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VALSARTAN 40 MG, 80 MG AND 160 MG CAPSULES

PL 19156/0117-9

LAY SUMMARY

On 10th January 2012, the MHRA granted Jubilant Pharmaceuticals NV Marketing Authorisations (licences) for Valsartan 40 mg, 80 mg and 160 mg Capsules.

Valsartan 40 mg, 80 mg and 160 mg Capsules contain the active ingredient, valsartan. 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.

**Valsartan 80 mg and 160 mg Capsules are used to treat high blood pressure.**
High blood pressure increases the workload on the heart and arteries. If not treated it can damage the blood vessels of the brain, heart, and kidneys, and may result in a stroke, heart failure, or kidney failure. High blood pressure increases the risk of heart attacks. Lowering blood pressure to normal reduces the risk of developing these disorders.

**Valsartan 40 mg, 80 mg and 160 mg Capsules are also used to treat symptomatic heart failure.** Valsartan is used when a group of medicines called Angiotensin Converting Enzyme (ACE) inhibitors (a medication to treat heart failure) cannot be used or it may be used in addition to ACE inhibitors when beta blockers (another medication to treat heart failure) cannot be used. Heart failure symptoms include shortness of breath, and swelling of the feet and legs due to fluid build-up. It is caused when the heart muscle cannot pump blood strongly enough to supply all the blood needed throughout the body.

Valsartan is not recommended for use in children below the age of 18 years of age.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Valsartan 40 mg, 80 mg and 160 mg Capsules outweigh the risks; hence Marketing Authorisations have been granted.
VALSARTAN 40 MG, 80 MG AND 160 MG CAPSULES

PL 19156/0117-9

SCIENTIFIC DISCUSSION

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Overall conclusions and risk benefit assessment Page 11
INTRODUCTION

The UK granted Jubilant Pharmaceuticals NV Marketing Authorisations for the medicinal products Valsartan 40 mg, 80 mg and 160 mg Capsules (PL 19156/0117-9) on 10th January 2012.

Valsartan 40 mg, 80 mg and 160 mg Capsules are prescription only medicines (POM) and are indicated for the treatment of essential hypertension in adults.

Valsartan 80 mg and 160 mg Capsules are also indicated for the treatment of symptomatic heart failure when Angiotensin Converting Enzyme (ACE) inhibitors cannot be used, or as add-on therapy to ACE inhibitors when beta blockers cannot be used.

Valsartan is not recommended for use in children below the age of 18 years of age.

These applications for Valsartan 40 mg, 80 mg and 160 mg Capsules are submitted under Article 10.1 of Directive 2001/83/EC, claiming to be generic medicinal products to Diovan 80 mg Capsules authorised in Germany to Novartis Pharma GmBH on 13th May 1996.

The UK reference products are Diovan 40 mg, 80 mg and 160 mg Capsules first authorised to Ciba-Geigy PLC MOD (PL 00001/0225 and PL 00001/0218-9). These licences then underwent a change of ownership to Novartis Pharmaceuticals UK Limited on 31st October 1997 (PL 00101/0524-6).

Valsartan is an orally active, potent, 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.

The pharmacovigilance system as described by the Marketing Authorisation Holder (MAH) fulfils the requirements and provides adequate evidence that the MAH 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.

A satisfactory justification was provided for the absence of a Risk Management Plan.
PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE
INN: Valsartan

Chemical name: (2S)-3-methyl-2-[N-([4-[2-(2H-1,2,3,4-tetrazol-5 yl)phenyl]phenyl]methyl)pentanamido]butanoic acid

Structure:

```
\begin{center}
\includegraphics[width=0.5\textwidth]{structure.png}
\end{center}
```

Physical form: A white or almost white hygroscopic powder.

Solubility: Practically insoluble in water, freely soluble in anhydrous ethanol, sparingly soluble in methylene chloride.

Molecular formula: C_{24}H_{29}N_{5}O_{3}
Molecular weight: 435.52

Valsartan complies with its 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.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised. Satisfactory Certificates of Analysis have been provided for all working standards. Batch analysis data are provided and comply with the proposed specification.

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

Stability studies have been performed with the active substance and no significant changes of the parameters were observed. On the basis of the results, a suitable re-test period could be approved.
**DRUG PRODUCT**

**Other ingredients**

Other ingredients are pharmaceutical excipients microcrystalline cellulose (E460), povidone (E1201), crospovidon (E1202), sodium laurilsulfate and magnesium stearate (E470b).

All the ingredients comply with their relevant European Pharmacopoeia monographs.

With the exception of magnesium stearate, none of the excipients used contain material of animal or human origin. The supplier of magnesium stearate has supplied a valid transmissible spongiform encephalopathy (TSE) free certificate.

**Pharmaceutical Development**

The objective of the development programme was to produce safe, efficacious products containing valsartan that could be considered generic medicinal products of Diovan 40 mg, 80 mg and 160 mg Capsules.

The applicant has provided suitable product development information. Valid justifications for the use and amounts of each excipient have been provided.

Comparative *in vitro* dissolution profiles have been provided for the proposed and reference products.

**Manufacturing Process**

A satisfactory batch formula has been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. Process validation data on pilot batches of each strength have been provided and are satisfactory.

The applicant has committed to perform process validation on future commercial-scale batches.

**Finished Product Specification**

The finished product specifications are acceptable. 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 products are packaged in blisters composed of:

i) aluminium, polyvinyl chloride (PVC) and polyvinylidene chloride (PVdC)

ii) aluminium, orientated polyamide (OPA) and PVC

The blisters are then packaged into cardboard boxes. Pack sizes are 7 and 28 capsules.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. EC Directive and food grade certificates have also been provided.

**Stability of the product**

Stability studies were performed on batches of the finished products in the packaging proposed for marketing and in accordance with current guidelines. These data support a shelf-life of 2 years with the storage instructions ‘Store below 30°C’ and ‘Store in the original package in order to protect from moisture’. This is satisfactory.
Summary of Product Characteristics (SmPCs), Patient Information Leaflet (PILs) and Labelling
The SmPCs, PILs and labelling are pharmaceutically acceptable. The UK approved SmPCs, PILs and label text are included in modules 2, 3 and 4 of this report.

User testing results have been submitted with a satisfactory bridging report. The results indicate that the PIL 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
These are pharmaceutically satisfactory.

Quality Overall Summary
The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion
From a quality point of view, it is recommended that Marketing Authorisations are granted for these applications.
NON-CLINICAL ASSESSMENT

No new non-clinical data have been supplied with these applications and none are required for applications of this type.

The non-clinical overview has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

A satisfactory justification was provided for the absence of an Environmental Risk Assessment.
CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY
To support the applications, the Marketing Authorisation Holder has included a single bioequivalence study:

An open label, single dose, randomized, four-period, two-treatment, two-sequence, crossover bioequivalence study comparing the pharmacokinetics of Valsartan 160 mg Capsules (Test) versus Diovan (valsartan) 160 mg Capsules (Novartis Pharmaceuticals UK Limited, UK) (Reference) in healthy volunteers under fasting conditions.

Blood sampling was performed pre-dose and at set time-points up to 48 hours post dose in each treatment period. There was a washout period of 8 days. Pharmacokinetic parameters were calculated and statistically analysed.

Results from this study are presented below as log-transformed values:

Geometric Least Mean Squares and 90% Confidence Interval

<table>
<thead>
<tr>
<th>Pharmacokinetic parameters of valsartan</th>
<th>Treatment</th>
<th>AUC_{0-\infty} (ng.hr/mL)</th>
<th>AUC_{0-t} (ng.hr/mL)</th>
<th>C_{max} (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>30972.05</td>
<td>31815.17</td>
<td>5010.34</td>
<td></td>
</tr>
<tr>
<td>Reference</td>
<td>28164.25</td>
<td>29046.91</td>
<td>4465.55</td>
<td></td>
</tr>
<tr>
<td>Ratio (90% CI)</td>
<td>109.97</td>
<td>102.386 – 118.114</td>
<td>109.53</td>
<td></td>
</tr>
<tr>
<td></td>
<td>102.386 – 118.114</td>
<td>102.021 – 117.592</td>
<td>112.20</td>
<td></td>
</tr>
<tr>
<td></td>
<td>102.021 – 117.592</td>
<td>103.473 – 121.663</td>
<td>113.20</td>
<td></td>
</tr>
</tbody>
</table>

AUC_{0-\infty} area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration

The results for the primary variables indicated that the 90% confidence intervals test/reference ratio of geometric means for AUC_{0-t} and C_{max} for valsartan lie within the normal 80-125% limits. Thus, bioequivalence has been shown between the test and reference products.

As the 160 mg capsule strength meet all the criteria as specified in the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1), the results and conclusions of the bioequivalence study on the 160 mg strength can be extrapolated to Valsartan 40 mg and 80 mg Capsules.

Efficacy
These are generic applications based on demonstration of bioequivalence and new data relating to efficacy are not required as per EU legislation once bioequivalence has been demonstrated.

Safety
These are generic applications based on demonstration of bioequivalence and new data relating to safety are not required as per EU legislation once bioequivalence has been demonstrated.
Summary of Product Characteristics (SmPCs), Patient Information Leaflet (PILs) and Labelling
The SmPCs, PILs and labelling are clinically satisfactory and consistent with those for the reference products.

MAA Forms
The MAA forms are clinically satisfactory.

Clinical Overview
The clinical expert report has been written by a suitably qualified person and is satisfactory.

Conclusion
The bioequivalence study has shown that Valsartan 40 mg, 80 mg and 160 mg Capsules can be considered as generic medicinal products to the reference products Diovan 40 mg, 80 mg and 160 mg Capsules.

From a clinical point of view, it is recommended that Marketing Authorisations are granted for these applications.
OVERALL CONCLUSIONS AND RISK BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Valsartan 40 mg, 80 mg and 160 mg Capsules 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 and none are required for applications of this type.

EFFICACY
Bioequivalence has been demonstrated between the applicant’s Valsartan 160 mg Capsules and the reference product, Diovan 160 mg Capsules.
This conclusion can be extrapolated to Valsartan 40 mg, 80 mg Capsules.

No new or unexpected safety concerns arise from these applications.

The SmPCs, PILs and labelling are satisfactory and consistent with those for the reference products.

RISK BENEFIT ASSESSMENT
The quality of the products is acceptable and no new non-clinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant’s products and the reference products are interchangeable. Clinical experience with valsartan is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.
## STEPS TAKEN FOR ASSESMENT

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>The MHRA received the Marketing Authorisation Applications on 24&lt;sup&gt;th&lt;/sup&gt; December 2010.</td>
</tr>
<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the applications valid on 4&lt;sup&gt;th&lt;/sup&gt; February 2011.</td>
</tr>
<tr>
<td>3</td>
<td>Following assessment of the application, the MHRA requested further information relating to the clinical and quality dossier on 13&lt;sup&gt;th&lt;/sup&gt; May 2011.</td>
</tr>
<tr>
<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information on 10&lt;sup&gt;th&lt;/sup&gt; August 2011 for the clinical and quality section.</td>
</tr>
<tr>
<td>5</td>
<td>The applications were determined on 10&lt;sup&gt;th&lt;/sup&gt; January 2012.</td>
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</table>
# STEPS TAKEN AFTER AUTHORISATION - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
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<tr>
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</tbody>
</table>
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Valsartan 40 mg capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each capsule contains 40 mg valsartan.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Capsules, hard.
Light grey coloured cap and body, size ‘3’ hard gelatine capsules, printed in black ink with “40” on cap, containing white to off white granular powder.

4 CLINICAL PARTICULARS
4.1 THERAPEUTIC INDICATIONS
Heart failure
Treatment of symptomatic heart failure when Angiotensin Converting Enzyme (ACE) inhibitors cannot be used, or as add-on therapy to ACE inhibitors when beta blockers cannot be used (see sections 4.4 and 5.1).

4.2 POSOLOGY AND METHOD OF ADMINISTRATION
Posology
Heart failure
The recommended starting dose of Valsartan is 40 mg twice daily. Uptitration to 80 mg and 160 mg twice daily should be done at intervals of at least two weeks to the highest dose, as tolerated by the patient. Consideration should be given to reducing the dose of concomitant diuretics. The maximum daily dose administered in clinical trials is 320 mg in divided doses.
Valsartan may be administered with other heart failure therapies. However, the triple combination of an ACE inhibitor, a beta blocker and valsartan is not recommended (see sections 4.4 and 5.1).
Evaluation of patients with heart failure should always include assessment of renal function.

Method of administration
Valsartan may be taken independently of a meal and should be administered with water.

Additional information on special populations
Elderly
No dose adjustment is required in elderly patients.

Renal impairment
No dosage adjustment is required for patients with a creatinine clearance >10 ml/min (see sections 4.4 and 5.2)

Hepatic impairment
Valsartan is contraindicated in patients with severe hepatic impairment, biliary cirrhosis and in patients with cholestasis (see sections 4.3, 4.4 and 5.2). In patients with mild to moderate hepatic impairment without cholestasis, the dose of valsartan should not exceed 80 mg.

Paediatric population
Valsartan is 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 the active substance or to any of the excipients.
- Severe hepatic impairment, biliary cirrhosis and cholestasis.
Second and third trimester of pregnancy (see sections 4.4 and 4.6).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE
Hyperkalaemia
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.
Sodium- and/or volume-depleted patients
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. Sodium and/or volume depletion should be corrected before starting treatment with Valsartan, for example by reducing the diuretic dose.

Renal artery stenosis
In patients with bilateral renal artery stenosis or stenosis to a solitary kidney, the safe use of Valsartan has not been established. Short-term administration of valsartan to twelve patients with renovascular hypertension secondary to unilateral renal artery stenosis did not induce any significant changes in renal haemodynamics, serum creatinine, or blood urea nitrogen (BUN). However, other agents that affect the renin-angiotensin system may increase blood urea and serum creatinine in patients with unilateral renal artery stenosis, therefore monitoring of renal function is recommended when patients are treated with valsartan.

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

Primary hyperaldosteronism
Patients with primary hyperaldosteronism should not be treated with Valsartan as their renin-angiotensin system is not activated.

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

Impaired renal function
No dosage adjustment is required for adult patients with a creatinine clearance >10 ml/min. There is currently no experience on the safe use in patients with a creatinine clearance <10 ml/min and patients undergoing dialysis, therefore valsartan should be used with caution in these patients (see sections 4.2 and 5.2).

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

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).

Recent myocardial infarction
The combination of captopril and valsartan has shown no additional clinical benefit, instead the risk for adverse events increased compared to treatment with the respective therapies (see sections 4.2 and 5.1). Therefore, the combination of valsartan with an ACE inhibitor is not recommended.

Caution should be observed when initiating therapy in post-myocardial infarction patients. Evaluation of post-myocardial infarction patients should always include assessment of renal function (see section 4.2).

Use of valsartan in post-myocardial infarction patients commonly results in some reduction in blood pressure, but discontinuation of therapy because of continuing symptomatic hypotension is not usually necessary provided dosing instructions are followed (see section 4.2).

Heart Failure
In patients with heart failure, the triple combination of an ACE inhibitor, a beta blocker and valsartan has not shown any clinical benefit (see section 5.1). This combination apparently increases the risk for adverse events and is therefore not recommended.
Caution should be observed when initiating therapy in patients with heart failure. Evaluation of patients with heart failure should always include assessment of renal function (see section 4.2).

Use of valsartan in patients with heart failure commonly results in some reduction in blood pressure, but discontinuation of therapy because of continuing symptomatic hypotension is not usually necessary provided dosing instructions are followed (see section 4.2).

In patients whose renal function may depend on the activity of the renin-angiotensin 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 and/or death. As valsartan is an angiotensin II antagonist, it cannot be excluded that the use of Valsartan may be associated with impairment of the renal function.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Concomitant use not recommended

Lithium
Reversible increases in serum lithium concentrations and toxicity have been reported during concurrent use of ACE inhibitors. 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.

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.

Caution required with concomitant use

Non-steroidal anti-inflammatory medicines (NSAIDs), including selective COX-2 inhibitors, acetylsalicylic acid >3 g/day, and non-selective NSAIDs
When angiotensin II antagonists are administered simultaneously with NSAIDs, attenuation of the antihypertensive effect may occur. Furthermore, concomitant use of angiotensin II antagonists and NSAIDs may lead to an increased risk of 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.

Others
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.

4.6 FERTILITY, PREGNANCY AND LACTATION

Pregnancy
The use of Angiotensin II Receptor Antagonists (AIIRAs) is not recommended during the 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 AIIRAs, similar risks may exist for this class of drugs. Unless continued AIIRA 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, hyperkalemia); 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 sections 4.3 and 4.4).
**Lactation**
Because no information is available regarding the use of valsartan during breastfeeding, Valsartan is not recommended and alternative treatments with better established safety profiles during breastfeeding are preferable, especially while nursing a newborn or preterm infant.

**Fertility**
Valsartan had no adverse effects on the reproductive performance of male or female rats at oral doses up to 200 mg/kg/day. This dose is 6 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).

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
No studies on the effects on the ability to drive 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
In controlled clinical studies in patients with hypertension, the overall incidence of adverse reactions (ADRs) was comparable with placebo and is consistent with the pharmacology of valsartan. The incidence of ADRs did not appear to be related to dose or treatment duration and also showed no association with gender, age or race.

The ADRs reported from clinical studies, post-marketing experience and laboratory findings are listed below according to system organ class.

Adverse 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), including isolated reports. Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.

For all the ADRs reported from post-marketing experience and laboratory findings, it is not possible to apply any ADR frequency and therefore they are mentioned with a "not known" frequency.

- **Hypertension**

<table>
<thead>
<tr>
<th>Blood and lymphatic system disorders</th>
<th>Not known</th>
<th>Decrease in haemoglobin, Decrease in haematocrit, Neutropenia, Thrombocytopenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune system disorders</td>
<td>Not known</td>
<td>Hypersensitivity including serum sickness</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Not known</td>
<td>Increase of serum potassium, Hyponatraemia</td>
</tr>
<tr>
<td>Ear and labyrinth system disorders</td>
<td>Uncommon</td>
<td>Vertigo</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Not known</td>
<td>Vasculitis</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Uncommon</td>
<td>Cough</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Uncommon</td>
<td>Abdominal pain</td>
</tr>
<tr>
<td>Hepato-biliary disorders</td>
<td>Not known</td>
<td>Elevation of liver function values including increase of serum bilirubin</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Not known</td>
<td>Angioedema, Rash, Pruritus</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Not known</td>
<td>Myalgia</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Not known</td>
<td>Renal failure and impairment, Elevation of serum creatinine</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Uncommon</td>
<td>Fatigue</td>
</tr>
</tbody>
</table>
The safety profile seen in controlled-clinical studies in patients with post-myocardial infarction and/or heart failure varies from the overall safety profile seen in hypertensive patients. This may relate to the patients underlying disease. ADRs that occurred in post-myocardial infarction and/or heart failure patients are listed below:

- **Post-myocardial infarction and/or heart failure (studied in adult patients only)**

<table>
<thead>
<tr>
<th>Blood and lymphatic system disorders</th>
<th>Thrombocytopenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune system disorders</td>
<td>Hypersensitivity including serum sickness</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Hyperkalaemia</td>
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<td></td>
<td>Increase of serum potassium</td>
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<tr>
<td></td>
<td>Hyponatraemia</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Dizziness, Postural dizziness</td>
</tr>
<tr>
<td></td>
<td>Syncope, Headache</td>
</tr>
<tr>
<td>Ear and labyrinth system disorders</td>
<td>Vertigo</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Cardiac failure</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Hypotension, Orthostatic hypotension</td>
</tr>
<tr>
<td></td>
<td>Vasculitis</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Cough</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Nausea, Diarrhoea</td>
</tr>
<tr>
<td>Hepato-biliary disorders</td>
<td>Elevation of liver function values</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Angioedema</td>
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<td></td>
<td>Rash, Pruritis</td>
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<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Myalgia</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Renal failure and impairment</td>
</tr>
<tr>
<td></td>
<td>Acute renal failure, Elevation of serum creatinine</td>
</tr>
<tr>
<td></td>
<td>Increase in Blood Urea Nitrogen</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Asthenia, Fatigue</td>
</tr>
</tbody>
</table>

### 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.

**Treatment**

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

If hypotension occurs, the patient should be placed in a supine position and blood volume correction should be undertaken.

Valsartan is unlikely to be removed by haemodialysis.

### 5 PHARMACOLOGICAL PROPERTIES

#### 5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Angiotensin II Antagonists, plain, ATC code: C09CA03

Valsartan is an orally active, potent, and specific angiotensin II (Ang II) receptor antagonist. It acts selectively on the AT\(_1\) receptor subtype, which is responsible for the known actions of angiotensin II.

The increased plasma levels of Ang II following AT\(_1\) receptor blockade with valsartan may stimulate
the unblocked 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) less 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).

Recent myocardial infarction
The VALsartan In Acute myocardial iNfarcTion trial (VALIANT) was a randomised, controlled, multinational, double-blind study in 14,703 patients with acute myocardial infarction and signs, symptoms or radiological evidence of congestive heart failure and/or evidence of left ventricular systolic dysfunction (manifested as an ejection fraction ≤40% by radionuclide ventriculography or ≤35% by echocardiography or ventricular contrast angiography). Patients were randomized within 12 hours to 10 days after the onset of myocardial infarction symptoms to valsartan, captopril, or the combination of both. The mean treatment duration was two years. The primary endpoint was time to all-cause mortality.

Valsartan was as effective as captopril in reducing all-cause mortality after myocardial infarction. All-cause mortality was similar in the valsartan (19.9%), captopril (19.5%), and valsartan + captopril (19.3%) groups. Combining valsartan with captopril did not add further benefit over captopril alone. There was no difference between valsartan and captopril in all-cause mortality based on age, gender, race, baseline therapies or underlying disease. Valsartan was also effective in prolonging the time to and reducing cardiovascular mortality, hospitalisation for heart failure, recurrent myocardial infarction, resuscitated cardiac arrest, and non-fatal stroke (secondary composite endpoint).

The safety profile of valsartan was consistent with the clinical course of patients treated in the post-myocardial infarction setting. Regarding renal function, doubling of serum creatinine was observed in 4.2% of valsartan-treated patients, 4.8% of valsartan+captopril-treated patients, and 3.4% of captopril-treated patients. Discontinuations due to various types of renal dysfunction occurred in 1.1% of valsartan-treated patients, 1.3% in valsartan+captopril patients, and 0.8% of captopril patients. An assessment of renal function should be included in the evaluation of patients post-myocardial infarction.

There was no difference in all-cause mortality, cardiovascular mortality or morbidity when beta blockers were administered together with the combination of valsartan + captopril, valsartan alone, or captopril alone. Irrespective of treatment, mortality was lower in the group of patients treated with a beta blocker, suggesting that the known beta blocker benefit in this population was maintained in this trial.

Heart failure
Val-HeFT was a randomised, controlled, multinational clinical trial of valsartan compared with placebo on morbidity and mortality in 5,010 NYHA class II (62%), III (36%) and IV (2%) heart failure patients receiving usual therapy with LVEF <40% and left ventricular internal diastolic diameter (LVIDD) ≥2.9 cm/m². Baseline therapy included ACE inhibitors (93%), diuretics (86%), digoxin (67%) and beta blockers (36%). The mean duration of follow-up was nearly two years. The mean daily dose of valsartan in Val-HeFT was 254 mg. The study had two primary endpoints: all cause mortality (time to death) and composite mortality and heart failure morbidity (time to first morbid event) defined as death, sudden death with resuscitation, hospitalisation for heart failure, or administration of intravenous inotropic or vasodilator agents for four hours or more without hospitalisation. All cause mortality was similar (p=NS) in the valsartan (19.7%) and placebo (19.4%) groups. The primary benefit was a 27.5% (95% CI: 17 to 37%) reduction in risk for time to first heart failure hospitalisation (13.9% vs. 18.5%). Results appearing to favour placebo (composite mortality and morbidity was 21.9% in placebo vs. 25.4% in valsartan group) were observed for those patients receiving the triple combination of an ACE inhibitor, a beta blocker and valsartan.
In a subgroup of patients not receiving an ACE inhibitor (n=366), the morbidity benefits were greatest. In this subgroup all-cause mortality was significantly reduced with valsartan compared to placebo by 33% (95% CI: -6% to 58%) (17.3% valsartan vs. 27.1% placebo) and the composite mortality and morbidity risk was significantly reduced by 44% (24.9% valsartan vs. 42.5% placebo).

In patients receiving an ACE inhibitor without a beta-blocker, all cause mortality was similar (p=NS) in the valsartan (21.8%) and placebo (22.5%) groups. Composite mortality and morbidity risk was significantly reduced by 18.3% (95% CI: 8% to 28%) with valsartan compared with placebo (31.0% vs. 36.3%).

In the overall Val-HeFT population, valsartan treated patients showed significant improvement in NYHA class, and heart failure signs and symptoms, including dyspnoea, fatigue, oedema and rales compared to placebo. Patients treated with valsartan had a better quality of life as demonstrated by change in the Minnesota Living with Heart Failure Quality of Life score from baseline at endpoint than placebo. Ejection fraction in valsartan treated patients was significantly increased and LVIDD significantly reduced from baseline at endpoint compared to placebo.

### 5.2 PHARMACOKINETIC PROPERTIES

**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.

**Excretion:**
Valsartan shows multieponential decay kinetics (t1/2α <1 h and t1/2β about 9 h). Valsartan is primarily eliminated by biliary excretion in faeces (about 83% of dose) and renally in 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.

In heart failure patients:
The average time to peak concentration and elimination half-life of valsartan in heart failure patients are similar to that observed in healthy volunteers. AUC and Cmax values of valsartan are essentially proportional with increasing dose over the clinical dosing range (40 to 160 mg twice a day). The average accumulation factor is about 1.7. The apparent clearance of valsartan following oral administration is approximately 4.5 l/h. Age does not affect the apparent clearance in heart failure patients.

**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.

**Impaired renal function**
As expected for a compound where renal clearance accounts for only 30% of total plasma clearance, no correlation was seen between renal function and systemic exposure to valsartan. Dose adjustment is therefore not required in patients with renal impairment (creatinine clearance >10 ml/min). There is currently no experience on the safe use in patients with a creatinine clearance <10 ml/min and patients undergoing dialysis, therefore valsartan should be used with caution in these patients (see sections 4.2 and 4.4). Valsartan is highly bound to plasma protein and is unlikely to be removed by dialysis.
Hepatic impairment
Approximately 70% of the dose absorbed is eliminated in the bile, essentially in the unchanged form. Valsartan does not undergo any noteworthy biotransformation. A doubling of exposure (AUC) was observed in patients with mild to moderate hepatic impairment compared to healthy subjects. However, no correlation was observed between plasma valsartan concentration versus degree of hepatic dysfunction. Valsartan has not been studied in patients with severe hepatic dysfunction (see sections 4.2, 4.3 and 4.4).

5.3 PRECLINICAL SAFETY DATA
Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential. In rats, maternally toxic doses (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).

In non-clinical safety studies, high doses of valsartan (200 to 600 mg/kg body weight) caused in rats a reduction of red blood cell parameters (erythrocytes, haemoglobin, haematocrit) and evidence of changes in renal haemodynamics (slightly raised plasma urea, and renal tubular hyperplasia and basophilia in males). These doses in rats (200 and 600 mg/kg/day) are approximately 6 and 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).

In marmosets at similar doses, the changes were similar though more severe, particularly in the kidney where the changes developed to a nephropathy which included raised urea and creatinine. Hypertrophy of the renal juxtaglomerular cells was also seen in both species. All changes were considered to be caused by the pharmacological action of valsartan which produces prolonged hypotension, particularly in marmosets. For therapeutic doses of valsartan in humans, the hypertrophy of the renal juxtaglomerular cells does not seem to have any relevance.

6 PHARMACEUTICAL PARTICULARS
6.1 LIST OF EXCIPIENTS
Microcrystalline cellulose (E460)
Povidone (E1201)
Crospovidon (E1202)
Sodium Laurylsulfate
Magnesium stearate (E470b)

6.2 INCOMPATIBILITIES
Not applicable.

6.3 SHELF LIFE
2 years.

6.4 SPECIAL PRECAUTIONS FOR STORAGE
Store below 30°C. Store in the original package in order to protect from moisture.

6.5 NATURE AND CONTENTS OF CONTAINER
Cardboard boxes containing blisters (Al/PVC/PVdC or Al/OPA/Al/PVC) with 7 or 28 capsules. Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Jubilant Pharmaceuticals nv
Axxes Business Park
Guldensporenpark 22 – Block C
9820 Merelbeke
Belgium
8 MARKETING AUTHORISATION NUMBER(S)
   PL 19156/0117

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
   10/01/2012

10 DATE OF REVISION OF THE TEXT
    10/01/2012
1 NAME OF THE MEDICINAL PRODUCT
Valsartan 80 mg capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each capsule contains 80 mg valsartan.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Capsules, hard.
Light grey coloured cap and flesh opaque coloured body, size ‘2’ hard gelatine capsules, printed in black ink with ‘80’ on cap, containing white to off white granular powder.

4 CLINICAL PARTICULARS
4.1 THERAPEUTIC INDICATIONS
Hypertension
Treatment of essential hypertension in adults.

Heart failure
Treatment of symptomatic heart failure when Angiotensin Converting Enzyme (ACE) inhibitors cannot be used, or as add-on therapy to ACE inhibitors when beta blockers cannot be used (see sections 4.4 and 5.1).

4.2 POSOLOGY AND METHOD OF ADMINISTRATION
Posology
Heart failure
The recommended starting dose of Valsartan is 40 mg twice daily. Uptitration to 80 mg and 160 mg twice daily should be done at intervals of at least two weeks to the highest dose, as tolerated by the patient. Consideration should be given to reducing the dose of concomitant diuretics. The maximum daily dose administered in clinical trials is 320 mg in divided doses.
Valsartan may be administered with other heart failure therapies. However, the triple combination of an ACE inhibitor, a beta blocker and valsartan is not recommended (see sections 4.4 and 5.1). Evaluation of patients with heart failure should always include assessment of renal function.

Method of administration
Valsartan may be taken independently of a meal and should be administered with water.

Additional information on special populations
Elderly
No dose adjustment is required in elderly patients.

Renal impairment
No dosage adjustment is required for patients with a creatinine clearance >10 ml/min (see sections 4.4 and 5.2)

Hepatic impairment
Valsartan is contraindicated in patients with severe hepatic impairment, biliary cirrhosis and in patients with cholestasis (see sections 4.3, 4.4 and 5.2). In patients with mild to moderate hepatic impairment without cholestasis, the dose of valsartan should not exceed 80 mg.

Paediatric population
Valsartan is 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 the active substance or to any of the excipients.
- Severe hepatic impairment, biliary cirrhosis and cholestasis.
Second and third trimester of pregnancy (see sections 4.4 and 4.6).
4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

**Hyperkalaemia**
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.

**Sodium- and/or volume-depleted patients**
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. Sodium and/or volume depletion should be corrected before starting treatment with Valsartan, for example by reducing the diuretic dose.

**Renal artery stenosis**
In patients with bilateral renal artery stenosis or stenosis to a solitary kidney, the safe use of Valsartan has not been established.
Short-term administration of valsartan to twelve patients with renovascular hypertension secondary to unilateral renal artery stenosis did not induce any significant changes in renal haemodynamics, serum creatinine, or blood urea nitrogen (BUN). However, other agents that affect the renin-angiotensin system may increase blood urea and serum creatinine in patients with unilateral renal artery stenosis, therefore monitoring of renal function is recommended when patients are treated with valsartan.

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

**Primary hyperaldosteronism**
Patients with primary hyperaldosteronism should not be treated with Valsartan as their renin-angiotensin system is not activated.

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

**Impaired renal function**
No dosage adjustment is required for adult patients with a creatinine clearance >10 ml/min. There is currently no experience on the safe use in patients with a creatinine clearance <10 ml/min and patients undergoing dialysis, therefore valsartan should be used with caution in these patients (see sections 4.2 and 5.2).

**Hepatic impairment**
In patients with mild to moderate hepatic impairment without cholestasis, Valsartan should be used with caution (see sections 4.2 and 5.2).

**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).

**Recent myocardial infarction**
The combination of captopril and valsartan has shown no additional clinical benefit, instead the risk for adverse events increased compared to treatment with the respective therapies (see sections 4.2 and 5.1). Therefore, the combination of valsartan with an ACE inhibitor is not recommended.

Caution should be observed when initiating therapy in post-myocardial infarction patients. Evaluation of post-myocardial infarction patients should always include assessment of renal function (see section 4.2).

Use of valsartan in post-myocardial infarction patients commonly results in some reduction in blood pressure, but discontinuation of therapy because of continuing symptomatic hypotension is not usually necessary provided dosing instructions are followed (see section 4.2).
Heart Failure
In patients with heart failure, the triple combination of an ACE inhibitor, a beta blocker and valsartan has not shown any clinical benefit (see section 5.1). This combination apparently increases the risk for adverse events and is therefore not recommended. Caution should be observed when initiating therapy in patients with heart failure. Evaluation of patients with heart failure should always include assessment of renal function (see section 4.2).
Use of valsartan in patients with heart failure commonly results in some reduction in blood pressure, but discontinuation of therapy because of continuing symptomatic hypotension is not usually necessary provided dosing instructions are followed (see section 4.2). In patients whose renal function may depend on the activity of the renin-angiotensin 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 and/or death. As valsartan is an angiotensin II antagonist, it cannot be excluded that the use of Valsartan may be associated with impairment of the renal function.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION
Concomitant use not recommended
Lithium
Reversible increases in serum lithium concentrations and toxicity have been reported during concurrent use of ACE inhibitors. 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.

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.

Caution required with concomitant use
Non-steroidal anti-inflammatory medicines (NSAIDs), including selective COX-2 inhibitors, acetylsalicylic acid >3 g/day, and non-selective NSAIDs
When angiotensin II antagonists are administered simultaneously with NSAIDs, attenuation of the antihypertensive effect may occur. Furthermore, concomitant use of angiotensin II antagonists and NSAIDs may lead to an increased risk of 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.

Others
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.

4.6 FERTILITY, PREGNANCY AND LACTATION
Pregnancy
The use of Angiotensin II Receptor Antagonists (AIIRAs) is not recommended during the 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 AIIRAs, similar risks may exist for this class of drugs. Unless continued AIIRA 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, hyperkalemia); 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 sections 4.3 and 4.4).

**Lactation**

Because no information is available regarding the use of valsartan during breastfeeding, Valsartan is not recommended and alternative treatments with better established safety profiles during breastfeeding are preferable, especially while nursing a newborn or preterm infant.

**Fertility**

Valsartan had no adverse effects on the reproductive performance of male or female rats at oral doses up to 200 mg/kg/day. This dose is 6 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).

### 4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects on the ability to drive 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

In controlled clinical studies in patients with hypertension, the overall incidence of adverse reactions (ADRs) was comparable with placebo and is consistent with the pharmacology of valsartan. The incidence of ADRs did not appear to be related to dose or treatment duration and also showed no association with gender, age or race.

The ADRs reported from clinical studies, post-marketing experience and laboratory findings are listed below according to system organ class.

Adverse 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), including isolated reports. Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness. For all the ADRs reported from post-marketing experience and laboratory findings, it is not possible to apply any ADR frequency and therefore they are mentioned with a "not known" frequency.

- **Hypertension**

<table>
<thead>
<tr>
<th>Blood and lymphatic system disorders</th>
<th></th>
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<tbody>
<tr>
<td>Not known</td>
<td>Decrease in haemoglobin, Decrease in haematocrit, Neutropenia, Thrombocytopenia</td>
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<table>
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<tr>
<th>Immune system disorders</th>
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<tbody>
<tr>
<td>Not known</td>
<td>Hypersensitivity including serum sickness</td>
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<tr>
<th>Metabolism and nutrition disorders</th>
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<tbody>
<tr>
<td>Not known</td>
<td>Increase of serum potassium Hyponatraemia</td>
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<tr>
<th>Ear and labyrinth system disorders</th>
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<tbody>
<tr>
<td>Uncommon</td>
<td>Vertigo</td>
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<table>
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<tr>
<th>Vascular disorders</th>
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<tbody>
<tr>
<td>Not known</td>
<td>Vasculitis</td>
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<thead>
<tr>
<th>Respiratory, thoracic and mediastinal disorders</th>
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<tr>
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<td>Cough</td>
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<th>Gastrointestinal disorders</th>
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<tbody>
<tr>
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<td>Abdominal pain</td>
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<th>Hepato-biliary disorders</th>
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<tbody>
<tr>
<td>Not known</td>
<td>Elevation of liver function values including increase of serum bilirubin</td>
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<tr>
<th>Skin and subcutaneous tissue disorders</th>
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<tbody>
<tr>
<td>Not known</td>
<td>Angioedema, Rash, Pruritus</td>
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<tr>
<th>Musculoskeletal and connective tissue disorders</th>
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<tbody>
<tr>
<td>Not known</td>
<td>Myalgia</td>
</tr>
</tbody>
</table>

| Renal and urinary disorders                 |  |
Not known Renal failure and impairment, Elevation of serum creatinine

General disorders and administration site conditions
Uncommon Fatigue

The safety profile seen in controlled-clinical studies in patients with post-myocardial infarction and/or heart failure varies from the overall safety profile seen in hypertensive patients. This may relate to the patients underlying disease. ADRs that occurred in post-myocardial infarction and/or heart failure patients are listed below:

- Post-myocardial infarction and/or heart failure (studied in adult patients only)

<table>
<thead>
<tr>
<th>Blood and lymphatic system disorders</th>
<th>Thrombocytopenia</th>
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<tbody>
<tr>
<td>Uncommon Hyperkalaemia</td>
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</table>

| Not known Increase of serum potassium |
| | Hyponatraemia |

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<thead>
<tr>
<th>Nervous system disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common Dizziness, Postural dizziness</td>
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| Uncommon Syncope, Headache |
| | |

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<thead>
<tr>
<th>Ear and labyrinth system disorders</th>
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<tbody>
<tr>
<td>Uncommon Vertigo</td>
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<th>Cardiac disorders</th>
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<tr>
<td>Uncommon Cardiac failure</td>
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<table>
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<th>Vascular disorders</th>
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<tbody>
<tr>
<td>Common Hypotension, Orthostatic hypotension</td>
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| Not known Vasculitis |
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<th>Skin and subcutaneous tissue disorders</th>
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<tbody>
<tr>
<td>Uncommon Angioedema</td>
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| Not known Rash, Pruritis |
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<tr>
<th>Musculoskeletal and connective tissue disorders</th>
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<tr>
<td>Not known Myalgia</td>
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<tr>
<th>Renal and urinary disorders</th>
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<tbody>
<tr>
<td>Common Renal failure and impairment</td>
</tr>
</tbody>
</table>

| Uncommon Acute renal failure, Elevation of serum creatinine |

| Not known Increase in Blood Urea Nitrogen |
| | |

<table>
<thead>
<tr>
<th>General disorders and administration site conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon Asthenia, Fatigue</td>
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</table>

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.

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

If hypotension occurs, the patient should be placed in a supine position and blood volume correction should be undertaken.

Valsartan is unlikely to be removed by haemodialysis.
5  PHARMACOLOGICAL PROPERTIES
5.1  PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Angiotensin II Antagonists, plain, ATC code: C09CA03
Valsartan is an orally active, potent, 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) less 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).

Recent myocardial infarction
The VALSartan In Acute myocardial iNfarcTion trial (VALIANT) was a randomised, controlled, multinational, double-blind study in 14,703 patients with acute myocardial infarction and signs, symptoms or radiological evidence of congestive heart failure and/or evidence of left ventricular systolic dysfunction (manifested as an ejection fraction ≤ 40% by radionuclide ventriculography or ≤ 35% by echocardiography or ventricular contrast angiography). Patients were randomized within 12 hours to 10 days after the onset of myocardial infarction symptoms to valsartan, captopril, or the combination of both. The mean treatment duration was two years. The primary endpoint was time to all-cause mortality.

Valsartan was as effective as captopril in reducing all-cause mortality after myocardial infarction. All-cause mortality was similar in the valsartan (19.9%), captopril (19.5%), and valsartan + captopril (19.3%) groups. Combining valsartan with captopril did not add further benefit over captopril alone. There was no difference between valsartan and captopril in all-cause mortality based on age, gender, race, baseline therapies or underlying disease. Valsartan was also effective in prolonging the time to and reducing cardiovascular mortality, hospitalisation for heart failure, recurrent myocardial infarction, resuscitated cardiac arrest, and non-fatal stroke (secondary composite endpoint).

The safety profile of valsartan was consistent with the clinical course of patients treated in the post-myocardial infarction setting. Regarding renal function, doubling of serum creatinine was observed in 4.2% of valsartan-treated patients, 4.8% of valsartan+captopril-treated patients, and 3.4% of captopril-treated patients. Discontinuations due to various types of renal dysfunction occurred in 1.1% of valsartan-treated patients, 1.3% in valsartan+captopril patients, and 0.8% of captopril patients. An assessment of renal function should be included in the evaluation of patients post-myocardial infarction.

There was no difference in all-cause mortality, cardiovascular mortality or morbidity when beta blockers were administered together with the combination of valsartan + captopril, valsartan alone, or captopril alone. Irrespective of treatment, mortality was lower in the group of patients treated with a beta blocker, suggesting that the known beta blocker benefit in this population was maintained in this trial.

Heart failure
Val-HeFT was a randomised, controlled, multinational clinical trial of valsartan compared with placebo on morbidity and mortality in 5,010 NYHA class II (62%), III (36%) and IV (2%) heart failure patients receiving usual therapy with LVEF <40% and left ventricular internal diastolic diameter (LVIDD) >2.9 cm/m². Baseline therapy included ACE inhibitors (93%), diuretics (86%), digoxin (67%) and beta blockers (36%). The mean duration of follow-up was nearly two years. The mean daily dose of valsartan in Val-HeFT was 254 mg. The study had two primary endpoints: all cause mortality (time to death) and composite mortality and heart failure morbidity (time to first morbid event) defined as death, sudden death with resuscitation, hospitalisation for heart failure, or administration of intravenous inotropic or vasodilator agents for four hours or more without hospitalisation.
All cause mortality was similar (p=NS) in the valsartan (19.7%) and placebo (19.4%) groups. The primary benefit was a 27.5% (95% CI: 17 to 37%) reduction in risk for time to first heart failure hospitalisation (13.9% vs. 18.5%). Results appearing to favour placebo (composite mortality and morbidity was 21.9% in placebo vs. 25.4% in valsartan group) were observed for those patients receiving the triple combination of an ACE inhibitor, a beta blocker and valsartan. In a subgroup of patients not receiving an ACE inhibitor (n=366), the morbidity benefits were greatest. In this subgroup all-cause mortality was significantly reduced with valsartan compared to placebo by 33% (95% CI: -6% to 58%) (17.3% valsartan vs. 27.1% placebo) and the composite mortality and morbidity risk was significantly reduced by 44% (24.9% valsartan vs. 42.5% placebo). In patients receiving an ACE inhibitor without a beta-blocker, all cause mortality was similar (p=NS) in the valsartan (21.8%) and placebo (22.5%) groups. Composite mortality and morbidity risk was significantly reduced by 18.3% (95% CI: 8% to 28%) with valsartan compared with placebo (31.0% vs. 36.3%). In the overall Val-HeFT population, valsartan treated patients showed significant improvement in NYHA class, and heart failure signs and symptoms, including dyspnoea, fatigue, oedema and rales compared to placebo. Patients treated with valsartan had a better quality of life as demonstrated by change in the Minnesota Living with Heart Failure Quality of Life score from baseline at endpoint than placebo. Ejection fraction in valsartan treated patients was significantly increased and LVIDD significantly reduced from baseline at endpoint compared to placebo.

5.2 PHARMACOKINETIC PROPERTIES

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.

Excretion:
Valsartan shows multieponential decay kinetics (t1/2α < 1 h and t1/2β about 9 h). Valsartan is primarily eliminated by biliary excretion in faeces (about 83% of dose) and renally in 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.

In Heart failure patients:
The average time to peak concentration and elimination half-life of valsartan in heart failure patients are similar to that observed in healthy volunteers. AUC and Cmax values of valsartan are almost proportional with increasing dose over the clinical dosing range (40 to 160 mg twice a day). The average accumulation factor is about 1.7. The apparent clearance of valsartan following oral administration is approximately 4.5 l/h. Age does not affect the apparent clearance in heart failure patients.

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.

Impaired renal function
As expected for a compound where renal clearance accounts for only 30% of total plasma clearance, no correlation was seen between renal function and systemic exposure to valsartan. Dose adjustment is
therefore not required in patients with renal impairment (creatinine clearance >10 ml/min). There is currently no experience on the safe use in patients with a creatinine clearance <10 ml/min and patients undergoing dialysis, therefore valsartan should be used with caution in these patients (see sections 4.2 and 4.4). Valsartan is highly bound to plasma protein and is unlikely to be removed by dialysis.

Hepatic impairment
Approximately 70% of the dose absorbed is eliminated in the bile, essentially in the unchanged form. Valsartan does not undergo any noteworthy biotransformation. A doubling of exposure (AUC) was observed in patients with mild to moderate hepatic impairment compared to healthy subjects. However, no correlation was observed between plasma valsartan concentration versus degree of hepatic dysfunction. Valsartan has not been studied in patients with severe hepatic dysfunction (see sections 4.2, 4.3 and 4.4).

5.3 PRECLINICAL SAFETY DATA
Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential. In rats, maternally toxic doses (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).

In non-clinical safety studies, high doses of valsartan (200 to 600 mg/kg body weight) caused in rats a reduction of red blood cell parameters (erythrocytes, haemoglobin, haematocrit) and evidence of changes in renal haemodynamics (slightly raised plasma urea, and renal tubular hyperplasia and basophilia in males). These doses in rats (200 and 600 mg/kg/day) are approximately 6 and 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).

In marmosets at similar doses, the changes were similar though more severe, particularly in the kidney where the changes developed to a nephropathy which included raised urea and creatinine. Hypertrophy of the renal juxtaglomerular cells was also seen in both species. All changes were considered to be caused by the pharmacological action of valsartan which produces prolonged hypotension, particularly in marmosets. For therapeutic doses of valsartan in humans, the hypertrophy of the renal juxtaglomerular cells does not seem to have any relevance.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS
Microcrystalline cellulose (E460)
Povidone (E1201)
Crospovidon (E1202)
Sodium Laurilsulfate
Magnesium stearate (E470b)

6.2 INCOMPATIBILITIES
Not applicable.

6.3 SHELF LIFE
2 years.

6.4 SPECIAL PRECAUTIONS FOR STORAGE
Store below 30°C. Store in the original package in order to protect from moisture.

6.5 NATURE AND CONTENTS OF CONTAINER
Cardboard boxes containing blisters (Al/PVC/PVdC or Al/OPA/Al/PVC) with 7 or 28 capsules. Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
No special requirements.
MARKETING AUTHORIZATION HOLDER
Jubilant Pharmaceuticals nv
Axxes Business Park
Guldensporenpark 22 – Block C
9820 Merelbeke
Belgium

MARKETING AUTHORIZATION NUMBER(S)
PL 19156/0118

DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION
10/01/2012

DATE OF REVISION OF THE TEXT
10/01/2012
NAME OF THE MEDICINAL PRODUCT
Valsartan 160 mg capsules

QUALITATIVE AND QUANTITATIVE COMPOSITION
Each capsule contains 160 mg valsartan.
For a full list of excipients, see section 6.1.

PHARMACEUTICAL FORM
Capsules, hard.
Dark grey coloured cap and flesh opaque coloured body, size ‘1’ hard gelatine capsules, printed in white ink with ‘160’ on cap, containing white to off white granular powder.

CLINICAL PARTICULARS
4.1 THERAPEUTIC INDICATIONS
Hypertension
Treatment of essential hypertension in adults.

Heart failure
Treatment of symptomatic heart failure when Angiotensin Converting Enzyme (ACE) inhibitors cannot be used, or as add-on therapy to ACE inhibitors when beta blockers cannot be used (see sections 4.4 and 5.1).

POSOLOGY AND METHOD OF ADMINISTRATION
Posology
Heart failure
The recommended starting dose of Valsartan is 40 mg twice daily. Uptitration to 80 mg and 160 mg twice daily should be done at intervals of at least two weeks to the highest dose, as tolerated by the patient. Consideration should be given to reducing the dose of concomitant diuretics. The maximum daily dose administered in clinical trials is 320 mg in divided doses.
Valsartan may be administered with other heart failure therapies. However, the triple combination of an ACE inhibitor, a beta blocker and valsartan is not recommended (see sections 4.4 and 5.1).
Evaluation of patients with heart failure should always include assessment of renal function.

Method of administration
Valsartan may be taken independently of a meal and should be administered with water.

Additional information on special populations
Elderly
No dose adjustment is required in elderly patients.

Renal impairment
No dosage adjustment is required for patients with a creatinine clearance >10 ml/min (see sections 4.4 and 5.2)

Hepatic impairment
Valsartan is contraindicated in patients with severe hepatic impairment, biliary cirrhosis and in patients with cholestasis (see sections 4.3, 4.4 and 5.2). In patients with mild to moderate hepatic impairment without cholestasis, the dose of valsartan should not exceed 80 mg.

Paediatric population
Valsartan is not recommended for use in children below the age of 18 years due to a lack of data on safety and efficacy.

CONTRAINDICATIONS
- Hypersensitivity to the active substance or to any of the excipients.
- Severe hepatic impairment, biliary cirrhosis and cholestasis.
Second and third trimester of pregnancy (see sections 4.4 and 4.6).
4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Hyperkalaemia
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.

Sodium- and/or volume-depleted patients
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. Sodium and/or volume depletion should be corrected before starting treatment with Valsartan, for example by reducing the diuretic dose.

Renal artery stenosis
In patients with bilateral renal artery stenosis or stenosis to a solitary kidney, the safe use of Valsartan has not been established.
Short-term administration of valsartan to twelve patients with renovascular hypertension secondary to unilateral renal artery stenosis did not induce any significant changes in renal haemodynamics, serum creatinine, or blood urea nitrogen (BUN). However, other agents that affect the renin-angiotensin system may increase blood urea and serum creatinine in patients with unilateral renal artery stenosis, therefore monitoring of renal function is recommended when patients are treated with valsartan.

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

Primary hyperaldosteronism
Patients with primary hyperaldosteronism should not be treated with Valsartan as their renin-angiotensin system is not activated.

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

Impaired renal function
No dosage adjustment is required for adult patients with a creatinine clearance >10 ml/min. There is currently no experience on the safe use in patients with a creatinine clearance <10 ml/min and patients undergoing dialysis, therefore valsartan should be used with caution in these patients (see sections 4.2 and 5.2).

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

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).

Recent myocardial infarction
The combination of captopril and valsartan has shown no additional clinical benefit, instead the risk for adverse events increased compared to treatment with the respective therapies (see sections 4.2 and 5.1). Therefore, the combination of valsartan with an ACE inhibitor is not recommended.

Caution should be observed when initiating therapy in post-myocardial infarction patients. Evaluation of post-myocardial infarction patients should always include assessment of renal function (see section 4.2).

Use of valsartan in post-myocardial infarction patients commonly results in some reduction in blood pressure, but discontinuation of therapy because of continuing symptomatic hypotension is not usually necessary provided dosing instructions are followed (see section 4.2).
Heart Failure
In patients with heart failure, the triple combination of an ACE inhibitor, a beta blocker and valsartan has not shown any clinical benefit (see section 5.1). This combination apparently increases the risk for adverse events and is therefore not recommended. Caution should be observed when initiating therapy in patients with heart failure. Evaluation of patients with heart failure should always include assessment of renal function (see section 4.2).

Use of valsartan in patients with heart failure commonly results in some reduction in blood pressure, but discontinuation of therapy because of continuing symptomatic hypotension is not usually necessary provided dosing instructions are followed (see section 4.2). In patients whose renal function may depend on the activity of the renin-angiotensin 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 and/or death. As valsartan is an angiotensin II antagonist, it cannot be excluded that the use of Valsartan may be associated with impairment of the renal function.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Concomitant use not recommended
Lithium
Reversible increases in serum lithium concentrations and toxicity have been reported during concurrent use of ACE inhibitors. 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.

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.

Caution required with concomitant use
Non-steroidal anti-inflammatory medicines (NSAIDs), including selective COX-2 inhibitors, acetylsalicylic acid >3 g/day), and non-selective NSAIDs
When angiotensin II antagonists are administered simultaneously with NSAIDs, attenuation of the antihypertensive effect may occur. Furthermore, concomitant use of angiotensin II antagonists and NSAIDs may lead to an increased risk of 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.

Others
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.

4.6 FERTILITY, PREGNANCY AND LACTATION

Pregnancy
The use of Angiotensin II Receptor Antagonists (AIIRAs) is not recommended during the 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 AIIRAs, similar risks may exist for this class of drugs. Unless continued AIIRA 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, hyperkalemia); 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 sections 4.3 and 4.4).

**Lactation**
Because no information is available regarding the use of valsartan during breastfeeding, Valsartan is not recommended and alternative treatments with better established safety profiles during breastfeeding are preferable, especially while nursing a newborn or preterm infant.

**Fertility**
Valsartan had no adverse effects on the reproductive performance of male or female rats at oral doses up to 200 mg/kg/day. This dose is 6 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).

### 4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
No studies on the effects on the ability to drive 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
In controlled clinical studies in patients with hypertension, the overall incidence of adverse reactions (ADRs) was comparable with placebo and is consistent with the pharmacology of valsartan. The incidence of ADRs did not appear to be related to dose or treatment duration and also showed no association with gender, age or race.

The ADRs reported from clinical studies, post-marketing experience and laboratory findings are listed below according to system organ class.

Adverse 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), including isolated reports. Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness. For all the ADRs reported from post-marketing experience and laboratory findings, it is not possible to apply any ADR frequency and therefore they are mentioned with a "not known" frequency.

- **Hypertension**

<table>
<thead>
<tr>
<th>Blood and lymphatic system disorders</th>
<th>Decrease in haemoglobin, Decrease in haematocrit, Neutropenia, Thrombocytopenia</th>
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<tbody>
<tr>
<td>Immune system disorders</td>
<td>Hypersensitivity including serum sickness</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Increase of serum potassium Hyponatraemia</td>
</tr>
<tr>
<td>Ear and labyrinth system disorders</td>
<td>Vertigo</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Vasculitis</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Cough</td>
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<tr>
<td>Gastrointestinal disorders</td>
<td>Abdominal pain</td>
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<tr>
<td>Hepato-biliary disorders</td>
<td>Elevation of liver function values including increase of serum bilirubin</td>
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<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Angioedema, Rash, Pruritus</td>
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<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Myalgia</td>
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<tr>
<td>Renal and urinary disorders</td>
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</table>
The safety profile seen in controlled-clinical studies in patients with post-myocardial infarction and/or heart failure varies from the overall safety profile seen in hypertensive patients. This may relate to the patients underlying disease. ADRs that occurred in post-myocardial infarction and/or heart failure patients are listed below:

- **Post-myocardial infarction and/or heart failure (studied in adult patients only)**

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<thead>
<tr>
<th>Blood and lymphatic system disorders</th>
<th>Thrombocytopenia</th>
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<tr>
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<tr>
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<th>Increase of serum potassium</th>
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<th>Nervous system disorders</th>
<th>Dizziness, Postural dizziness</th>
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<th>Hypotension, Orthostatic hypotension</th>
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<tr>
<th>Uncommon</th>
<th>Acute renal failure, Elevation of serum creatinine</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Not known</th>
<th>Increase in Blood Urea Nitrogen</th>
</tr>
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<table>
<thead>
<tr>
<th>General disorders and administration site conditions</th>
<th>Asthenia, Fatigue</th>
</tr>
</thead>
</table>

| Uncommon                                             |              |

### 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.

**Treatment**

The therapeutic measures depend on the time of ingestion and the type and severity of the symptoms; stabilisation of the circulatory condition is of prime importance. If hypotension occurs, the patient should be placed in a supine position and blood volume correction should be undertaken. Valsartan is unlikely to be removed by haemodialysis.
5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacological group: Angiotensin II Antagonists, plain, ATC code: C09CA03

Valsartan is an orally active, potent, 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) less 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).

Recent myocardial infarction

The VALSartan In Acute myocardial iNfarctiOn trial (VALIANT) was a randomised, controlled, multinational, double-blind study in 14,703 patients with acute myocardial infarction and signs, symptoms or radiological evidence of congestive heart failure and/or evidence of left ventricular systolic dysfunction (manifested as an ejection fraction ≤40% by radionuclide ventriculography or ≤35% by echocardiography or ventricular contrast angiography). Patients were randomized within 12 hours to 10 days after the onset of myocardial infarction symptoms to valsartan, captopril, or the combination of both. The mean treatment duration was two years. The primary endpoint was time to all-cause mortality.

Valsartan was as effective as captopril in reducing all-cause mortality after myocardial infarction. All-cause mortality was similar in the valsartan (19.9%), captopril (19.5%), and valsartan + captopril (19.3%) groups. Combining valsartan with captopril did not add further benefit over captopril alone. There was no difference between valsartan and captopril in all-cause mortality based on age, gender, race, baseline therapies or underlying disease. Valsartan was also effective in prolonging the time to and reducing cardiovascular mortality, hospitalisation for heart failure, recurrent myocardial infarction, resuscitated cardiac arrest, and non-fatal stroke (secondary composite endpoint).

The safety profile of valsartan was consistent with the clinical course of patients treated in the post-myocardial infarction setting. Regarding renal function, doubling of serum creatinine was observed in 4.2% of valsartan-treated patients, 4.8% of valsartan+captopril-treated patients, and 3.4% of captopril-treated patients. Discontinuations due to various types of renal dysfunction occurred in 1.1% of valsartan-treated patients, 1.3% in valsartan+captopril patients, and 0.8% of captopril patients. An assessment of renal function should be included in the evaluation of patients post-myocardial infarction.

There was no difference in all-cause mortality, cardiovascular mortality or morbidity when beta blockers were administered together with the combination of valsartan + captopril, valsartan alone, or captopril alone. Irrespective of treatment, mortality was lower in the group of patients treated with a beta blocker, suggesting that the known beta blocker benefit in this population was maintained in this trial.

Heart failure

Val-HeFT was a randomised, controlled, multinational clinical trial of valsartan compared with placebo on morbidity and mortality in 5,010 NYHA class II (62%), III (36%) and IV (2%) heart failure patients receiving usual therapy with LVEF <40% and left ventricular internal diastolic diameter (LVIDD) >2.9 cm/m². Baseline therapy included ACE inhibitors (93%), diuretics (86%), digoxin (67%) and beta blockers (36%). The mean duration of follow-up was nearly two years. The mean daily dose of valsartan in Val-HeFT was 254 mg. The study had two primary endpoints: all cause mortality (time to death) and composite mortality and heart failure morbidity (time to first morbid event) defined as death, sudden death with resuscitation, hospitalisation for heart failure, or administration of intravenous inotropic or vasodilator agents for four hours or more without hospitalisation.
All-cause mortality was similar (p=NS) in the valsartan (19.7%) and placebo (19.4%) groups. The primary benefit was a 27.5% (95% CI: 17 to 37%) reduction in risk for time to first heart failure hospitalisation (13.9% vs. 18.5%). Results appearing to favour placebo (composite mortality and morbidity was 21.9% in placebo vs. 25.4% in valsartan group) were observed for those patients receiving the triple combination of an ACE inhibitor, a beta blocker and valsartan.

In a subgroup of patients not receiving an ACE inhibitor (n=366), the morbidity benefits were greatest. In this subgroup all-cause mortality was significantly reduced with valsartan compared to placebo by 33% (95% CI: -6% to 58%) (17.3% valsartan vs. 27.1% placebo) and the composite mortality and morbidity risk was significantly reduced by 44% (24.9% valsartan vs. 42.5% placebo).

In patients receiving an ACE inhibitor without a beta-blocker, all-cause mortality was similar (p=NS) in the valsartan (21.8%) and placebo (22.5%) groups. Composite mortality and morbidity risk was significantly reduced by 18.3% (95% CI: 8% to 28%) with valsartan compared with placebo (31.0% vs. 36.3%).

In the overall Val-HeFT population, valsartan treated patients showed significant improvement in NYHA class, and heart failure signs and symptoms, including dyspnoea, fatigue, oedema and rales compared to placebo. Patients treated with valsartan had a better quality of life as demonstrated by change in the Minnesota Living with Heart Failure Quality of Life score from baseline at endpoint than placebo. Ejection fraction in valsartan treated patients was significantly increased and LVIDD significantly reduced from baseline at endpoint compared to placebo.

5.2 PHARMACOKINETIC PROPERTIES

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.

Excretion:
Valsartan shows multiexponential decay kinetics (t1/2α <1 h and t1/2β about 9 h). Valsartan is primarily eliminated by biliary excretion in faeces (about 83% of dose) and renally in 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.

In Heart failure patients:
The average time to peak concentration and elimination half-life of valsartan in heart failure patients are similar to that observed in healthy volunteers. AUC and Cmax values of valsartan are almost proportional with increasing dose over the clinical dosing range (40 to 160 mg twice a day). The average accumulation factor is about 1.7. The apparent clearance of valsartan following oral administration is approximately 4.5 l/h. Age does not affect the apparent clearance in heart failure patients.

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.

Impaired renal function
As expected for a compound where renal clearance accounts for only 30% of total plasma clearance, no correlation was seen between renal function and systemic exposure to valsartan. Dose adjustment is
therefore not required in patients with renal impairment (creatinine clearance >10 ml/min). There is currently no experience on the safe use in patients with a creatinine clearance <10 ml/min and patients undergoing dialysis, therefore valsartan should be used with caution in these patients (see sections 4.2 and 4.4). Valsartan is highly bound to plasma protein and is unlikely to be removed by dialysis.

**Hepatic impairment**

Approximately 70% of the dose absorbed is eliminated in the bile, essentially in the unchanged form. Valsartan does not undergo any noteworthy biotransformation. A doubling of exposure (AUC) was observed in patients with mild to moderate hepatic impairment compared to healthy subjects. However, no correlation was observed between plasma valsartan concentration versus degree of hepatic dysfunction. Valsartan has not been studied in patients with severe hepatic dysfunction (see sections 4.2, 4.3 and 4.4).

5.3 **PRECLINICAL SAFETY DATA**

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential. In rats, maternally toxic doses (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).

In non-clinical safety studies, high doses of valsartan (200 to 600 mg/kg body weight) caused in rats a reduction of red blood cell parameters (erythrocytes, haemoglobin, haematocrit) and evidence of changes in renal haemodynamics (slightly raised plasma urea, and renal tubular hyperplasia and basophilia in males). These doses in rats (200 and 600 mg/kg/day) are approximately 6 and 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).

In marmosets at similar doses, the changes were similar though more severe, particularly in the kidney where the changes developed to a nephropathy which included raised urea and creatinine. Hypertrophy of the renal juxtaglomerular cells was also seen in both species. All changes were considered to be caused by the pharmacological action of valsartan which produces prolonged hypotension, particularly in marmosets. For therapeutic doses of valsartan in humans, the hypertrophy of the renal juxtaglomerular cells does not seem to have any relevance.

6 **PHARMACEUTICAL PARTICULARS**

6.1 **LIST OF EXCIPIENTS**

- Microcrystalline cellulose (E460)
- Povidone (E1201)
- Crospovidon (E1202)
- Sodium Laurilsulfate
- Magnesium stearate (E470b)

6.2 **INCOMPATIBILITIES**

Not applicable.

6.3 **SHELF LIFE**

2 years.

6.4 **SPECIAL PRECAUTIONS FOR STORAGE**

Store below 30°C. Store in the original package in order to protect from moisture.

6.5 **NATURE AND CONTENTS OF CONTAINER**

Cardboard boxes containing blisters (Al/PVC/PVdC or Al/OPA/Al/PVC) with 7 or 28 capsules. Not all pack sizes may be marketed.

6.6 **SPECIAL PRECAUTIONS FOR DISPOSAL**

No special requirements.
7 MARKETING AUTHORISATION HOLDER
Jubilant Pharmaceuticals nv
Axxes Business Park
Guldensporenpark 22 – Block C
9820 Merelbeke
Belgium

8 MARKETING AUTHORISATION NUMBER(S)
PL 19156/0119

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
10/01/2012

10 DATE OF REVISION OF THE TEXT
10/01/2012
UKPAR Valsartan 40 mg, 80 mg and 160 mg Capsules

PL 19156/0117-9

PACKAGE LEAFLET: INFORMATION FOR THE USER

Valsartan 40 mg capsules
Valsartan 80 mg capsules
Valsartan 160 mg capsules
Valsartan

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 is and what it is used for
2. How to take Valsartan
3. Possible side effects
4. How to store Valsartan
5. Further information

1. WHAT VALSARTAN IS AND WHAT IT IS USED FOR

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.

Valsartan 40 mg capsules can be used for the following conditions:
- to treat symptomatic heart failure: Valsartan is used when a group of medicines called Angiotensin Converting Enzyme (ACE) inhibitors (a medication to treat heart failure) cannot be used or if it may be used in addition to ACE inhibitors when beta blockers (another medication to treat heart failure) cannot be used. Heart failure symptoms include shortness of breath, swelling of the feet and legs due to fluid build-up. It is caused when the heart muscle cannot pump blood strongly enough to supply all the blood needed throughout the body.

Valsartan 80 mg capsules can be used for two different conditions:
- to treat high blood pressure: High blood pressure increases the workload on the heart and arteries. If left untreated it can damage the blood vessels of the brain, heart, and kidneys, and may result in a stroke, heart failure, or kidney failure. High blood pressure increases the risk of heart attacks. Lowering your blood pressure to normal reduces the risk of developing these disorders.
- to treat symptomatic heart failure: Valsartan is used when a group of medicines called Angiotensin Converting Enzyme (ACE) inhibitors (a medication to treat heart failure) cannot be used or if it may be used in addition to ACE inhibitors when beta blockers (another medication to treat heart failure) cannot be used. Heart failure symptoms include shortness of breath, swelling of the feet and legs due to fluid build-up. It is caused when the heart muscle cannot pump blood strongly enough to supply all the blood needed throughout the body.

Valsartan 160 mg capsules can be used for two different conditions:
- to treat high blood pressure: High blood pressure increases the workload on the heart and arteries. If left untreated it can damage the blood vessels of the brain, heart, and kidneys, and may result in a stroke, heart failure, or kidney failure. High blood pressure increases the risk of heart attacks. Lowering your blood pressure to normal reduces the risk of developing these disorders.
- to treat symptomatic heart failure: Valsartan is used when a group of medicines called Angiotensin Converting Enzyme (ACE) inhibitors (a medication to treat heart failure) cannot be used or if it may be used in addition to ACE inhibitors when beta blockers (another medication to treat heart failure) cannot be used. Heart failure symptoms include shortness of breath, swelling of the feet and legs due to fluid build-up. It is caused when the heart muscle cannot pump blood strongly enough to supply all the blood needed throughout the body.

2. BEFORE YOU TAKE VALSARTAN

Do not take Valsartan:
- if you are allergic (hypersensitive) to Valsartan or any of the other ingredients of Valsartan
- if you have severe kidney disease
- if you are more than 3 months pregnant (it is also better to avoid Valsartan in early pregnancy - see pregnancy section).

If any of these apply to you, do not take Valsartan

Take special care with Valsartan:
- if you have liver disease
- if you have severe kidney disease or if you are undergoing dialysis
- if you are suffering from a narrowing of the kidney artery
- if you have recently undergone kidney transplantation (received a new kidney)
- if you are treated after a heart attack or for heart failure, your doctor may check your kidney function
- if you have severe heart disease other than heart failure or heart attack
- if you are taking medicines that increase the amount of potassium in your blood. These include potassium supplements or salt substitutes containing potassium, potassium-sparing medicines and heparin. It may be necessary to check the amount of potassium in your blood at regular intervals
- if you suffer from aldosteronism. This is a disease in which your adrenal glands make too much of the hormone aldosterone. If this applies to you, the use of Valsartan is not recommended.

- if you have lost a lot of fluid (dehydration) caused by diarrhoea, vomiting, or high doses of water pills (diuretics).
- The use of Valsartan in children and adolescents is not recommended (below the age of 18 years).
- you must tell your doctor if you think you are (or might become) pregnant. Valsartan is not recommended in early pregnancy and must not be taken if you are more than 3 months pregnant, as it may cause serious harm to your baby if used at that stage (see pregnancy section).

If any of these apply to you, tell your doctor before you take Valsartan.

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

The effect of the treatment can be influenced if Valsartan is taken together with certain other medicines. It may be necessary to change the dose, to take other precautions, or in some cases to stop taking one of the medicines. This applies to both prescription and non-prescription medicines, especially:

- other medicines that lower blood pressure, especially water pills (diuretics),
- medicines that increase the amount of potassium in your blood. These include potassium supplements or salt substitutes containing potassium, potassium-sparing medicines and heparin,
- certain type of painkillers called non-steroidal anti-inflammatory medicines (NSAIDs),
- lithium, a medicine used to treat some types of psychiatric illnesses.

In addition:

- if you are being treated for heart failure, a triple combination with ACE inhibitors and beta blockers (medications to treat heart failure) is not recommended.

Taking Valsartan with food and drink

You can take Valsartan with or without food.

Pregnancy and breast-feeding

Ask your doctor or pharmacist for advice before taking any medicine.

- You must tell your doctor if you think that you are (or might become) pregnant. Your doctor will normally advise you to stop taking Valsartan before you become pregnant or as soon as you know you are pregnant, and will advise you to take another medicine instead of Valsartan. Valsartan is not recommended in early pregnancy and must not be taken when more than 3 months pregnant, as it may cause serious harm to your baby if it is used after the third month of pregnancy.
- Tell your doctor if you are breast-feeding or about to start breast-feeding. Valsartan is not recommended for mothers who are breast-feeding, and your doctor may choose another treatment for you if you wish to breast-feed, especially if your baby is newborn, or was born prematurely.

Driving and using machines

Before you drive a vehicle, use tools or operate machines, or carry out other activities that require concentration, make sure you know how Valsartan affects you. Like many other medicines used to treat high blood pressure, Valsartan may in rare cases cause dizziness and affect the ability to concentrate.

3. HOW TO TAKE VALSARTAN

Always take Valsartan exactly as your doctor has told you in order to get the best results and reduce the risk of side effects. You should check with your doctor or pharmacist if you are not sure. People with high blood pressure often do not notice any signs of this problem. Many may feel quite normal. This makes it all the more important for you to keep your appointments with the doctor even if you are feeling well.

Valsartan 40 mg capsules

Adolescent patients with heart failure: Treatment starts generally with 40 mg twice daily.
Your doctor will increase the dose gradually over several weeks to a maximum of 160 mg twice daily. The final dose depends on what you are an individual patient can tolerate.

Valsartan 80 mg capsules

Adolescent patients with high blood pressure: The usual dose is 80 mg daily. In some cases your doctor may prescribe higher doses (e.g. 160 mg or 240 mg). He may also combine Valsartan with an additional medicine (e.g. a diuretic).

Adolescent patients with heart failure: Treatment starts generally with 80 mg twice daily.
Your doctor will increase the dose gradually over several weeks to a maximum of 160 mg twice daily. The final dose depends on what you are an individual patient can tolerate.

Valsartan can be given together with other treatment for heart failure, and your doctor will decide which treatment is suitable for you.

Valsartan 160 mg capsules

Adolescent patients with high blood pressure: The usual dose is 80 mg daily. In some cases your doctor may prescribe higher doses (e.g. 160 mg or 240 mg). He may also combine Valsartan with an additional medicine (e.g. a diuretic).
UKPAR Valsartan 40 mg, 80 mg and 160 mg Capsules

PL 19156/0117-9

Adult patients with heart failure: Treatment starts generally with 40 mg twice daily. Your doctor will increase the dose gradually over several weeks to a maximum of 160 mg twice daily. The exact dose depends on what your doctor determines is suitable for your individual patient. Valsartan can be given together with other treatment for heart failure, and your doctor will decide which treatment is suitable for you.

You can take Valsartan with or without food. Swallow Valsartan with a glass of water. Take Valsartan at about the same time each day.

If you take more Valsartan than you should
If you experience severe dizziness and/or fainting, lie down and contact your doctor immediately. If you have accidentally taken too many capsules, contact your doctor, pharmacist, or hospital.

If you forget to take Valsartan
Do not take a double dose to make up for a forgotten dose. 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.

If you stop taking Valsartan
Stopping your treatment with Valsartan may cause your disease to get worse. Do not stop taking your doctor's prescribed medication unless your doctor tells you to.

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

4. POSSIBLE SIDE EFFECTS

Like all medicines, Valsartan can cause side effects, although not everybody gets them. These side effects may occur with certain frequencies, which are described as follows:

- very common: affects more than 1 in 10 people
- common: affects 1 in 10 to 100 people
- uncommon: affects 1 in 100 to 1,000 people
- rare: affects 1 in 1,000 to 10,000 people
- very rare: affects less than 1 in 10,000 people
- not known: frequency cannot be estimated from the available data.

Some symptoms need immediate medical attention:

- You may experience symptoms of angioedema (a specific allergic reaction), such as:
  - swelling of the face, lips, tongue or throat
  - difficulty in breathing or swallowing
  - hives, itching

If you get any of these, see a doctor immediately.

Other side effects include:

Common:
- dizziness
- low blood pressure with or without symptoms such as dizziness and fainting when standing up
- decreased kidney function (signs of renal impairment)

Uncommon:
- angioedema (see section “Some symptoms need immediate medical attention”)
- sudden loss of consciousness (syncope)
- spinning sensation (vertigo)
- severely decreased kidney function (signs of acute renal failure)

Not known:
- allergic reactions with rash, itching and hives; symptoms of fever, swelling of joints and pain in joints, muscle pain, swollen lymph nodes and/or flu-like symptoms may occur (signs of serum sickness)
- purplish-red spots, fever, itching (signs of inflammation of blood vessels also called vasculitis)
- unusual bleeding or bruising (signs of thrombocytopenia)
- muscle pain (myalgia)
- fever, sore throat or mouth ulcers due to infections (symptoms of low level of white blood cells also called neutropenia)

The frequency of some side effects may vary depending on your condition. For example, side effects such as dizziness, and decreased kidney function, were seen less frequently in adult patients treated with high blood pressure than in adult patients treated for heart failure or after a recent heart attack.

Side effects in children and adolescents are similar to those seen in adults.

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.

5. HOW TO STORE VALSARTAN

- Store below 30°C. Store in the original package in order to protect from moisture.
- Keep out of the reach and sight of children.
- Do not use Valsartan after the expiry date which is stated on the pack. The expiry date refers to the last day of that month.
- Do not use Valsartan if you notice that the pack is damaged or shows signs of tampering.

Medicines should not be disposed of via wastewater or 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 40 mg capsules contain
The active substance is Valsartan.
Each capsule contains 40 mg Valsartan.

The other ingredients are:
- Microcrystalline cellulose (E460), povidone, crospovidone (E1202), sodium lauryl sulphate and magnesium stearate (E470).

What Valsartan 40 mg capsules look like and contents of the pack
Valsartan 40 mg capsules consist of light grey coloured cap and body, size ‘3’ hard gelatin capsules, printed in black ink with ‘40’ on cap, containing white to off white granular powder.

The capsules are available in blister packs of 7 or 28 capsules.

Not all pack sizes may be marketed.

What Valsartan 80 mg capsules contain
The active substance is Valsartan.
Each capsule contains 80 mg Valsartan.

The other ingredients are:
- Microcrystalline cellulose (E460), povidone, crospovidone (E1202), sodium lauryl sulphate and magnesium stearate (E470).

What Valsartan 80 mg capsules look like and contents of the pack
Valsartan 80 mg capsules consist of light grey coloured cap and flesh opaque coloured body, size ‘2’ hard gelatin capsules, printed in black ink with ‘80’ on cap, containing white to off white granular powder.

The capsules are available in blister packs of 7, 28 or 98 capsules.

Not all pack sizes may be marketed.

What Valsartan 160 mg capsules contain
The active substance is Valsartan.
Each capsule contains 160 mg Valsartan.

The other ingredients are:
- Microcrystalline cellulose (E460), povidone, crospovidone (E1202), sodium lauryl sulphate and magnesium stearate (E470).

What Valsartan 160 mg capsules look like and contents of the pack
Valsartan 160 mg capsules consist of dark grey coloured cap and flesh opaque coloured body, size ‘1’ hard gelatin capsules, printed in white ink with ‘160’ on cap, containing white to off white granular powder.

The capsules are available in blister packs of 7, 28 or 98 capsules.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder
Jubilant Pharmaceuticals Ltd
Axxess Business Park
Golders Green Trade Park
22–30 Broomfield Road
London NW11 0EJ
United Kingdom

Manufacturer
PSI supplies
Axxess Business Park
Golders Green Trade Park
22–30 Broomfield Road
London NW11 0EJ
United Kingdom

For any information about this medicine, please contact the Marketing Authorisation Holder.

This leaflet was last approved in 12/2011
UKPAR Valsartan 40 mg, 80 mg and 160 mg Capsules

PL 19156/0117-9

Leaflet for other distributor Aspire Pharma Limited:

PACKAGE LEAFLET: INFORMATION FOR THE USER

Valsartan 40 mg capsules
Valsartan 80 mg capsules
Valsartan 160 mg capsules

Valsartan

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.

1. WHAT Valsartan IS AND WHAT IT IS USED FOR

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.

2. HOW TO TAKE Valsartan

Valsartan 40 mg capsules may be used for the following conditions:

- to treat heart failure.
- to treat hypertension (high blood pressure).

3. POSSIBLE SIDE EFFECTS

As with all medicines, side effects are possible. However, not everyone gets side effects.

4. HOW TO STORE Valsartan

Store in a cool, dry place away from direct heat and light.

5. FURTHER INFORMATION

For full information about Valsartan, please see the summary of product characteristics (SMPC).

Leaflet for other distributor Aspire Pharma Limited:

- The use of Valsartan in children and adolescents is not recommended (below the age of 18 years).
- You must tell your doctor if you think you are (or might become) pregnant. Valsartan is not recommended in early pregnancy, and must not be taken if you are more than 3 months pregnant, as it may cause serious harm to your baby if used at that stage (see pregnancy section).

If any of these apply to you, tell your doctor before you take Valsartan.

Taking other medicines

- Please tell your doctor or pharmacist if you are taking or have been recently taking other medicines, including medicines obtained without a prescription.

The effect of the treatment can be influenced by the use of Valsartan.

- You must tell your doctor if you think that you are (or might become) pregnant.
- Your doctor will normally advise you to stop taking Valsartan before you become pregnant or as soon as you know you are pregnant, and will advise you to take another medicine instead of Valsartan.
- If you are pregnant, it is important that you are not using another medicine containing potassium, potassium-sparing medicines or heparin.

4. HOW TO TAKE Valsartan

Always take Valsartan exactly as your doctor has told you in order to get the best results and reduce the risk of side effects. You should check with your doctor or pharmacist if you are not sure. People with high blood pressure often do not notice any signs of this problem. Many may feel quite normal. This makes it all the more important for you to keep your appointments with your doctor even if you do not feel well.

Valsartan 40 mg capsules:

Adult patients with heart failure: Treatment starts generally with 40 mg twice daily. Your doctor will increase the dose gradually over several weeks to a maximum of 100 mg twice daily. The final dose depends on what your individual patient can tolerate.

Valsartan 80 mg capsules:

Adult patients with heart failure: Treatment starts generally with 40 mg twice daily. Your doctor will increase the dose gradually over several weeks to a maximum of 160 mg twice daily. The final dose depends on what your individual patient can tolerate.

5. HOW TO STORE Valsartan

Store in a cool, dry place away from direct heat and light.

6. FURTHER INFORMATION

For full information about Valsartan, please see the summary of product characteristics (SMPC).

Leaflet for other distributor Aspire Pharma Limited:

- The use of Valsartan in children and adolescents is not recommended (below the age of 18 years).
- You must tell your doctor if you think you are (or might become) pregnant. Valsartan is not recommended in early pregnancy, and must not be taken if you are more than 3 months pregnant, as it may cause serious harm to your baby if used at that stage (see pregnancy section).

If any of these apply to you, tell your doctor before you take Valsartan.

Taking other medicines

- Please tell your doctor or pharmacist if you are taking or have been recently taking other medicines, including medicines obtained without a prescription.

The effect of the treatment can be influenced by the use of Valsartan.

- You must tell your doctor if you think that you are (or might become) pregnant.
- Your doctor will normally advise you to stop taking Valsartan before you become pregnant or as soon as you know you are pregnant, and will advise you to take another medicine instead of Valsartan.
- If you are pregnant, it is important that you are not using another medicine containing potassium, potassium-sparing medicines or heparin.

4. HOW TO TAKE Valsartan

Always take Valsartan exactly as your doctor has told you in order to get the best results and reduce the risk of side effects. You should check with your doctor or pharmacist if you are not sure. People with high blood pressure often do not notice any signs of this problem. Many may feel quite normal. This makes it all the more important for you to keep your appointments with your doctor even if you do not feel well.

Valsartan 40 mg capsules:

Adult patients with heart failure: Treatment starts generally with 40 mg twice daily. Your doctor will increase the dose gradually over several weeks to a maximum of 100 mg twice daily. The final dose depends on what your individual patient can tolerate.

Valsartan 80 mg capsules:

Adult patients with heart failure: Treatment starts generally with 40 mg twice daily. Your doctor will increase the dose gradually over several weeks to a maximum of 160 mg twice daily. The final dose depends on what your individual patient can tolerate.

5. HOW TO STORE Valsartan

Store in a cool, dry place away from direct heat and light.

6. FURTHER INFORMATION

For full information about Valsartan, please see the summary of product characteristics (SMPC).
UKPAR Valsartan 40 mg, 80 mg and 160 mg Capsules

You can take Valsartan with or without food. Swallow Valsartan with a glass of water.
Take Valsartan at about the same time each day.

If you take more Valsartan than you should
If you experience severe dizziness and/or fainting, lie down and contact your doctor immediately. If you have accidentally taken too many capsules, contact your doctor, pharmacist, or hospital.

If you forget to take Valsartan
Do not take a double dose to make up for a forgotten dose.
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.

If you stop taking Valsartan
Stopping your treatment with Valsartan may cause your disease to get worse. Do not stop taking your medicine unless your doctor tells you to.
If you have further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Valsartan 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 user in 10
• common: affects 1 to 10 users in 100
• uncommon: affects 1 to 10 users in 1,000
• rare: affects 1 to 10 users in 10,000
• very rare: less than 1 user in 10,000
Not known: frequency cannot be estimated from the available data.

Some symptoms need immediate medical attention:
You may experience symptoms of angioedema (a specific allergic reaction), such as:
• swollen face, lips, tongue or throat
• difficulty in breathing or swallowing
• larynx, itching

If you get any of these, see a doctor immediately.

Other side effects include:

Common:
• dizziness
• low blood pressure with or without symptoms such as dizziness and fainting when standing up
• decreased kidney function (signs of renal impairment)

Uncommon:
• angioedema (see section "Some symptoms need immediate medical attention")
• sudden loss of consciousness (syncope)
• spinning sensation (vertigo)
• severely decreased kidney function (signs of acute renal failure)
• muscle spasm, abnormal heart rhythm (signs of hyperkalaemia)
• breathlessness, difficulty breathing when lying down, swelling of the feet or legs (signs of cardiac failure)
• headache
• cough
• abdominal pain
• nausea
• diarrhoea
• tiredness
• weakness

Not known:
• allergic reactions with rash, itching and livers; symptoms of fever, swollen joints and joint pain, muscle pain, swollen lymph nodes and/or flu-like symptoms may occur (signs of serum sickness)
• purplish-red spots, fever, itching (signs of infarction of blood vessels also called vasculitis)
• unusual bleeding or bruising (signs of thrombocytopenia)
• muscle pain (myalgia)
• fever, sore throat or mouth ulcers due to infection (symptoms of low level of white blood cells also called neutropenia)
• decrease of level of haemoglobin and decrease of the percentage of red blood cells in the blood (which can, in severe cases, lead to anaemia)
• increase of level of potassium in the blood (which can, in severe cases, trigger muscle spasm, abnormal heart rhythm)
• low level of sodium in the blood (which can trigger tiredness, confusion, muscle twitching and/or convulsions in severe cases)
• elevation of liver function values (which can indicate liver damage) including an increase of bilirubin in the blood (which can, in severe cases, trigger yellow skin and eyes)
• increase of level of blood uric nitrogen and increase of level of serum creatinine (which can indicate abnormal kidney function)

The frequency of some side effects may vary depending on your condition. For example, side effects such as dizziness, and decreased kidney function, were seen less frequently in adult patients treated with high blood pressure than in adult patients treated for heart failure or after a recent heart attack.

Side effects in children and adolescents are similar to those seen in adults.

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

5. HOW TO STORE VALSARTAN

• Store below 30°C. Store in the original package in order to protect from moisture.
• Keep out of the reach and sight of children.
• Do not use Valsartan after the expiry date which is stated on the pack. The expiry date refers to the last day of that month.
• Do not use Valsartan if you notice that the pack is damaged or shows signs of tampering.
• Medicines should not be disposed of via wastewater or 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 40 mg capsules contain
• The active substance is valsartan.
Each capsule contains 40 mg valsartan.
The other ingredients are:
Microcrystalline cellulose (E460), povidone, crospovidone (E1202), sodium laurylsulphate and magnesium stearate (E470).

What Valsartan 40 mg capsules look like and contents of the pack
Valsartan 40 mg capsules consist of light grey coloured cap and body, size '1' hard gelatin capsules, printed in black ink with "40" on cap, containing white to off white granular powder.
The capsules are available in blister packs of 7 or 28 capsules.
Not all pack sizes may be marketed.

What Valsartan 80 mg capsules contain
• The active substance is valsartan.
Each capsule contains 80 mg valsartan.
The other ingredients are:
Microcrystalline cellulose (E460), povidone, crospovidone (E1202), sodium laurylsulphate and magnesium stearate (E470).

What Valsartan 80 mg capsules look like and contents of the pack
Valsartan 80 mg capsules consist of light grey coloured cap and flesh opaque coloured body, size '2' hard gelatin capsules, printed in black ink with '80' on cap, containing white to off white granular powder.
The capsules are available in blister packs of 7, 28 or 98 capsules.
Not all pack sizes may be marketed.

What Valsartan 160 mg capsules contain
• The active substance is valsartan.
Each capsule contains 160 mg valsartan.
The other ingredients are:
Microcrystalline cellulose (E460), povidone, crospovidone (E1202), sodium laurylsulphate and magnesium stearate (E470).

What Valsartan 160 mg capsules look like and contents of the pack
Valsartan 160 mg capsules consist of dark grey coloured cap and flesh opaque coloured body, size '3' hard gelatin capsules, printed in white ink with '160' on cap, containing white to off white granular powder.
The capsules are available in blister packs of 7, 28 or 98 capsules.
Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder
Jubilant Pharmaceuticals (UK) Limited

Address: 22-24 - Block C
9820 Merlewood
Belgium

Manufacturer
PSC supply (UK) Limited

Address: 22-24 - Block C
9820 Merlewood
Belgium

Distributed by
Aspire Pharma Ltd

Address: 18 College Street
Petersfield, Hampshire
GU31 4AD
United Kingdom

For any information about this medicine, please contact the Marketing Authorisation Holder.

This leaflet was last amended in 12/2011

PL 19156/0117-9
Leaflet for other distributor Waymade Healthcare PLC:

**UKPAR Valsartan 40 mg, 80 mg and 160 mg Capsules**

**PL 19156/0117-9**

**Valsartan 40 mg capsules**

**Valsartan 80 mg capsules**

**Valsartan 160 mg capsules**

**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 is and what it is used for
2. Before you take Valsartan
3. How to take Valsartan
4. Possible side effects
5. How to store Valsartan
6. Further information

**1. WHAT VALSARTAN IS AND WHAT IT IS USED FOR**

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 muscles 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.

**Valsartan 40 mg capsules can be used for the following conditions:**

- To treat symptomatic heart failure. Valsartan is used when a group of medicines called Angiotensin Converting Enzyme (ACE) inhibitors (a medication to treat heart failure) cannot be used or may be used in addition to ACE inhibitors when beta blockers (another medication to treat heart failure) cannot be used. Heart failure symptoms include shortness of breath, and swelling of the feet and legs due to fluid build-up. It is caused when the heart muscle cannot pump blood strongly enough to supply all the blood needed throughout the body.

**Valsartan 80 mg capsules can be used for two different conditions:**

- To treat high blood pressure. High blood pressure increases the workload on the heart and arteries. If not treated it can damage the blood vessels of the brain, heart, and kidneys, and may result in a stroke, heart failure, or kidney failure. High blood pressure increases the risk of heart attacks. Lowering your blood pressure helps to reduce the risk of developing these disorders.

- To treat symptomatic heart failure. Valsartan is used when a group of medicines called Angiotensin Converting Enzyme (ACE) inhibitors (a medication to treat heart failure) cannot be used or may be used in addition to ACE inhibitors when beta blockers (another medication to treat heart failure) cannot be used. Heart failure symptoms include shortness of breath, and swelling of the feet and legs due to fluid build-up. It is caused when the heart muscle cannot pump blood strongly enough to supply all the blood needed throughout the body.

**Valsartan 160 mg capsules can be used for two different conditions:**

- To treat high blood pressure. High blood pressure increases the workload on the heart and arteries. If not treated it can damage the blood vessels of the brain, heart, and kidneys, and may result in a stroke, heart failure, or kidney failure. High blood pressure increases the risk of heart attacks. Lowering your blood pressure helps to reduce the risk of developing these disorders.

- To treat symptomatic heart failure. Valsartan is used when a group of medicines called Angiotensin Converting Enzyme (ACE) inhibitors (a medication to treat heart failure) cannot be used or may be used in addition to ACE inhibitors when beta blockers (another medication to treat heart failure) cannot be used. Heart failure symptoms include shortness of breath, and swelling of the feet and legs due to fluid build-up. It is caused when the heart muscle cannot pump blood strongly enough to supply all the blood needed throughout the body.

**2. BEFORE YOU TAKE VALSARTAN**

Do not take Valsartan:

- If you are allergic (hypersensitive) to Valsartan or any of the other ingredients of Valsartan.
- If you have severe liver disease.
- If you have more than 3 months pregnant (it is also better to avoid Valsartan in early pregnancy - see pregnancy section).

If any of these apply to you, do not take Valsartan.

Take special care with Valsartan:

- If you have liver disease.
- If you have severe kidney disease or if you are undergoing dialysis.
- If you are suffering from a narrowing of the kidney artery.
- If you have recently undergone a kidney transplantation (received a new kidney).
- If you have been treated with heart attacks or blood pressure, your doctor may check your kidney function.
- If you have severe heart disease or other heart failure or heart attack.
- If you are taking medicines that increase the amount of potassium in your blood. These include potassium supplements or salt substitutes containing potassium, potassium-sparing medicines and heparin. It is necessary to check the amount of potassium in your blood at regular intervals.
- If you suffer from diabetes and high blood pressure. High blood pressure can cause damage to your kidneys. If diabetes and high blood pressure are not properly treated, then diabetes and high blood pressure may cause severe complications.
- If you have lost a lot of fluid (dehydration) caused by diarrhoea, vomitting, or high doses of water pills (diuretics).

**3. HOW TO TAKE VALSARTAN**

Always take Valsartan exactly as your doctor has told you. In order to get the best results and reduce the risk of side effects, you should check with your doctor or pharmacist if you are not sure. People with high blood pressure often do not notice any signs of this problem. Many may feel quite normal. This makes it all the more important for you to keep your appointments with the doctor even if you are feeling well.

**Valsartan 40 mg capsules**

**Adult patients with heart failure:** Treatment starts generally with 40 mg twice daily. Your doctor will increase the dose gradually over several weeks to a maximum of 160 mg twice daily. The final dose depends on what you as an individual patient can tolerate. Valsartan can be given on its own or in combination with other treatment for heart failure, and your doctor will decide which treatment is suitable for you.

**Valsartan 80 mg capsules**

**Adult patients with high blood pressure:** The usual dose is 80 mg daily. In some cases your doctor may prescribe higher doses (e.g. 160 mg or 320 mg). He may also combine Valsartan with an additional medicine (e.g. a diuretic).

**Adult patients with heart failure:** Treatment starts generally with 80 mg twice daily. Your doctor will increase the dose gradually over several weeks to a maximum of 160 mg twice daily. The final dose depends on what you as an individual patient can tolerate. Valsartan can be given on its own or in combination with other treatment for heart failure, and your doctor will decide which treatment is suitable for you.

**Valsartan 160 mg capsules**

**Adult patients with high blood pressure:** The usual dose is 80 mg daily. In some cases your doctor may prescribe higher doses (e.g. 160 mg or 320 mg). He may also combine Valsartan with an additional medicine (e.g. a diuretic).

**Adult patients with heart failure:** Treatment starts generally with 80 mg twice daily. Your doctor will increase the dose gradually over several weeks to a maximum of 160 mg twice daily. The final dose depends on what you as an individual patient can tolerate. Valsartan can be given on its own or in combination with other treatment for heart failure, and your doctor will decide which treatment is suitable for you.

You can take Valsartan with or without food. Swallow Valsartan with a glass of water. Take Valsartan at about the same time each day.
UKPAR Valsartan 40 mg, 80 mg and 160 mg Capsules

If you take more Valsartan than you should
If you experience severe dizziness and/or fainting, lie down and contact your doctor immediately. If you have accidentally taken too many capsules, contact your doctor, pharmacist, or hospital.

If you forget to take Valsartan
Do not take a double dose to make up for a forgotten dose. 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.

If you stop taking Valsartan
Stopping your treatment with Valsartan may cause your disease to get worse. Do not stop taking your medicine unless your doctor tells you to.

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

4. POSSIBLE SIDE EFFECTS

Like all medicines, Valsartan 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 user in 10
• common: affects 1 to 10 users in 100
• uncommon: affects 1 to 10 users in 1,000
• rare: affects 1 to 10 users in 10,000
• very rare: affects less than 1 user in 10,000
• not known: frequency cannot be estimated from the available data.

Some symptoms need immediate medical attention:
You may experience symptoms of angioedema (a specific allergic reaction), such as:

• swelling face, lips, tongue or throat
• difficulty in breathing or swallowing
• hives, itching

If you get any of these, see a doctor immediately.

Other side effects include:

Common:

• dizziness
• low blood pressure with or without symptoms such as dizziness and fainting when standing up
• decreased kidney function (signs of renal impairment)

Uncommon:

• angioedema (see section “Some symptoms need immediate medical attention”)
• sudden loss of consciousness (syncope)
• severe decreased kidney function (signs of acute renal failure)
• muscle spasms, abnormal heart rhythm (signs of hyperkalaemia)
• breathlessness, difficulty breathing when lying down, swelling of the feet or legs (signs of cardiac failure)
• headache
• cough
• abdominal pain
• nausea
• diarrhoea
• tiredness
• weakness

Not known:

• allergic reactions with rash, itching and hives; symptoms of fever, swollen joints and joint pain, muscle pain, swollen lymph nodes and/or flu-like symptoms may occur (signs of severe sickness)
• purplish-red spots, fever, itching (signs of inflammation of blood vessels, also called vasculitis)
• unusual bleeding or bruising (signs of thrombocytopenia)
• muscle pain (myalgia)
• fever, sore throat or mouth ulcers due to infections (signs of low level of white blood cells, also called neutropenia)
• decrease of level of haemoglobin and decrease of the percentage of red blood cells in the blood (which can, in severe cases, lead to anemia)
• increase of level of potassium in the blood (which can, in severe cases, trigger muscle spasms, abnormal heart rhythm)
• low level of sodium in the blood (which can trigger tiredness, confusion, muscle twitching and/or convulsions in severe cases)
• elevation of liver function values (which can indicate liver damage) including an increase of bilirubin in the blood (which can, in severe cases, trigger yellow skin and eyes)
• increase of level of blood urea nitrogen and increase of level of serum creatinine (which can indicate abnormal kidney function)

The frequency of some side effects may vary depending on your condition. For example, side effects such as dizziness, and decreased kidney function, were seen less frequently in adult patients treated with high blood pressure than in adult patients treated for heart failure or after a recent heart attack.

Side effects in children and adolescents are similar to those seen in adults.

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.

5. HOW TO STORE VALSARTAN

• Store below 30°C. Store in the original package in order to protect from moisture.
• Keep out of the reach of children.
• Do not use Valsartan after the expiry date which is stated on the pack. The expiry date refers to the last day of that month.
• Do not use Valsartan if you notice that the pack is damaged or shows signs of tampering.

Medicines should not be disposed of via wastewater or 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 40 mg capsules contain
• The active substance is valsartan.
• Each capsule contains 40 mg valsartan.
• The other ingredients are: Meclohydroxypropylcellulose (E462), povidone, croscarmellose (E102), sodium lauryldiste and magnesium stearate (E470b).

What Valsartan 40 mg capsules look like and contents of the pack
Valsartan 40 mg capsules consist of light grey coloured cap and body, size 3” hard gelatin capsules, printed in black ink with “40” on cap, containing white to off white granular powder.

The capsules are available in blister packs of 7 or 28 capsules.

Not all pack sizes may be marketed.

What Valsartan 89 mg capsules contain
• The active substance is valsartan.
• Each capsule contains 89 mg valsartan.
• The other ingredients are: Meclohydroxypropylcellulose (E462), povidone, croscarmellose (E102), sodium lauryldiste and magnesium stearate (E470b).

What Valsartan 89 mg capsules look like and contents of the pack
Valsartan 89 mg capsules consist of light grey coloured cap and flesh opaque coloured body, size 2” hard gelatin capsules, printed in black ink with “89” on cap, containing white to off white granular powder.

The capsules are available in blister packs of 7, 28 or 98 capsules.

Not all pack sizes may be marketed.

What Valsartan 160 mg capsules contain
• The active substance is valsartan.
• Each capsule contains 160 mg valsartan.
• The other ingredients are: Meclohydroxypropylcellulose (E462), povidone, croscarmellose (E102), sodium lauryldiste and magnesium stearate (E470b).

What Valsartan 160 mg capsules look like and contents of the pack
Valsartan 160 mg capsules consist of dark grey coloured cap and flesh opaque coloured body, size 2” hard gelatin capsules, printed in black ink with “160” on cap, containing white to off white granular powder.

The capsules are available in blister packs of 7, 28 or 98 capsules.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder
Jubilant Pharmaceuticals ltd
Jubilant Pharma Park
Guldmanspark 22 – Blox C
9820 Merelbeke
Belgium

Manufacturer
PSM supply srl
Axxess Business Park
Guldmanspark 22 – Blox C
9820 Merelbeke
Belgium

Distributed by
Sovereign Medical
Sovereign House
MilesGray Road
Basildon
Essex
SS14 3FR
United Kingdom

For any information about this medicine, please contact the Marketing Authorisation Holder.

This leaflet was last approved in 12/2011
UKPAR Valsartan 40 mg, 80 mg and 160 mg Capsules

PL 19156/0117-9

Valsartan 40 mg capsules
Valsartan
7 capsules

Each capsule contains 40 mg valsartan.

Marketing authorisation holder:
Jubilant Pharmaceuticals nv
Axxes Business Park
Guldensporenpark 22 – Block C
9220 Merelbeke
Belgium
Valsartan 40 mg capsules
Valsartan

Each capsule contains 40 mg valsartan.

Marketing authorisation holder:
Jubilant Pharmaceuticals nv
Axces Business Park
Guldensporenpark 22 – Block C
9820 Merelbeke
Belgium

PL 19156/0117-9
UKPAR Valsartan 40 mg, 80 mg and 160 mg Capsules

Valsartan 80 mg capsules

Valsartan 80 mg capsules

Each capsule contains 80 mg valsartan.

Marketing authorisation holder:
Jubilant Pharmaceuticals nv
Axxes Business Park
Guldensporenpark 22 – Block C
9220 Meerbeke
Belgium
UKPAR Valsartan 40 mg, 80 mg and 160 mg Capsules

Valsartan 80 mg capsules

Each capsule contains 80 mg valsartan.

Marketing authorisation holder:
Jubilant Pharmaceuticals nv
Axces Business Park
Guldensporenpark 22 - Block C
9020 Merelbeke
Belgium
UKPAR Valsartan 40 mg, 80 mg and 160 mg Capsules

PL 19156/0117-9

Labelling for other distributor Aspire Pharma Limited:
UKPAR Valsartan 40 mg, 80 mg and 160 mg Capsules

Labelling for other distributor Waymade Healthcare PLC:

Valsartan 40 mg capsules
28 capsules

Valsartan 40 mg capsules
28 capsules

Marketing authorisation holder:
Jubilant Pharmaceuticals N.V.
Access Business Park
Guillevangepark 22 – Block C
9820梅利贝克
Belgium

Distributed by:
Sovereign Medical
Sovereign House
Mills Grey Road, Basildon
Essex SS14 3FR
United Kingdom
UKPAR Valsartan 40 mg, 80 mg and 160 mg Capsules

Valsartan 80 mg capsules
28 capsules

Marketing authorisation holder:
Jubilant Pharmaceuticals nv
Axxes Business Park
Guldensporenpark 22 – Block C
9820 Merelbeke
Belgium

Distributed by:
Sovereign Medical
Sovereign House
Miles Gray Road, Basildon
Essex SS16 3FR
United Kingdom