
A somewhat higher systemic exposure to valsartan was observed in some elderly subjects than in young subjects; however, this has not been shown to have any clinical significance. Limited data suggest that the systemic clearance of hydrochlorothiazide is reduced in both healthy and hypertensive elderly subjects compared to young healthy volunteers.

**Renal impairment**
At the recommended dose of Valsartan/Hydrochlorothiazide Film-coated tablets no dose adjustment is required for patients with a creatinine clearance of 30-70mL/min.

In patients with severe renal impairment (creatinine clearance <30mL/min) and patients undergoing dialysis, no data are available for Valsartan/Hydrochlorothiazide Film-coated Tablets. Valsartan is highly bound to plasma protein and is not to be removed by dialysis, whereas clearance of hydrochlorothiazide will be achieved by dialysis.

Renal clearance of hydrochlorothiazide is composed of passive filtration and active secretion into the renal tubule. As expected for a compound which is cleared almost exclusively via the kidneys, renal function has a marked effect on the kinetics of hydrochlorothiazide (see Section 4.3).

**Hepatic impairment**
In a pharmacokinetics trial in patients with mild (n=6) to moderate (n=5) hepatic dysfunction, exposure to valsartan was increased approximately twofold compared with healthy volunteers. There are no data available on the use of valsartan in patients with severe hepatic dysfunction (see section 4.3). Hepatic disease does not significantly affect the pharmacokinetics of hydrochlorothiazide.

5.3 **Preclinical safety data**
The potential toxicity of the valsartan - hydrochlorothiazide combination after oral administration was investigated in rats and marmosets in studies lasting up to six months. No findings emerged that would exclude the use of therapeutic doses in man.

The changes produced by the combination in the chronic toxicity studies are most likely to have been caused by the valsartan component. The toxicological target organ was the kidney, the reaction being more marked in the marmoset than the rat. The combination led to kidney damage (nephropathy with tubular basophilia, rises in plasma urea, plasma creatinine and
serum potassium, increases in urine volume and urinary electrolytes from 30 mg/kg/day valsartan + 9 mg/kg/day hydrochlorothiazide in rats and 10 + 3 mg/kg/d in marmosets), probably by way of altered renal haemodynamics. These doses in rat, respectively, represent 0.9 and 3.5–times the maximum recommended human dose (MRHD) of valsartan and hydrochlorothiazide on a mg/m² basis. These doses in marmoset, respectively, represent 0.3 and 1.2–times the maximum recommended human dose (MRHD) of valsartan and hydrochlorothiazide on a mg/m² basis. (Calculations assume an oral dose of 320 mg/day valsartan in combination with 25 mg/day hydrochlorothiazide and a 60-kg patient.)

High doses of the valsartan - hydrochlorothiazide combination caused falls in red blood cell indices (red cell count, haemoglobin, haematocrit, from 100 + 31 mg/kg/d in rats and 30 + 9 mg/kg/d in marmosets). These doses in rat, respectively, represent 3.0 and 12 times the maximum recommended human dose (MRHD) of valsartan and hydrochlorothiazide on a mg/m² basis. These doses in marmoset, respectively, represent 0.9 and 3.5 times the maximum recommended human dose (MRHD) of valsartan and hydrochlorothiazide on a mg/m² basis. These doses in marmoset, respectively, represent 0.9 and 3.5 times the maximum recommended human dose (MRHD) of valsartan and hydrochlorothiazide on a mg/m² basis. (Calculations assume an oral dose of 320 mg/day valsartan in combination with 25 mg/day hydrochlorothiazide and a 60-kg patient).

In marmosets, damage was observed in the gastric mucosa (from 30 + 9 mg/kg/d). The combination also led in the kidney to hyperplasia of the afferent aterioles (at 600 + 188 mg/kg/d in rats and from 30 + 9 mg/kg/d in marmosets). These doses in marmoset, respectively, represent 0.9 and 3.5 times the maximum recommended human dose (MRHD) of valsartan and hydrochlorothiazide on a mg/m² basis. These doses in rat, respectively, represent 18 and 73 times the maximum recommended human dose (MRHD) of valsartan and hydrochlorothiazide on a mg/m² basis. (Calculations assume an oral dose of 320 mg/day valsartan in combination with 25 mg/day hydrochlorothiazide and a 60-kg patient).

The above mentioned effects appear to be due to the pharmacological effects of high valsartan doses (blockade of angiotensin II-induced inhibition of renin release, with stimulation of the renin-producing cells) and also occur with ACE inhibitors. These findings appear to have no relevance to the use of therapeutic doses of valsartan in humans.

The valsartan - hydrochlorothiazide combination was not tested for mutagenicity, chromosomal breakage or carcinogenicity, since there is no evidence of interaction between the two substances. However, these tests were performed separately with valsartan and hydrochlorothiazide, and produced no evidence of mutagenicity, chromosomal breakage or carcinogenicity.

In rats, maternally toxic doses of valsartan (600 mg/kg/day) during the last days of gestation and lactation led to lower survival, lower weight gain and delayed development (pinna detachment and ear-canal opening) in the offspring (see section 4.6). These doses in rats (600 mg/kg/day) are approximately 18 times the maximum recommended human dose on a mg/m² basis (calculations assume an oral dose of 320 mg/day and a 60-kg patient). Similar findings were seen with valsartan/hydrochlorothiazide in rats and rabbits. In embryo-fetal development (Segment II) studies with valsartan/hydrochlorothiazide in rat and rabbit, there was no evidence of teratogenicity; however, fetotoxicity associated with maternal toxicity was observed.

### 6 PHARMACEUTICAL PARTICULARS

#### 6.1 List of excipients

- Tablet core
- Microcrystalline Cellulose
- Lactose Monohydrate
- Croscarmellose Sodium
- Povidone K29-K32
- Talc
- Magnesium Stearate
- Colloidal Anhydrous Silica
Coating
Opadry II 85G23675 Orange:
Polyvinyl Alcohol
Talc
Titanium Dioxide (E171)
Macrogol 3350
Lecithin (E322)
Iron Oxide Red (E172)
Iron oxide yellow (E172)
Iron oxide black (E172)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
4 years for tablets packed in PVC/PE/PVDC-Al blisters
5 years for tablets packed in polyethylene tablet containers

6.4 Special precautions for storage
Tablets packed in PVC/PE/PVDC-Al blisters: Do not store above 30°C.
Tablets packed in polyethylene tablet containers: This medicinal product does not require any
special storage conditions.

6.5 Nature and contents of container
PVC/PE/PVDC-Al blisters and HDPE containers with PE closure.
Pack sizes of 7, 14, 28, 30, 56, 98 and 280 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements
Any unused or waste material should be disposed of in accordance to local requirements.

7 MARKETING AUTHORISATION HOLDER
Caduceus Pharma Limited
6th Floor
94 Wigmore Street
London
W1U 3RF
UK

8 MARKETING AUTHORISATION NUMBER(S)
PL 24668/0071
PL 24668/0074
PL 24668/0077

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
17/12/2010

10 DATE OF REVISION OF THE TEXT
17/12/2010
Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Valsartan/Hydrochlorothiazide Tablets are and what they are used for
2. Before you take Valsartan/Hydrochlorothiazide Tablets
3. How to take Valsartan/Hydrochlorothiazide Tablets
4. Possible side effects
5. How to store Valsartan/Hydrochlorothiazide Tablets
6. Further Information

What Valsartan/Hydrochlorothiazide Tablets are and what they are used for
Valsartan/Hydrochlorothiazide Tablets contain two active substances called valsartan and hydrochlorothiazide. Both of these substances are used to control high blood pressure (hypertension).

Valsartan belongs to a class of medicines called 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 raising your 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.

Valsartan/Hydrochlorothiazide is used to treat high blood pressure in patients who are 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 attack. Lowering your blood pressure to normal reduces the risk of developing these disorders.

Before you take Valsartan/Hydrochlorothiazide Tablets
Do not take Valsartan/Hydrochlorothiazide Tablets if:
- If you are allergic (hypersensitive) to valsartan or hydrochlorothiazide, its derivatives, sulphonamide derivatives (substances chemically related to hydrochlorothiazide), soy, cereal, wheat or barley, or any of the other ingredients of Valsartan/Hydrochlorothiazide Tablets.
- If you are more than 3 months pregnant, it is also better to avoid Valsartan/Hydrochlorothiazide Tablets in early pregnancy (see pregnancy section).
- If you have a severe liver disease.
- If you are unable to swallow.
- If you have an enlarged (enlarged) kidney or kidney failure.
- If the level of potassium in your blood is lower than normal, or if you have severe heart disease.
- If you have liver disease.

If any of the above apply to you, do not take this medicine and speak to your doctor.

Take special care with Valsartan/Hydrochlorothiazide Tablets
- If you are taking potassium-sparing medicines, potassium supplements, salt substitutes containing potassium or other medicines that increase the amount of potassium in your blood, such as heparin. Your doctor may need to check the amount of potassium in your blood.
- If you have low levels of potassium in your blood.
- If you have had an acute kidney injury.
- If you are taking diuretics or water tablets (diuretics).
- If you have severe heart disease.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
- If you have had a recent kidney injury.
UKPAR Valsartan/Hydrochlorothiazide 80/12.5, 160/12.5 & 160mg/25mg Film-coated Tablets  PL 24668/0069-77

3 HOW TO TAKE VALSARTAN/HYDROCHLOROTHIAZIDE TABLETS

Always take Valsartan/Hydrochlorothiazide tablets exactly as your doctor has told you. This will help you to get the best results and lower the risk of side effects. You should check with your doctor or pharmacist if you have not done so.

People with high blood pressure often do not notice any signs of this problem. Many may feel quite normal. This makes it even more important for you to keep your appointments with your doctor even if you feel well.

Your doctor will tell you exactly how many tablets of Valsartan/Hydrochlorothiazide to take. Depending on how you respond to the treatment, your doctor may suggest a higher or lower dose.

• The usual dose of Valsartan/Hydrochlorothiazide is one tablet per day.
• Do not change the dose or stop taking the tablets without consulting your doctor.
• The medicine should be taken at the same time each day, usually in the morning.
• You can take Valsartan/Hydrochlorothiazide Tablets with or without food.
• Swallow the tablet with a glass of water.

If you take more Valsartan/Hydrochlorothiazide Tablets than you should:

• If you experience severe dizziness and/or fainting lay down and remain still.

If you have accidentally taken too many tablets, contact your doctor, pharmacist or hospital.

If you forget to take Valsartan/Hydrochlorothiazide Tablets:

• If you forget to take a dose, take it as soon as you remember. However, if it is almost time for your next dose, skip the dose you missed.
• Do not take a double dose to make up for a forgotten dose.

If you stop taking Valsartan/Hydrochlorothiazide Tablets:

• Stopping your treatment with Valsartan/Hydrochlorothiazide may cause your blood pressure to get worse. Do not stop taking your medicine unless your doctor tells you to.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4 POSSIBLE SIDE EFFECTS

Like all medicines, Valsartan/Hydrochlorothiazide can cause side effects, although not everybody gets them.

These side effects may occur with certain frequencies, which are defined as follows:

• very common: affects more than 1 in 10 people
• common: affects 1 in 10 to 1 in 100 people
• uncommon: affects 1 in 100 to 1 in 1000 people
• rare: affects less than 1 in 1000 people

Not known: frequency cannot be estimated from the available data

Some side effects can be serious and need immediate medical attention:

• You should see your doctor immediately if you experience symptoms of angioedema, such as:
  • swelling in face, tongue or pharynx
  • difficulty in breathing
• Swelling of arms, legs or face

Other side effects include:

• cough
• low blood pressure
• light-headedness
• diarrhea (with signs of thirst, dry mouth and tongue, infrequent urination, dark coloured urine, dry skin)
• muscle pain
• weakness
• feeling or numbness
• blurred vision
• skin rash (e.g. itching, burning in ears)

Very rare:

• abnormality
• joint pain

Not known:

• dizziness
• breathing difficulty
• dryness of mouth or nose
• dry mouth
• low blood pressure
• low levels of uric acid in the blood
• low levels of bone salts in the blood
• loss of bone density

• level of blood sugars in the blood
• level of blood sodium levels in the blood
• level of blood potassium in the blood (sometimes with muscle weakness, nausea, vomiting, heart palpitations, convulsions, problems in breathing)

• allergic reactions (such as rash, itching, fever, inflammation of the mouth, throat and/ or nose)
• low levels of blood sugars in the blood

The most common side effects are:

• high level of potassium in the blood (sometimes with muscle spasms, abnormal heart rhythm)
• allergic reactions (such as rash, itching, fever, difficulty breathing or swallowing, difficulty in breathing, swelling of the face, tongue, lips or throat)
• swelling of the face, tongue, lips or throat
• elevation of liver function values
• the levels of haemoglobin (Hb) decreased and the percentage of red blood cells decreased in the blood (which will rarely causes, in severe cases, triggers an anemia)
• kidney failure
• fluid retention
• fever
• sweats and blisters of the skin (due to increased sensitivity to sunlight)
• constipation, discomfort of the stomach or bowels, liver disorders (yellow skin or eyes)
• irregular heart beat
• headache
• sleep disturbances
• anemia (depression)
• low level of blood platelets (sometimes with bleeding or bruising under the skin)

Very rare:

• Inflammation of blood vessels with symptoms such as red, purple, red or brown skin, fever
• itching or rash
• blistering of the lips, eyes or mouth
• skin peeling
• fever
• facial rash associated with joint pain
• muscle disorder
• severe upper stomach pain or loss of levels of different blood cells
• severe allergic reactions
• difficulty breathing
• lung infection
• breathlessness

If any of these side effects get worse, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5 HOW TO STORE VALSARTAN/HYDROCHLOROTHIAZIDE TABLETS

Keep out of reach of children.

• Do not use Valsartan/Hydrochlorothiazide after the expiry date which is stated on the pack or blister. The expiry date refers to the last day of that month.
• Pesticides, detergents: Do not store above 30°C.
• Do not use any Valsartan/Hydrochlorothiazide pack that is damaged or shows signs of tampering.

Medicines should not be disposed of via household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6 FURTHER INFORMATION

What Valsartan/Hydrochlorothiazide Tablets contain:

The active substances are Valsartan and Hydrochlorothiazide.

Valsartan: Hydrochlorothiazide 80/12.5 mg tablets:
Each film-coated tablet contains 80 mg of valsartan and 12.5 mg of hydrochlorothiazide.

Valsartan: Hydrochlorothiazide 160/25 mg tablets:
Each film-coated tablet contains 160 mg of valsartan and 25 mg of hydrochlorothiazide.

The other ingredients are:
Sodium, microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, povidone K30, talc, magnesium stearate, colloidal silicon dioxide.

Film Coating:
Valstar: Hydrochlorothiazide 80/12.5 mg tablets: Polyvinyl alcohol, Talc, titanium dioxide (E171), Macrogol 3350, hydroxypropyl cellulose (contains soy) (E463), Talc, Iron oxide red (E172), Iron Oxide Black (E172).

Valstar: Hydrochlorothiazide 160/25 mg tablets: Polyvinyl alcohol, Talc, titanium dioxide (E171), iron oxide red (E172), sunset yellow FCF aluminium lake (E110), colloidal calcium carbonate (contains soy) (E522).

Valstar: Hydrochlorothiazide 160/25 mg tablets: Polyvinyl alcohol, Talc, titanium dioxide (E171), Macrogol 3350, hydroxypropyl cellulose (contains soy) (E463), Talc, Iron oxide red (E172), Iron Oxide Black (E172).

Valstar: Hydrochlorothiazide 160/25 mg tablets: Polyvinyl alcohol, Talc, titanium dioxide (E171), Macrogol 3350, hydroxypropyl cellulose (contains soy) (E463), Talc, Iron oxide red (E172), Iron Oxide Black (E172).

What Valsartan/Hydrochlorothiazide Tablets look like and contents of the pack:

Valsartan: Hydrochlorothiazide 80/12.5 mg tablets: Pink oval, biocoat film-coated tablets, 11 x 5 mm, marked “V” on one side and “12.5” on the other.

Valsartan: Hydrochlorothiazide 160/25 mg tablets: Red, oval, biocoat film-coated tablets, 15 x 6 mm, marked “V” on one side and “25” on the other.

Valsartan: Hydrochlorothiazide 180/25 mg tablets: Orange, oval, biocoat film-coated tablets, 15 x 6 mm, marked “V” on one side and “180” on the other.

All strengths are available in blister packs of 7, 14, 28, 30, 56, 98 and 280 tablets.

Not all pack sizes may be marked.

Marketing Authorisation Holder:
CROUSE CECIL PHARMACEUTICALS LIMITED, 36 Wolf, 94 Wigan Street, London, W11 3HT, UK.

Manufacturer:
Balkanpharm - Dupata AD 3 Samokovlovo Schoule Str, Dupata, 2300, Bulgaria.

This leaflet was last updated in September 2018.
LABELLING

Please note that representative labelling for Valsartan/ Hydrochlorothiazide 80 mg/12.5 mg Film-coated Tablets, PL 24668/0069, are shown below. The labelling text details for Valsartan/ Hydrochlorothiazide 160 mg/12.5 mg Film-coated Tablets, PL 24668/0072 and PL 24668/0075, are consistent with these labels, with the exception of the product licence numbers.
Please note that representative labelling for Valsartan/ Hydrochlorothiazide 160 mg/12.5 mg Film-coated Tablets, PL 24668/0070, are shown below. The labelling text details for Valsartan/ Hydrochlorothiazide 160 mg/12.5 mg Film-coated Tablets, PL 24668/0073 and PL 24668/0076, are consistent with these labels, with the exception of the product licence numbers.
Please note that representative labelling for Valsartan/Hydrochlorothiazide 160 mg/25 mg Film-coated Tablets, PL 24668/0071, are shown below. The labelling text details for Valsartan/Hydrochlorothiazide 160 mg/25 mg Film-coated Tablets, PL 24668/0074 and PL 24668/0077, are consistent with these labels, with the exception of the product licence numbers.