Public Assessment Report

Decentralised Procedure

Valsartan 40 mg film-coated Tablets
Valsartan 80 mg film-coated Tablets
Valsartan 160 mg film-coated Tablets
Valsartan 320 mg film-coated Tablets

PL 08553/0394-0397
PL 08553/0462-0465

UK/H/2636/001-004/DC
UK/H/4641/001-004/DC

Dr. Reddy’s Laboratories (UK) Ltd.
Lay summary

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Dr. Reddy’s Laboratories (UK) Ltd. Marketing Authorisations (licences) for the medicinal products Valsartan 40 mg, 80 mg, 160 mg and 320 mg film-coated Tablets (product licence numbers: PL 08553/0394-0397 and PL 08553/0462-0465) on 19 September 2011. These medicines are available on prescription only.

Valsartan belongs to a class of medicines called angiotensin II receptor antagonists, which help to control high blood pressure. Angiotensin II is a substance in the body that causes blood vessels to tighten, thus causing an increase in blood pressure. Valsartan works by blocking the effect of angiotensin II. As a result, blood vessels relax and blood pressure is lowered.

Valsartan Tablets are used to treat:

Valsartan 40 mg, 80 mg, 160 mg and 320 mg tablets:
High blood pressure in children and adolescents aged to 6 to 18 years

Valsartan 80 mg, 160 mg, 320 mg tablets:
High blood pressure in adults

Valsartan 40 mg, 80 mg and 160 mg tablets:
Symptomatic heart failure in adults

The data submitted in support of these applications for Valsartan 40 mg, 80 mg, 160 mg and 320 mg film-coated Tablets raised no clinically significant safety concerns and it was, therefore, judged that the benefits of using these products outweigh the risks; hence Marketing Authorisations have been granted.
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## Module 1

### Information about Decentralised Procedure

| Name of the products in the Reference Member State | Valsartan 40 mg film-coated Tablets  
Valsartan 80 mg film-coated Tablets  
Valsartan 160 mg film-coated Tablets  
Valsartan 320 mg film-coated Tablets |
<table>
<thead>
<tr>
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<tr>
<td>Type of application</td>
<td>Generic (Article 10.1)</td>
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<td>Name of the active substance (INN)</td>
<td>Valsartan</td>
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<tr>
<td>Pharmacothereapeutic classification (ATC code)</td>
<td>Angiotensin II antagonists, plain (C09CA03)</td>
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<tr>
<td>Pharmaceutical form and strengths</td>
<td>Film-coated Tablets; 40 mg, 80 mg, 160 mg and 320 mg</td>
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</tbody>
</table>
| Reference numbers for the Decentralised Procedure  | UK/H/2636/001-004/DC  
UK/H/4641/001-004/DC |
| Reference Member State                            | United Kingdom                                                                   |
| Member States concerned                           | UK/H/2636/001-004/DC: DE, IT, RO  
UK/H/4641/001-004/DC: IT                                                          |
| Start of Decentralised Procedure                  | 1 September 2010                                                                 |
| End date of Decentralised Procedure               | 24 August 2011                                                                   |
| Marketing Authorisation numbers                    | PL 08553/0394-0397  
PL 08553/0462-0465                                                               |
| Name and address of the authorisation holder       | Dr. Reddy’s Laboratories (UK) Ltd.  
6 Riverview Road  
Beverley  
East Yorkshire HU17 0LD  
UK                                                   |
Module 2

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Valsartan 40 mg film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 40 mg valsartan. Also contains 14.25 mg of lactose monohydrate.

3 PHARMACEUTICAL FORM
Film-coated tablet.
Yellow coloured, oval shaped, film-coated tablet with beveled edge debossed ‘V’ on one side and ‘4’ and ‘0’ on either side of the breakline on the other side.

The tablets can be divided into two equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Hypertension
Treatment of hypertension in children and adolescents 6 to 18 years of age
Heart Failure
Treatment of symptomatic heart failure in adult patients 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.

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 tablets are 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 80mg.

Paediatric population
Paediatric hypertension

Children and adolescents 6 to 18 years of age

The initial dose is 40 mg once daily for children weighing below 35 kg and 80 mg once daily for those weighing 35 kg or more. The dose should be adjusted based on blood pressure response. For maximum doses studied in clinical trials please refer to the table below.

Doses higher than those listed have not been studied and are therefore not recommended.

<table>
<thead>
<tr>
<th>Weight</th>
<th>Maximum dose studied in clinical trials</th>
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<tbody>
<tr>
<td>≥18 kg to &lt;35 kg</td>
<td>80 mg</td>
</tr>
<tr>
<td>≥35 kg to &lt;80 kg</td>
<td>160 mg</td>
</tr>
<tr>
<td>≥80 kg to ≤160 kg</td>
<td>320 mg</td>
</tr>
</tbody>
</table>

Children less than 6 years of age

Available data are described in sections 4.8, 5.1 and 5.2. However safety and efficacy of valsartan in children aged 1 to 6 years have not been established.

Use in paediatric patients aged 6 to 18 years with renal impairment

Use in paediatric patients with a creatinine clearance <30 ml/min and paediatric patients undergoing dialysis has not been studied, therefore valsartan is not recommended in these patients. No dose adjustment is required for paediatric patients with a creatinine clearance >30 ml/min. Renal function and serum potassium should be closely monitored (see sections 4.4 and 5.2).

Use in paediatric patients aged 6 to 18 years with hepatic impairment

As in adults, Valsartan tablets are contraindicated in paediatric patients with severe hepatic impairment, biliary cirrhosis and in patients with cholestasis (see sections 4.3, 4.4 and 5.2). There is limited clinical experience with Valsartan in paediatric patients with mild to moderate hepatic impairment. The dose of valsartan should not exceed 80 mg in these patients.

Paediatric heart failure and recent myocardial infarction

Valsartan tablets are not recommended for the treatment of heart failure or recent myocardial infarction in children and adolescents below the age of 18 years due to the lack of data on safety and efficacy.

Method of administration

Valsartan tablets may be taken independently of a meal and should be administered with water

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.
- Severe hepatic impairment, biliary cirrhosis and cholestasis.
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
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. No dosage adjustment is required for patients with a creatinine clearance >10 ml/min. (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.

Paediatric population
Impaired renal function
Use in paediatric patients with a creatinine clearance <30 ml/min and paediatric patients undergoing dialysis has not been studied, therefore valsartan is not recommended in these patients. No dose adjustment is required for paediatric patients with a creatinine clearance >30 ml/min (see sections 4.2 and 5.2). Renal function and serum potassium should be closely monitored during treatment with valsartan. This applies particularly when valsartan is given in the presence of other conditions (fever, dehydration) likely to impair renal function.

Impaired hepatic function
As in adults, Valsartan tablets are contraindicated in paediatric patients with severe hepatic impairment, biliary cirrhosis and in patients with cholestasis (see sections 4.3 and 5.2). There is limited clinical experience with Valsartan in paediatric patients with mild to moderate hepatic impairment. The dose of valsartan should not exceed 80 mg in these patients.
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.

Paediatric population
In hypertension in children and adolescents, where underlying renal abnormalities are common, caution is recommended with the concomitant use of valsartan and other substances that inhibit the renin angiotensin aldosterone system which may increase serum potassium. Renal function and serum potassium should be closely monitored.

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 breast-feeding 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 (≥1/1000 to <1/100); rare (≥1/10,000 to <1/1000); 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**
  - **Blood and lymphatic system disorders**
    - Not known
      - Decrease in haemoglobin
      - Decrease in haematocrit
      - Neutropenia
      - Thrombocytopenia
Immune system disorders
Not known  Hypersensitivity including serum sickness

Metabolism and nutrition disorders
Not known  Increase of serum potassium

Ear and labyrinth system disorders
Uncommon  Vertigo

Vascular disorders
Not known  Vasculitis

Respiratory, thoracic and mediastinal disorders
Uncommon  Cough

Gastrointestinal disorders
Uncommon  Abdominal pain

Hepato-biliary Disorders
Not known  Elevation of liver function values including increase of serum bilirubin.

Skin and subcutaneous tissue disorders
Not known  Angioedema, Rash, Pruritus

Musculoskeletal and connective tissue disorders
Not known  Myalgia

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

General disorders and administration site conditions
Uncommon:  Fatigue

Paediatric population

Hypertension
The antihypertensive effect of valsartan has been evaluated in two randomised, double-blind clinical studies in 561 paediatric patients from 6 to 18 years of age. With the exception of isolated gastrointestinal disorders (like abdominal pain, nausea, vomiting) and dizziness, no relevant differences in terms of type, frequency and severity of adverse reactions were identified between the safety profile for paediatric patients aged 6 to 18 years and that previously reported for adult patients.

Neurocognitive and developmental assessment of paediatric patients aged 6 to 16 years of age revealed no overall clinically relevant adverse impact after treatment with valsartan for up to one year.

In a double-blind randomized study in 90 children aged 1 to 6 years, which was followed by a one-year open-label extension, two deaths and isolated cases of marked liver transaminases elevations were observed. These cases occurred in a population who had significant comorbidities. A causal
relationship to valsartan has not been established. In a second study in which 75 children aged 1 to 6 years were randomised, no significant liver transaminase elevations or death occurred with valsartan treatment. Hyperkalaemia was more frequently observed in children and adolescents aged 6 to 18 years with underlying chronic kidney disease. 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

Blood and lymphatic system disorders
- Not known Thrombocytopenia

Immune system disorders
- Not known Hypersensitivity including serum sickness

Metabolism and nutrition disorders
- Uncommon Hyperkalaemia
- Not known Increase of serum potassium

Nervous system disorders
- Common Dizziness, Postural dizziness
- Uncommon Syncope, Headache

Ear and labyrinth system disorders
- Uncommon Vertigo

Cardiac disorders
- Uncommon Cardiac failure

Vascular disorders
- Common Hypotension, Orthostatic hypotension
- Not known Vasculitis

Respiratory, thoracic and mediastinal disorders
- Uncommon Cough

Gastrointestinal disorders
- Uncommon Nausea, Diarrhoea

Hepatobiliary Disorders
- Not known Elevation of liver function values

Skin and subcutaneous tissue disorders
- Uncommon Angioedema
- Not known Rash, Pruritus

Musculoskeletal and connective tissue disorders
Not known Myalgia

Renal and urinary disorders
Common Renal failure and impairment
Uncommon Acute renal failure, Elevation of serum creatinine
Not known Increase in Blood Urea Nitrogen

General disorders and administration site conditions
Uncommon Asthenia, Fatigue

4.9 Overdose
Symptoms
Overdose with Valsartan may result in marked hypotension, which could lead to depressed levels 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 groups: 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, and 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 patient’s post-myocardial infarction.

There was no difference in all-cause mortality or 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.

**Paediatric population**

**Hypertension**

The antihypertensive effect of valsartan have been evaluated in four randomized, double-blind clinical studies in 561 paediatric patients from 6 to 18 years of age and 165 paediatric patients 1 to 6 years of age. Renal and urinary disorders, and obesity were the most common underlying medical conditions potentially contributing to hypertension in the children enrolled in these studies.

**Clinical experience in children at or above 6 years of age**

In a clinical study involving 261 hypertensive paediatric patients 6 to 16 years of age, patients who weighed <35 kg received 10, 40 or 80 mg of valsartan daily (low, medium and high doses), and patients who weighed ≥35 kg received 20, 80, and 160 mg of valsartan daily (low, medium and high doses). At the end of 2 weeks, valsartan reduced both systolic and diastolic blood pressure in a dose-dependent manner. Overall, the three dose levels of valsartan (low, medium and high) significantly reduced systolic blood pressure by 8, 10, 12 mm Hg from the baseline, respectively. Patients were re-randomized to either continue receiving the same dose of valsartan or were switched to placebo. In patients who continued to receive the medium and high doses of valsartan, systolic blood pressure at trough was -4 and -7 mm Hg lower than patients who received the placebo treatment. In patients receiving the low dose of valsartan, systolic blood pressure at trough was similar to that
of patients who received the placebo treatment. Overall, the dose-dependent antihypertensive effect of valsartan was consistent across all the demographic subgroups.

In another clinical study involving 300 hypertensive paediatric patients 6 to 18 years of age, eligible patients were randomized to receive valsartan or enalapril tablets for 12 weeks. Children weighing between ≥18 kg and <35 kg received valsartan 80 mg or enalapril 10 mg; those between ≥35 kg and <80 kg received valsartan 160 mg or enalapril 20 mg; those ≥80 kg received valsartan 320 mg or enalapril 40 mg. Reductions in systolic blood pressure were comparable in patients receiving valsartan (15 mmHg) and enalapril (14 mm Hg) (non-inferiority p-value <0.0001). Consistent results were observed for diastolic blood pressure with reductions of 9.1 mmHg and 8.5 mmHg with valsartan and enalapril, respectively.

Clinical experience in children less than 6 years of age
Two clinical studies were conducted in patients aged 1 to 6 years with 90 and 75 patients, respectively. No children below the age of 1 year were enrolled in these studies. In the first study, the efficacy of valsartan was confirmed compared to placebo but a dose-response could not be demonstrated. In the second study, higher doses of valsartan were associated with greater BP reductions, but the dose response trend did not achieve statistical significance and the treatment difference compared to placebo was not significant. Because of these inconsistencies, valsartan is not recommended in this age group (see section 4.8).

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 (t1/2a <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 C\text{max} 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 use of valsartan 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 concentrations 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).

Paediatric population
In a study of 26 paediatric hypertensive patients (aged 1 to 16 years) given a single dose of a suspension of valsartan (mean: 0.9 to 2 mg/kg, with a maximum dose of 80 mg), the clearance (litres/h/kg) of valsartan was comparable across the age range of 1 to 16 years and similar to that of adults receiving the same formulation.

Impaired renal function
Use in paediatric patients with a creatinine clearance <30 ml/min and paediatric patients undergoing dialysis has not been studied, therefore valsartan is not recommended in these patients. No dose adjustment is required for paediatric patients with a creatinine clearance >30 ml/min. Renal function and serum potassium should be closely monitored (see sections 4.2 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.

**Paediatric population**
Daily oral dosing of neonatal/juvenile rats (from a postnatal day 7 to postnatal
day 70) with valsartan at doses as low as 1 mg/kg/day (about 10-35% of the
maximum recommended paediatric dose of 4 mg/kg/day on systemic exposure
basis) produced persistent, irreversible kidney damage. These effects above
mentioned represent an expected exaggerated pharmacological effect of
angiotensin converting enzyme inhibitors and angiotensin II type 1 blockers;
such effects are observed if rats are treated during the first 13 days of life. This
period coincides with 36 weeks of gestation in humans, which could
occasionally extend up to 44 weeks after conception in humans. The rats in the
juvenile valsartan study were dosed up to day 70, and effects on renal
maturation (postnatal 4-6 weeks) cannot be excluded. Functional renal
maturation is an ongoing process within the first year of life in humans.
Consequently, a clinical relevance in children <1 year of age cannot be
excluded, while preclinical data do not indicate a safety concern for children
older than 1 year.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Lactose monohydrate
Cellulose, Microcrystalline
Maize starch
Crospovidone (Type-A)
Povidone (PVP-K 30)
Silica, Colloidal anhydrous
Magnesium stearate

**Tablet Coating**
Hypromellose 6cP (E464)
Titanium dioxide (E171)
Macrogol
Talc (E553b)
Yellow Iron oxide (E172)

6.2 **Incompatibilities**
Not applicable.

6.3 **Shelf life**
2 years

6.4 **Special precautions for storage**
Do not store above 30°C. Store in the original package.

6.5 **Nature and contents of container**
Aluminium-PVC/Aluminium/OPA blister in packs of 14, 28, 30, 50, 56, 60, 98 & 100 tablets
Not all pack sizes may be marketed

6.6 **Special precautions for disposal**
None

7 **MARKETING AUTHORISATION HOLDER**
Dr. Reddy’s Laboratories (UK) Ltd.
6 Riverview Road
Beverley
East Yorkshire
HU17 0LD
United Kingdom

8 **MARKETING AUTHORISATION NUMBER(S)**
PL 08553/0394

9 **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
19/09/2011

10 **DATE OF REVISION OF THE TEXT**
19/09/2011
1 NAME OF THE MEDICINAL PRODUCT
Valsartan 80 mg film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 80 mg valsartan. Also contains 28.50 mg of lactose monohydrate.

3 PHARMACEUTICAL FORM
Film-coated tablet.
Pink coloured, round, film-coated tablet with beveled edge debossed with ‘V’ on one side of the tablet 80 and breakline on the other side.

The tablets can be divided in to two equal halves

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Hypertension
Treatment of essential hypertension in adults, children and adolescents 6 to 18 years of age
Heart Failure
Treatment of symptomatic heart failure in adult patients 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
Hypertension
The recommended dose of Valsartan is 80 mg once daily. The antihypertensive effect is substantially present within 2 weeks, and maximal effects are attained within 4 weeks. In some patients whose blood pressure is not adequately controlled, the dose can be increased to 160 mg and to a maximum of 320 mg.
Valsartan may also be administered with other antihypertensive agents. The addition of a diuretic such as hydrochlorothiazide will decrease blood pressure even further in these patients.
Heart failure
The recommended starting dose of Valsartan is 40 mg twice daily. Up titration 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.

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 tablets are 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 80mg.

Paediatric population

Paediatric hypertension

Children and adolescents 6 to 18 years of age
The initial dose is 40 mg once daily for children weighing below 35 kg and 80 mg once daily for those weighing 35 kg or more. The dose should be adjusted based on blood pressure response. For maximum doses studied in clinical trials please refer to the table below.

Doses higher than those listed have not been studied and are therefore not recommended.

<table>
<thead>
<tr>
<th>Weight</th>
<th>Maximum dose studied in clinical trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥18 kg to &lt;35 kg</td>
<td>80 mg</td>
</tr>
<tr>
<td>≥35 kg to &lt;80 kg</td>
<td>160 mg</td>
</tr>
<tr>
<td>≥80 kg to ≤160 kg</td>
<td>320 mg</td>
</tr>
</tbody>
</table>

Children less than 6 years of age
Available data are described in sections 4.8, 5.1 and 5.2. However safety and efficacy of Valsartan in children aged 1 to 6 years have not been established.

Use in paediatric patients aged 6 to 18 years with renal impairment
Use in paediatric patients with a creatinine clearance <30 ml/min and paediatric patients undergoing dialysis has not been studied, therefore valsartan is not recommended in these patients. No dose adjustment is required for paediatric patients with a creatinine clearance >30 ml/min. Renal function and serum potassium should be closely monitored (see sections 4.4 and 5.2).

Use in paediatric patients aged 6 to 18 years with hepatic impairment
As in adults, Valsartan tablets are contraindicated in paediatric patients with severe hepatic impairment, biliary cirrhosis and in patients with cholestasis (see sections 4.3, 4.4 and 5.2). There is limited clinical experience with Valsartan in paediatric patients with mild to moderate hepatic impairment. The dose of valsartan should not exceed 80 mg in these patients.

Paediatric heart failure and recent myocardial infarction
Valsartan tablets are not recommended for the treatment of heart failure or recent myocardial infarction in children and adolescents below the age of 18 years due to the lack of data on safety and efficacy.
**Method of administration**
Valsartan tablets may be taken independently of a meal and should be administered with water.

### 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
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. No dosage adjustment is required for patients with a creatinine clearance>10 ml/min. (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.

Paediatric population
Impaired renal function
Use in paediatric patients with a creatinine clearance <30 ml/min and paediatric patients undergoing dialysis has not been studied, therefore valsartan is not recommended in these patients. No dose adjustment is required for paediatric patients with a creatinine clearance >30 ml/min (see sections 4.2 and 5.2). Renal function and serum potassium should be closely monitored during treatment with valsartan. This applies particularly when valsartan is given in the presence of other conditions (fever, dehydration) likely to impair renal function.
Impaired hepatic function
As in adults, Valsartan tablets are contraindicated in paediatric patients with severe hepatic impairment, biliary cirrhosis and in patients with cholestasis (see sections 4.3 and 5.2). There is limited clinical experience with Valsartan in paediatric patients with mild to moderate hepatic impairment. The dose of valsartan should not exceed 80 mg in these patients.

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.

Paediatric population
In hypertension in children and adolescents, where underlying renal abnormalities are common, caution is recommended with the concomitant use of valsartan and other substances that inhibit the renin angiotensin aldosterone system which may increase serum potassium. Renal function and serum potassium should be closely monitored.

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 breast-feeding 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 (≥1/1000 to <1/100); rare (≥1/10,000 to <1/1000); 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**

**Blood and lymphatic system disorders**
- Not known: Decrease in haemoglobin, Decrease in haematocrit, Neutropenia, Thrombocytopenia

**Immune system disorders**
- Not known: Hypersensitivity including serum sickness

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

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

**Vascular disorders**
- Not known: Vasculitis

**Respiratory, thoracic and mediastinal disorders**
- Uncommon: Cough

**Gastrointestinal disorders**
- Uncommon: Abdominal pain

**Hepato-biliary Disorders**
- Not known: Elevation of liver function values including increase of serum bilirubin.

**Skin and subcutaneous tissue disorders**
- Not known: Angioedema, Rash, Pruritus

**Musculoskeletal and connective tissue disorders**
- Not known: Myalgia

**Renal and urinary disorders**
- Not known: Renal failure and impairment, Elevation of serum creatinine

**General disorders and administration site conditions**
- Uncommon: Fatigue

*Paediatric population*
**Hypertension**
The antihypertensive effect of valsartan has been evaluated in two randomised, double-blind clinical studies in 561 paediatric patients from 6 to 18 years of age. With the exception of isolated gastrointestinal disorders (like abdominal pain, nausea, vomiting) and dizziness, no relevant differences in terms of type, frequency and severity of adverse reactions were identified between the safety profile for paediatric patients aged 6 to 18 years and that previously reported for adult patients.
Neurocognitive and developmental assessment of paediatric patients aged 6 to 16 years of age revealed no overall clinically relevant adverse impact after treatment with valsartan for up to one year.

In a double-blind randomized study in 90 children aged 1 to 6 years, which was followed by a one-year open-label extension, two deaths and isolated cases of marked liver transaminases elevations were observed. These cases occurred in a population who had significant comorbidities. A causal relationship to valsartan has not been established. In a second study in which 75 children aged 1 to 6 years were randomised, no significant liver transaminase elevations or death occurred with valsartan treatment. Hyperkalaemia was more frequently observed in children and adolescents aged 6 to 18 years with underlying chronic kidney disease.

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**
  - **Blood and lymphatic system disorders**
    - Not known: Thrombocytopenia
  - **Immune system disorders**
    - Not known: Hypersensitivity including serum sickness
  - **Metabolism and nutrition disorders**
    - Uncommon: Hyperkalaemia
    - Not known: Increase of serum potassium
  - **Nervous system disorders**
    - Common: Dizziness, Postural dizziness
    - Uncommon: Syncope, Headache
  - **Ear and labyrinth system disorders**
    - Uncommon: Vertigo
  - **Cardiac disorders**
    - Uncommon: Cardiac failure
  - **Vascular disorders**
    - Common: Hypotension, Orthostatic hypotension
    - Not known: Vasculitis
  - **Respiratory, thoracic and mediastinal disorders**
    - Uncommon: Cough
  - **Gastrointestinal disorders**
    - Uncommon: Nausea, Diarrhoea
  - **Hepatobiliary Disorders**
Not known  Elevation of liver function values

**Skin and subcutaneous tissue disorders**

Uncommon  Angioedema

Not known  Rash, Pruritus

**Musculoskeletal and connective tissue disorders**

Not known  Myalgia

**Renal and urinary disorders**

Common  Renal failure and impairment

Uncommon  Acute renal failure, Elevation of serum creatinine

Not known  Increase in Blood Urea Nitrogen

**General disorders and administration site conditions**

Uncommon  Asthenia, Fatigue

4.9 **Overdose**

**Symptoms**

Overdose with Valsartan may result in marked hypotension, which could lead to depressed levels 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 groups: 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).

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

Abrupt withdrawal of valsartan has not been associated with rebound hypertension or other adverse clinical events.
In hypertensive patients with type 2 diabetes and microalbuminuria, valsartan has been shown to reduce the urinary excretion of albumin. The MARVAL (Micro Albuminuria Reduction with Valsartan) study assessed the reduction in urinary albumin excretion (UAE) with valsartan (80-160 mg/od) versus amlodipine (5-10 mg/od), in 332 type 2 diabetic patients (mean age: 58 years; 265 men) with microalbuminuria (valsartan: 58 µg/min; amlodipine: 55.4 µg/min), normal or high blood pressure and with preserved renal function (blood creatinine <120 µmol/l). At 24 weeks, UAE was reduced (p<0.001) by 42% (–24.2 µg/min; 95% CI: –40.4 to –19.1) with valsartan and approximately 3% (–1.7 µg/min; 95% CI: –5.6 to 14.9) with amlodipine despite similar rates of blood pressure reduction in both groups.

Furthermore another study examined that the efficacy of valsartan in reducing UAE in 391 hypertensive patients (BP=150/88 mmHg) with type 2 diabetes, albuminuria (mean=102 µg/min; 20-700 µg/min) and preserved renal function (mean serum creatinine = 80 µmol/l). Patients were randomized to one of 3 doses of valsartan (160, 320 and 640 mg/od) and treated for 30 weeks. The purpose of the study was to determine the optimal dose of valsartan for reducing UAE in hypertensive patients with type 2 diabetes. At 30 weeks, the percentage change in UAE was significantly reduced by 36% from baseline with valsartan 160 mg (95%CI: 22 to 47%), and by 44% with valsartan 320 mg (95%CI: 31 to 54%). It was concluded that 160-320 mg of valsartan produced clinically relevant reductions in UAE in hypertensive patients with type 2 diabetes.

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 \( \leq 35\% \) 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, and 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 patient’s post-myocardial infarction.

There was no difference in all-cause mortality or 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.

**Paediatric population**

**Hypertension**

The antihypertensive effect of valsartan have been evaluated in four randomized, double-blind clinical studies in 561 paediatric patients from 6 to 18 years of age and 165 paediatric patients 1 to 6 years of age. Renal and urinary disorders, and obesity were the most common underlying medical conditions potentially contributing to hypertension in the children enrolled in these studies.

**Clinical experience in children at or above 6 years of age**

In a clinical study involving 261 hypertensive paediatric patients 6 to 16 years of age, patients who weighed <35 kg received 10, 40 or 80 mg of valsartan daily (low, medium and high doses), and patients who weighed ≥35 kg received 20, 80, and 160 mg of valsartan daily (low, medium and high doses). At the end of 2 weeks, valsartan reduced both systolic and diastolic blood pressure in a dose-dependent manner. Overall, the three dose levels of valsartan (low, medium and high) significantly reduced systolic blood pressure by 8, 10, 12 mm Hg from the baseline, respectively. Patients were re-randomized to either continue receiving the same dose of valsartan or were switched to placebo. In patients who continued to receive the medium and high doses of valsartan, systolic blood pressure at trough was -4 and -7 mm Hg lower than patients who received the placebo treatment. In patients receiving the low dose of valsartan, systolic blood pressure at trough was similar to that of patients who received the placebo treatment. Overall, the dose-dependent antihypertensive effect of valsartan was consistent across all the demographic subgroups.

In another clinical study involving 300 hypertensive paediatric patients 6 to 18 years of age, eligible patients were randomized to receive valsartan or enalapril tablets for 12 weeks. Children weighing between ≥18 kg and <35 kg received valsartan 80 mg or enalapril 10 mg; those between ≥35 kg and <80 kg received valsartan 160 mg or enalapril 20 mg; those ≥80 kg received valsartan 320 mg or enalapril 40 mg. Reductions in systolic blood pressure
were comparable in patients receiving valsartan (15 mmHg) and enalapril (14 mm Hg) (non-inferiority p-value <0.0001). Consistent results were observed for diastolic blood pressure with reductions of 9.1 mmHg and 8.5 mmHg with valsartan and enalapril, respectively.

**Clinical experience in children less than 6 years of age**

Two clinical studies were conducted in patients aged 1 to 6 years with 90 and 75 patients, respectively. No children below the age of 1 year were enrolled in these studies. In the first study, the efficacy of valsartan was confirmed compared to placebo but a dose-response could not be demonstrated. In the second study, higher doses of valsartan were associated with greater BP reductions, but the dose response trend did not achieve statistical significance and the treatment difference compared to placebo was not significant. Because of these inconsistencies, valsartan is not recommended in this age group (see section 4.8).

### 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 (C\text{max}) by about 50%, although from about 8 h post dosing plasma valsartan concentrations are similar for the fed and fasted groups. This reduction in AUC is not, however, accompanied by a clinically significant reduction in the therapeutic effect, and valsartan can therefore be given either with or without food.

**Distribution:**

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

**Biotransformation:**

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

**Excretion:**

Valsartan shows multiexponential decay kinetics (t\text{½α} <1 h and t\text{½β} 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 C\text{max} 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 concentrations 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).

Paediatric population
In a study of 26 paediatric hypertensive patients (aged 1 to 16 years) given a single dose of a suspension of valsartan (mean: 0.9 to 2 mg/kg, with a maximum dose of 80 mg), the clearance (litres/h/kg) of valsartan was comparable across the age range of 1 to 16 years and similar to that of adults receiving the same formulation.

Impaired renal function
Use in paediatric patients with a creatinine clearance < 30 ml/min and paediatric patients undergoing dialysis has not been studied, therefore valsartan is not recommended in these patients. No dose adjustment is required for paediatric patients with a creatinine clearance > 30 ml/min. Renal function and serum potassium should be closely monitored (see sections 4.2 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.

**Paediatric population**

Daily oral dosing of neonatal/juvenile rats (from a postnatal day 7 to postnatal day 70) with valsartan at doses as low as 1 mg/kg/day (about 10-35% of the maximum recommended paediatric dose of 4 mg/kg/day on systemic exposure basis) produced persistent, irreversible kidney damage. These effects above mentioned represent an expected exaggerated pharmacological effect of angiotensin converting enzyme inhibitors and angiotensin II type 1 blockers; such effects are observed if rats are treated during the first 13 days of life. This period coincides with 36 weeks of gestation in humans, which could occasionally extend up to 44 weeks after conception in humans. The rats in the juvenile valsartan study were dosed up to day 70, and effects on renal maturation (postnatal 4-6 weeks) cannot be excluded. Functional renal maturation is an ongoing process within the first year of life in humans. Consequently, a clinical relevance in children <1 year of age cannot be excluded, while preclinical data do not indicate a safety concern for children older than 1 year.

### 6 PHARMACEUTICAL PARTICULARS

#### 6.1 List of excipients

- Lactose monohydrate
- Cellulose, Microcrystalline
- Maize starch
- Crospovidone (Type-A)
- Povidone (PVP-K 30)
- Silica, Colloidal anhydrous
- Magnesium stearate

**Tablet coating**

- Hypromellose (E464)
- Titanium dioxide (E171)
- Macrogol
- Iron oxide Yellow (E172)
- Iron oxide Black (E172)
- Iron oxide Red (E172)
6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years

6.4 Special precautions for storage
Do not store above 30°C. Store in the original package.

6.5 Nature and contents of container
Aluminum-PVC/Aluminum/OPA blister in packs of 14, 28, 30, 50, 56, 60, 98 & 100 tablets
Not all pack sizes may be marketed

6.6 Special precautions for disposal
No specific instructions for use/handling.

7 MARKETING AUTHORITY NUMBER(S)
PL 08553/0394-0397 AND PL 08553/0462-0465

8 MARKETING AUTHORITY NUMBER(S)
PL 08553/0395

9 DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION
19/09/2011

10 DATE OF REVOLUTION OF THE TEXT
19/09/2011
1 NAME OF THE MEDICINAL PRODUCT
Valsartan 160 mg film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
One tablet contains 160 mg valsartan. Also contains 57.00 mg of lactose monohydrate

3 PHARMACEUTICAL FORM
Film-coated tablet.
Grey-orange coloured, oval shaped, film-coated tablet with beveled edge debossed ‘V160’ on one side of the tablet and breakline on the other side.
The tablets can be divided in to two equal halves

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Hypertension
Treatment of essential hypertension in adults, children and adolescents 6 to 18 years of age
Heart Failure
Treatment of symptomatic heart failure in adult patients 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
Hypertension
The recommended dose of Valsartan is 80 mg once daily. The antihypertensive effect is substantially present within 2 weeks, and maximal effects are attained within 4 weeks. In some patients whose blood pressure is not adequately controlled, the dose can be increased to 160 mg and to a maximum of 320 mg.
Valsartan may also be administered with other antihypertensive agents. The addition of a diuretic such as hydrochlorothiazide will decrease blood pressure even further in these patients.
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.

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 tablets are 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

Paediatric hypertension
Children and adolescents 6 to 18 years of age
The initial dose is 40 mg once daily for children weighing below 35 kg and 80 mg once daily for those weighing 35 kg or more. The dose should be adjusted based on blood pressure response. For maximum doses studied in clinical trials please refer to the table below. Doses higher than those listed have not been studied and are therefore not recommended.

<table>
<thead>
<tr>
<th>Weight</th>
<th>Maximum dose studied in clinical trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥18 kg to &lt;35 kg</td>
<td>80 mg</td>
</tr>
<tr>
<td>≥35 kg to &lt;80 kg</td>
<td>160 mg</td>
</tr>
<tr>
<td>≥80 kg to ≤160 kg</td>
<td>320 mg</td>
</tr>
</tbody>
</table>

Children less than 6 years of age
Available data are described in sections 4.8, 5.1 and 5.2. However safety and efficacy of Valsartan in children aged 1 to 6 years have not been established.

Use in paediatric patients aged 6 to 18 years with renal impairment
Use in paediatric patients with a creatinine clearance < 30 ml/min and paediatric patients undergoing dialysis has not been studied, therefore valsartan is not recommended in these patients. No dose adjustment is required for paediatric patients with a creatinine clearance ≥ 30 ml/min. Renal function and serum potassium should be closely monitored (see sections 4.4 and 5.2).

Use in paediatric patients aged 6 to 18 years with hepatic impairment
As in adults, Valsartan tablets are contraindicated in paediatric patients with severe hepatic impairment, biliary cirrhosis and in patients with cholestasis (see sections 4.3, 4.4 and 5.2). There is limited clinical experience with Valsartan in paediatric patients with mild to moderate hepatic impairment. The dose of valsartan should not exceed 80 mg in these patients.

Paediatric heart failure and recent myocardial infarction
Valsartan tablets are not recommended for the treatment of heart failure or recent myocardial infarction in children and adolescents below the age of 18 years due to the lack of data on safety and efficacy.

Method of administration
Valsartan tablets may be taken independently of a meal and should be administered with water.
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
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. No dosage adjustment is required for patients with a creatinine clearance >10 ml/min. (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.

**Paediatric population**

**Impaired renal function**

Use in paediatric patients with a creatinine clearance <30 ml/min and paediatric patients undergoing dialysis has not been studied, therefore valsartan is not recommended in these patients. No dose adjustment is required for paediatric patients with a creatinine clearance >30 ml/min (see sections 4.2 and 5.2). Renal function and serum potassium should be closely monitored during treatment with valsartan. This applies particularly when valsartan is given in the presence of other conditions (fever, dehydration) likely to impair renal function.

**Impaired hepatic function**

As in adults, Valsartan tablets are contraindicated in paediatric patients with severe hepatic impairment, biliary cirrhosis and in patients with cholestasis (see sections 4.3 and 5.2). There is limited clinical experience with Valsartan
in paediatric patients with mild to moderate hepatic impairment. The dose of valsartan should not exceed 80 mg in these patients.

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.

Paediatric population
In hypertension in children and adolescents, where underlying renal abnormalities are common, caution is recommended with the concomitant use of valsartan and other substances that inhibit the renin angiotensin aldosterone system which may increase serum potassium. Renal function and serum potassium should be closely monitored.

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 breast-feeding 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 (≥1/1000 to <1/100); rare (≥1/10,000 to <1/1000); 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

Blood and lymphatic system disorders
<table>
<thead>
<tr>
<th>System</th>
<th>Adverse Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not known</td>
<td>Decrease in haemoglobin, Decrease in haematocrit, Neutropenia, Thrombocytopenia</td>
</tr>
<tr>
<td><strong>Immune system disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Not known</td>
<td>Hypersensitivity including serum sickness</td>
</tr>
<tr>
<td><strong>Metabolism and nutrition disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Not known</td>
<td>Increase of serum potassium</td>
</tr>
<tr>
<td><strong>Ear and labyrinth system disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td>Vertigo</td>
</tr>
<tr>
<td><strong>Vascular disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Not known</td>
<td>Vasculitis</td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td>Cough</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td>Abdominal pain</td>
</tr>
<tr>
<td><strong>Hepato-biliary Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Not known</td>
<td>Elevation of liver function values including increase of serum bilirubin.</td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Not known</td>
<td>Angioedema, Rash, Pruritus</td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Not known</td>
<td>Myalgia</td>
</tr>
<tr>
<td><strong>Renal and urinary disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Not known</td>
<td>Renal failure and impairment, Elevation of serum creatinine</td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td>Fatigue</td>
</tr>
</tbody>
</table>

**Paediatric population**

**Hypertension**

The antihypertensive effect of valsartan has been evaluated in two randomised, double-blind clinical studies in 561 paediatric patients from 6 to 18 years of age. With the exception of isolated gastrointestinal disorders (like abdominal pain, nausea, vomiting) and dizziness, no relevant differences in terms of type, frequency and severity of adverse reactions were identified between the safety profile for paediatric patients aged 6 to 18 years and that previously reported for adult patients.

Neurocognitive and developmental assessment of paediatric patients aged 6 to 16 years of age revealed no overall clinically relevant adverse impact after treatment with valsartan for up to one year.
In a double-blind randomized study in 90 children aged 1 to 6 years, which was followed by a one-year open-label extension, two deaths and isolated cases of marked liver transaminases elevations were observed. These cases occurred in a population who had significant comorbidities. A causal relationship to valsartan has not been established. In a second study in which 75 children aged 1 to 6 years were randomised, no significant liver transaminase elevations or death occurred with valsartan treatment. Hyperkalaemia was more frequently observed in children and adolescents aged 6 to 18 years with underlying chronic kidney disease.

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**
  - **Blood and lymphatic system disorders**
    - Not known Thrombocytopenia
  - **Immune system disorders**
    - Not known Hypersensitivity including serum sickness
  - **Metabolism and nutrition disorders**
    - Uncommon Hyperkalaemia
    - Not known Increase of serum potassium
  - **Nervous system disorders**
    - Common Dizziness, Postural dizziness
    - Uncommon Syncope, Headache
  - **Ear and labyrinth system disorders**
    - Uncommon Vertigo
  - **Cardiac disorders**
    - Uncommon Cardiac failure
  - **Vascular disorders**
    - Common Hypotension, Orthostatic hypotension
    - Not known Vasculitis
  - **Respiratory, thoracic and mediastinal disorders**
    - Uncommon Cough
  - **Gastrointestinal disorders**
    - Uncommon Nausea, Diarrhoea
  - **Hepatobiliary Disorders**
    - Not known Elevation of liver function values
  - **Skin and subcutaneous tissue disorders**
Uncommon Angioedema
Not known Rash, Pruritus

**Musculoskeletal and connective tissue disorders**
Not known Myalgia

**Renal and urinary disorders**
Common Renal failure and impairment
Uncommon Acute renal failure, Elevation of serum creatinine
Not known Increase in Blood Urea Nitrogen

**General disorders and administration site conditions**
Uncommon Asthenia, Fatigue

### 4.9 Overdose

**Symptoms**
Overdose with Valsartan may result in marked hypotension, which could lead to depressed levels 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 groups: 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).

Hypertension
Administration of Valsartan tablets to patients with hypertension results in reduction of blood pressure without affecting pulse rate.

In most patients, after administration of a single oral dose, onset of antihypertensive activity occurs within 2 hours, and the peak reduction of blood pressure is achieved within 4-6 hours. The antihypertensive effect persists over 24 hours after dosing. During repeated dosing, the antihypertensive effect is substantially present within 2 weeks, and maximal effects are attained within 4 weeks and persist during long-term therapy. Combined with hydrochlorothiazide, a significant additional reduction in blood pressure is achieved.

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

In hypertensive patients with type 2 diabetes and microalbuminuria, valsartan has been shown to reduce the urinary excretion of albumin. The MARVAL (Micro Albuminuria Reduction with Valsartan) study assessed the reduction in urinary albumin excretion (UAE) with valsartan (80-160 mg/od) versus amlodipine (5-10 mg/od), in 332 type 2 diabetic patients (mean age: 58 years; 265 men) with microalbuminuria (valsartan: 58 µg/min; amlodipine: 55.4 µg/min), normal or high blood pressure and with preserved renal function (blood creatinine <120 µmol/l). At 24 weeks, UAE was reduced (p<0.001) by 42% (–24.2 µg/min; 95% CI: –40.4 to –19.1) with valsartan and approximately 3% (–1.7 µg/min; 95% CI: –5.6 to 14.9) with amlodipine despite similar rates of blood pressure reduction in both groups.

Furthermore a valsartan tablets study examined that the efficacy of valsartan in reducing UAE in 391 hypertensive patients (BP=150/88 mmHg) with type 2 diabetes, albuminuria (mean=102 µg/min; 20-700 µg/min) and preserved renal function (mean serum creatinine = 80 µmol/l). Patients were randomized to one of 3 doses of valsartan (160, 320 and 640 mg/od) and treated for 30 weeks. The purpose of the study was to determine the optimal dose of valsartan for reducing UAE in hypertensive patients with type 2 diabetes. At 30 weeks, the percentage change in UAE was significantly reduced by 36% from baseline with valsartan 160 mg (95%CI: 22 to 47%), and by 44% with valsartan 320 mg (95%CI: 31 to 54%). It was concluded that 160-320 mg of valsartan produced clinically relevant reductions in UAE in hypertensive patients with type 2 diabetes.

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, and 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 patient’s post-myocardial infarction.
There was no difference in all-cause mortality or 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 (LVIDDI)>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.

**Paediatric population**

**Hypertension**

The antihypertensive effect of valsartan have been evaluated in four randomized, double-blind clinical studies in 561 paediatric patients from 6 to 18 years of age and 165 paediatric patients 1 to 6 years of age. Renal and urinary disorders, and obesity were the most common underlying medical conditions potentially contributing to hypertension in the children enrolled in these studies.

**Clinical experience in children at or above 6 years of age**

In a clinical study involving 261 hypertensive paediatric patients 6 to 16 years of age, patients who weighed <35 kg received 10, 40 or 80 mg of valsartan daily (low, medium and high doses), and patients who weighed ≥35 kg received 20, 80, and 160 mg of valsartan daily (low, medium and high doses). At the end of 2 weeks, valsartan reduced both systolic and diastolic blood pressure in a dose-dependent manner. Overall, the three dose levels of valsartan (low, medium and high) significantly reduced systolic blood pressure by 8, 10, 12 mm Hg from the baseline, respectively. Patients were re-randomized to either continue receiving the same dose of valsartan or were switched to placebo. In patients who continued to receive the medium and high doses of valsartan, systolic blood pressure at trough was -4 and -7 mm Hg lower than patients who received the placebo treatment. In patients receiving the low dose of valsartan, systolic blood pressure at trough was similar to that of patients who received the placebo treatment. Overall, the dose-dependent antihypertensive effect of valsartan was consistent across all the demographic subgroups.

In another clinical study involving 300 hypertensive paediatric patients 6 to 18 years of age, eligible patients were randomized to receive valsartan or enalapril tablets for 12 weeks. Children weighing between ≥18 kg and <35 kg received valsartan 80 mg or enalapril 10 mg; those between ≥35 kg and <80 kg received valsartan 160 mg or enalapril 20 mg; those ≥80 kg received valsartan 320 mg or enalapril 40 mg. Reductions in systolic blood pressure were comparable in patients receiving valsartan (15 mmHg) and enalapril (14 mm Hg) (non-inferiority p-value <0.0001). Consistent results were
observed for diastolic blood pressure with reductions of 9.1 mmHg and 8.5 mmHg with valsartan and enalapril, respectively.

Clinical experience in children less than 6 years of age
Two clinical studies were conducted in patients aged 1 to 6 years with 90 and 75 patients, respectively. No children below the age of 1 year were enrolled in these studies. In the first study, the efficacy of valsartan was confirmed compared to placebo but a dose-response could not be demonstrated. In the second study, higher doses of valsartan were associated with greater BP reductions, but the dose response trend did not achieve statistical significance and the treatment difference compared to placebo was not significant. Because of these inconsistencies, valsartan is not recommended in this age group (see section 4.8).

The European Medicines Agency has waived the obligation to submit the results of studies with valsartan tablets in all subsets of the paediatric population in heart failure and heart failure after recent myocardial infarction. See section 4.2 for information on paediatric use.

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 (C_max) by about 50%, although from about 8 h post dosing plasma valsartan concentrations are similar for the fed and fasted groups. This reduction in AUC is not, however, accompanied by a clinically significant reduction in the therapeutic effect, and valsartan can therefore be given either with or without food.

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

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

Excretion:
Valsartan shows multiexponential decay kinetics (t_{1/α} < 1 h and t_{β} 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 C_max 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 concentrations versus degree of hepatic dysfunction. Valsartan tablets have not been studied in patients with severe hepatic dysfunction (see sections 4.2, 4.3 and 4.4).

**Paediatric population**
In a study of 26 paediatric hypertensive patients (aged 1 to 16 years) given a single dose of a suspension of valsartan (mean: 0.9 to 2 mg/kg, with a maximum dose of 80 mg), the clearance (litres/h/kg) of valsartan was comparable across the age range of 1 to 16 years and similar to that of adults receiving the same formulation.

**Impaired renal function**
Use in paediatric patients with a creatinine clearance <30 ml/min and paediatric patients undergoing dialysis has not been studied, therefore valsartan is not recommended in these patients. No dose adjustment is required for paediatric patients with a creatinine clearance >30 ml/min. Renal function and serum potassium should be closely monitored (see sections 4.2 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.

Paediatric population
Daily oral dosing of neonatal/juvenile rats (from a postnatal day 7 to postnatal day 70) with valsartan at doses as low as 1 mg/kg/day (about 10-35% of the maximum recommended paediatric dose of 4 mg/kg/day on systemic exposure basis) produced persistent, irreversible kidney damage. These effects above mentioned represent an expected exaggerated pharmacological effect of angiotensin converting enzyme inhibitors and angiotensin II type 1 blockers; such effects are observed if rats are treated during the first 13 days of life. This period coincides with 36 weeks of gestation in humans, which could occasionally extend up to 44 weeks after conception in humans. The rats in the juvenile valsartan study were dosed up to day 70, and effects on renal maturation (postnatal 4-6 weeks) cannot be excluded. Functional renal maturation is an ongoing process within the first year of life in humans. Consequently, a clinical relevance in children <1 year of age cannot be excluded, while preclinical data do not indicate a safety concern for children older than 1 year.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Lactose Monohydrate
Cellulose, Microcrystalline
Maize starch
Crospovidone (Type-A)
Povidone
Silica, Colloidal anhydrous
Magnesium stearate

Coating
Hypermellose (E464)
Titanium dioxide (E171)
Macrogol
Iron oxide Yellow (E172)
Iron oxide Black (E172)
Iron oxide Red (E172)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years

6.4 Special precautions for storage
Do not store above 30°C. Store in the original package.

6.5 Nature and contents of container
Aluminium-PVC/Aluminium/OPA blisters in packs of 14, 28, 30, 50, 56, 60, 98 & 100 tablets
Not all pack sizes may be marketed

6.6 Special precautions for disposal
No specific instructions for use/handling.

7 MARKETING AUTHORISATION HOLDER
Dr. Reddy’s Laboratories (UK) Ltd.
6 Riverview Road
Beverley
East Yorkshire
HU17 0LD
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 08553/0396

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
19/09/2011

10 DATE OF REVISION OF THE TEXT
19/09/2011
1 NAME OF THE MEDICINAL PRODUCT
Valsartan 320 mg film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
One tablet contains 320 mg valsartan. Also contains 114.00 mg of lactose monohydrate.

3 PHARMACEUTICAL FORM
Film-coated tablet.
Light brown coloured, oval shaped, film-coated tablet with beveled edge debossed with ‘V’320 on one side of the tablet and breakline on the other side. The tablets can be divided into two equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
**Hypertension**
Treatment of essential hypertension in adults, children and adolescents 6 to 18 years of age.

4.2 Posology and method of administration
**Posology**
**Hypertension**
The recommended dose of Valsartan is 80 mg once daily. The antihypertensive effect is substantially present within 2 weeks, and maximal effects are attained within 4 weeks. In some patients whose blood pressure is not adequately controlled, the dose can be increased to 160 mg and to a maximum of 320 mg.
Valsartan may also be administered with other antihypertensive agents. The addition of a diuretic such as hydrochlorothiazide will decrease blood pressure even further in these patients.

**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 tablets are 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 80mg.

**Paediatric population**
**Paediatric hypertension**
Children and adolescents 6 to 18 years of age
The initial dose is 40 mg once daily for children weighing below 35 kg and 80 mg once daily for those weighing 35 kg or more. The dose should be adjusted based on blood pressure response. For maximum doses studied in clinical trials please refer to the table below.
Doses higher than those listed have not been studied and are therefore not recommended.

<table>
<thead>
<tr>
<th>Weight</th>
<th>Maximum dose studied in clinical trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥18 kg to &lt;35 kg</td>
<td>80 mg</td>
</tr>
<tr>
<td>≥35 kg to &lt;80 kg</td>
<td>160 mg</td>
</tr>
<tr>
<td>≥80 kg to ≤160 kg</td>
<td>320 mg</td>
</tr>
</tbody>
</table>

Children less than 6 years of age
Available data are described in sections 4.8, 5.1 and 5.2. However safety and efficacy of Valsartan in children aged 1 to 6 years have not been established.  

Use in paediatric patients aged 6 to 18 years with renal impairment
Use in paediatric patients with a creatinine clearance <30 ml/min and paediatric patients undergoing dialysis has not been studied, therefore valsartan is not recommended in these patients. No dose adjustment is required for paediatric patients with a creatinine clearance >30 ml/min. Renal function and serum potassium should be closely monitored (see sections 4.4 and 5.2).

Use in paediatric patients aged 6 to 18 years with hepatic impairment
As in adults, Valsartan tablets are contraindicated in paediatric patients with severe hepatic impairment, biliary cirrhosis and in patients with cholestasis (see sections 4.3, 4.4 and 5.2). There is limited clinical experience with Valsartan in paediatric patients with mild to moderate hepatic impairment. The dose of valsartan should not exceed 80 mg in these patients.

Paediatric heart failure and recent myocardial infarction
Valsartan tablets are not recommended for the treatment of heart failure or recent myocardial infarction in children and adolescents below the age of 18 years due to the lack of data on safety and efficacy.

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

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
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. No dosage adjustment is required for patients with a creatinine clearance>10 ml/min. (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).

Other conditions with stimulation of the renin-angiotensin system
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.
**Paediatric population**

**Impaired renal function**

Use in paediatric patients with a creatinine clearance <30 ml/min and paediatric patients undergoing dialysis has not been studied, therefore valsartan is not recommended in these patients. No dose adjustment is required for paediatric patients with a creatinine clearance >30 ml/min (see sections 4.2 and 5.2). Renal function and serum potassium should be closely monitored during treatment with valsartan. This applies particularly when valsartan is given in the presence of other conditions (fever, dehydration) likely to impair renal function.

**Impaired hepatic function**

As in adults, Valsartan tablets are contraindicated in paediatric patients with severe hepatic impairment, biliary cirrhosis and in patients with cholestasis (see sections 4.3 and 5.2). There is limited clinical experience with Valsartan in paediatric patients with mild to moderate hepatic impairment. The dose of valsartan should not exceed 80 mg in these patients.

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.

**Paediatric population**

In hypertension in children and adolescents, where underlying renal abnormalities are common, caution is recommended with the concomitant use of valsartan and other substances that inhibit the renin angiotensin aldosterone system which may increase serum potassium. Renal function and serum potassium should be closely monitored.
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 breast-feeding 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 (≥1/1000 to <1/100); rare (≥1/10,000 to <1/1000); 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**
  - Blood and lymphatic system disorders
    - Not known: Decrease in haemoglobin, Decrease in haematocrit, Neutropenia, Thrombocytopenia
  - Immune system disorders
    - Not known: Hypersensitivity including serum sickness
  - Metabolism and nutrition disorders
    - Not known: Increase of serum potassium
  - Ear and labyrinth system disorders
    - Uncommon: Vertigo
  - Vascular disorders
    - Not known: Vasculitis
  - Respiratory, thoracic and mediastinal disorders
    - Uncommon: Cough
  - Gastrointestinal disorders
    - Uncommon: Abdominal pain
  - Hepato-biliary Disorders
    - Not known: Elevation of liver function values including increase of serum bilirubin.
  - Skin and subcutaneous tissue disorders
    - Not known: Angioedema, Rash, Pruritus
  - Musculoskeletal and connective tissue disorders
    - Not known: Myalgia
  - Renal and urinary disorders
    - Not known: Renal failure and impairment, Elevation of serum creatinine
  - General disorders and administration site conditions
    - Uncommon: Fatigue

**Paediatric population**

Hypertension
The antihypertensive effect of valsartan has been evaluated in two randomised, double-blind clinical studies in 561 paediatric patients from 6 to 18 years of age. With the exception of isolated gastrointestinal disorders (like abdominal pain, nausea, vomiting) and dizziness, no relevant differences in terms of type, frequency and severity of adverse reactions were identified between the safety profile for paediatric patients aged 6 to 18 years and that previously reported for adult patients.

Neurocognitive and developmental assessment of paediatric patients aged 6 to 16 years of age revealed no overall clinically relevant adverse impact after treatment with valsartan for up to one year.

In a double-blind randomized study in 90 children aged 1 to 6 years, which was followed by a one-year open-label extension, two deaths and isolated cases of marked liver transaminases elevations were observed. These cases occurred in a population who had significant comorbidities. A causal relationship to valsartan has not been established. In a second study in which 75 children aged 1 to 6 years were randomised, no significant liver transaminase elevations or death occurred with valsartan treatment. Hyperkalaemia was more frequently observed in children and adolescents aged 6 to 18 years with underlying chronic kidney disease.

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**

  **Blood and lymphatic system disorders**
  - Not known: Thrombocytopenia

  **Immune system disorders**
  - Not known: Hypersensitivity including serum sickness

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

  **Nervous system disorders**
  - Common: Dizziness, Postural dizziness
  - Uncommon: Syncope, Headache

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

  **Cardiac disorders**
  - Uncommon: Cardiac failure

  **Vascular disorders**
  - Common: Hypotension, Orthostatic hypotension
  - Not known: Vasculitis
Respiratory, thoracic and mediastinal disorders
Uncommon Cough

Gastrointestinal disorders
Uncommon Nausea, Diarrhoea

Hepatobiliary Disorders
Not known Elevation of liver function values

Skin and subcutaneous tissue disorders
Uncommon Angioedema
Not known Rash, Pruritus

Musculoskeletal and connective tissue disorders
Not known Myalgia

Renal and urinary disorders
Common Renal failure and impairment
Uncommon Acute renal failure, Elevation of serum creatinine
Not known Increase in Blood Urea Nitrogen

General disorders and administration site conditions
Uncommon Asthenia, Fatigue

4.9 Overdose
Symptoms
Overdose with Valsartan may result in marked hypotension, which could lead to depressed levels 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 groups: 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).

**Hypertension**

Administration of Valsartan tablets to patients with hypertension results in reduction of blood pressure without affecting pulse rate.

In most patients, after administration of a single oral dose, onset of antihypertensive activity occurs within 2 hours, and the peak reduction of blood pressure is achieved within 4-6 hours. The antihypertensive effect persists over 24 hours after dosing. During repeated dosing, the antihypertensive effect is substantially present within 2 weeks, and maximal effects are attained within 4 weeks and persist during long-term therapy. Combined with hydrochlorothiazide, a significant additional reduction in blood pressure is achieved.

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

In hypertensive patients with type 2 diabetes and microalbuminuria, valsartan has been shown to reduce the urinary excretion of albumin. The MARVAL (Micro Albuminuria Reduction with Valsartan) study assessed the reduction in urinary albumin excretion (UAE) with valsartan (80-160 mg/od) versus amlodipine (5-10 mg/od), in 332 type 2 diabetic patients (mean age: 58 years; 265 men) with microalbuminuria (valsartan: 58 µg/min; amlodipine: 55.4 µg/min), normal or high blood pressure and with preserved renal function (blood creatinine <120 µmol/l). At 24 weeks, UAE was reduced (p<0.001) by 42% (–24.2 µg/min; 95% CI: –40.4 to –19.1) with valsartan and approximately 3% (–1.7 µg/min; 95% CI: –5.6 to 14.9) with amlodipine despite similar rates of blood pressure reduction in both groups.

Furthermore a valsartan tablets study examined that the efficacy of valsartan in reducing UAE in 391 hypertensive patients (BP=150/88 mmHg) with type 2 diabetes, albuminuria (mean=102 µg/min; 20-700 µg/min) and preserved renal function (mean serum creatinine = 80 µmol/l). Patients were randomized to one of 3 doses of valsartan (160, 320 and 640 mg/od) and treated for 30 weeks. The purpose of the study was to determine the optimal dose of valsartan for reducing UAE in hypertensive patients with type 2 diabetes. At 30 weeks, the percentage change in UAE was significantly reduced by 36% from baseline with valsartan 160 mg (95%CI: 22 to 47%), and by 44% with valsartan 320 mg (95%CI: 31 to 54%). It was concluded that 160-320 mg of
valsartan produced clinically relevant reductions in UAE in hypertensive patients with type 2 diabetes.

**Paediatric population**

**Hypertension**

The antihypertensive effect of valsartan have been evaluated in four randomized, double-blind clinical studies in 561 paediatric patients from 6 to 18 years of age and 165 paediatric patients 1 to 6 years of age. Renal and urinary disorders, and obesity were the most common underlying medical conditions potentially contributing to hypertension in the children enrolled in these studies.

**Clinical experience in children at or above 6 years of age**

In a clinical study involving 261 hypertensive paediatric patients 6 to 16 years of age, patients who weighed <35 kg received 10, 40 or 80 mg of valsartan daily (low, medium and high doses), and patients who weighed ≥35 kg received 20, 80, and 160 mg of valsartan daily (low, medium and high doses). At the end of 2 weeks, valsartan reduced both systolic and diastolic blood pressure in a dose-dependent manner. Overall, the three dose levels of valsartan (low, medium and high) significantly reduced systolic blood pressure by 8, 10, 12 mm Hg from the baseline, respectively. Patients were re-randomized to either continue receiving the same dose of valsartan or were switched to placebo. In patients who continued to receive the medium and high doses of valsartan, systolic blood pressure at trough was -4 and -7 mm Hg lower than patients who received the placebo treatment. In patients receiving the low dose of valsartan, systolic blood pressure at trough was similar to that of patients who received the placebo treatment. Overall, the dose-dependent antihypertensive effect of valsartan was consistent across all the demographic subgroups.

In another clinical study involving 300 hypertensive paediatric patients 6 to 18 years of age, eligible patients were randomized to receive valsartan or enalapril tablets for 12 weeks. Children weighing between ≥18 kg and <35 kg received valsartan 80 mg or enalapril 10 mg; those between ≥35 kg and <80 kg received valsartan 160 mg or enalapril 20 mg; those ≥80 kg received valsartan 320 mg or enalapril 40 mg. Reductions in systolic blood pressure were comparable in patients receiving valsartan (15 mmHg) and enalapril (14 mm Hg) (non-inferiority p-value <0.0001). Consistent results were observed for diastolic blood pressure with reductions of 9.1 mmHg and 8.5 mmHg with valsartan and enalapril, respectively.

**Clinical experience in children less than 6 years of age**

Two clinical studies were conducted in patients aged 1 to 6 years with 90 and 75 patients, respectively. No children below the age of 1 year were enrolled in these studies. In the first study, the efficacy of valsartan was confirmed compared to placebo but a dose-response could not be demonstrated. In the second study, higher doses of valsartan were associated with greater BP reductions, but the dose-response trend did not achieve statistical significance and the treatment difference compared to placebo was not significant. Because of these inconsistencies, valsartan is not recommended in this age group (see section 4.8).

The European Medicines Agency has waived the obligation to submit the results of studies with valsartan tablets in all subsets of the paediatric...
population in heart failure and heart failure after recent myocardial infarction. See section 4.2 for information on paediatric use.

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 (C_{max}) by about 50%, although from about 8 h post dosing plasma valsartan concentrations are similar for the fed and fasted groups. This reduction in AUC is not, however, accompanied by a clinically significant reduction in the therapeutic effect, and valsartan can therefore be given either with or without food.

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

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

Excretion:
Valsartan shows multiexponential decay kinetics (t_{1/2\alpha} < 1 h and t_{1/2\beta} 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.

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
concentrations versus degree of hepatic dysfunction. Valsartan tablets have not been studied in patients with severe hepatic dysfunction (see sections 4.2, 4.3 and 4.4).

**Paediatric population**
In a study of 26 paediatric hypertensive patients (aged 1 to 16 years) given a single dose of a suspension of valsartan (mean: 0.9 to 2 mg/kg, with a maximum dose of 80 mg), the clearance (litres/h/kg) of valsartan was comparable across the age range of 1 to 16 years and similar to that of adults receiving the same formulation.

**Impaired renal function**
Use in paediatric patients with a creatinine clearance <30 ml/min and paediatric patients undergoing dialysis has not been studied, therefore valsartan is not recommended in these patients. No dose adjustment is required for paediatric patients with a creatinine clearance >30 ml/min. Renal function and serum potassium should be closely monitored (see sections 4.2 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.

**Paediatric population**
Daily oral dosing of neonatal/juvenile rats (from a postnatal day 7 to postnatal day 70) with valsartan at doses as low as 1 mg/kg/day (about 10-35% of the maximum recommended paediatric dose of 4 mg/kg/day on systemic exposure basis) produced persistent, irreversible kidney damage. These effects above mentioned represent an expected exaggerated pharmacological effect of
angiotensin converting enzyme inhibitors and angiotensin II type 1 blockers; such effects are observed if rats are treated during the first 13 days of life. This period coincides with 36 weeks of gestation in humans, which could occasionally extend up to 44 weeks after conception in humans. The rats in the juvenile valsartan study were dosed up to day 70, and effects on renal maturation (postnatal 4-6 weeks) cannot be excluded. Functional renal maturation is an ongoing process within the first year of life in humans. Consequently, a clinical relevance in children <1 year of age cannot be excluded, while preclinical data do not indicate a safety concern for children older than 1 year.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Lactose monohydrate
Cellulose, Microcrystalline
Maize starch
Crospovidone (Type-A)
Povidone (PVP-K 30)
Silica, Colloidal anhydrous
Magnesium stearate

Tablet Coating
Hyromellose
Titanium dioxide
Macrogol
Iron oxide Yellow (E172)
Iron oxide Black (E172)
Iron oxide Red (E172)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years

6.4 Special precautions for storage
Do not store above 30°C. Store in the original package

6.5 Nature and contents of container
Aluminium-PVC/Aluminium/OPA blister packs of 14, 28, 30, 50, 56, 60, 98 & 100 tablets
Not all pack sizes may be marketed

6.6 Special precautions for disposal
No specific instructions for use/handling.
MARKETING AUTHORISATION HOLDER
Dr. Reddy's Laboratories (UK) Ltd.
6 Riverview Road
Beverley
East Yorkshire
HU17 0LD
United Kingdom

MARKETING AUTHORISATION NUMBER(S)
PL 08553/0397

DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
19/09/2011

DATE OF REVISION OF THE TEXT
19/09/2011
1 NAME OF THE MEDICINAL PRODUCT
Valsartan 40 mg film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 40 mg valsartan. Also contains 14.25 mg of lactose monohydrate.

3 PHARMACEUTICAL FORM
Film-coated tablet.
Yellow coloured, oval shaped, film-coated tablet with beveled edge debossed ‘V’ on one side and ‘4’ and ‘0’ on either side of the breakline on the other side.

The tablets can be divided into two equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Hypertension
Treatment of hypertension in children and adolescents 6 to 18 years of age
Heart Failure
Treatment of symptomatic heart failure in adult patients 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.

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 tablets are 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 80mg.

**Paediatric population**

**Paediatric hypertension**

**Children and adolescents 6 to 18 years of age**

The initial dose is 40 mg once daily for children weighing below 35 kg and 80 mg once daily for those weighing 35 kg or more. The dose should be adjusted based on blood pressure response. For maximum doses studied in clinical trials please refer to the table below.

Doses higher than those listed have not been studied and are therefore not recommended.

<table>
<thead>
<tr>
<th>Weight</th>
<th>Maximum dose studied in clinical trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥18 kg to &lt;35 kg</td>
<td>80 mg</td>
</tr>
<tr>
<td>≥35 kg to &lt;80 kg</td>
<td>160 mg</td>
</tr>
<tr>
<td>≥80 kg to ≤160 kg</td>
<td>320 mg</td>
</tr>
</tbody>
</table>

**Children less than 6 years of age**

Available data are described in sections 4.8, 5.1 and 5.2. However safety and efficacy of valsartan in children aged 1 to 6 years have not been established.

**Use in paediatric patients aged 6 to 18 years with renal impairment**

Use in paediatric patients with a creatinine clearance <30 ml/min and paediatric patients undergoing dialysis has not been studied, therefore valsartan is not recommended in these patients. No dose adjustment is required for paediatric patients with a creatinine clearance >30 ml/min. Renal function and serum potassium should be closely monitored (see sections 4.4 and 5.2).

**Use in paediatric patients aged 6 to 18 years with hepatic impairment**

As in adults, Valsartan tablets are contraindicated in paediatric patients with severe hepatic impairment, biliary cirrhosis and in patients with cholestasis (see sections 4.3, 4.4 and 5.2). There is limited clinical experience with Valsartan in paediatric patients with mild to moderate hepatic impairment. The dose of valsartan should not exceed 80 mg in these patients.

**Paediatric heart failure and recent myocardial infarction**

Valsartan tablets are not recommended for the treatment of heart failure or recent myocardial infarction in children and adolescents below the age of 18 years due to the lack of data on safety and efficacy.

**Method of administration**

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

### 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
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. No dosage adjustment is required for patients with a creatinine clearance >10 ml/min. (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.

Paediatric population

Impaired renal function

Use in paediatric patients with a creatinine clearance <30 ml/min and paediatric patients undergoing dialysis has not been studied, therefore valsartan is not recommended in these patients. No dose adjustment is required for paediatric patients with a creatinine clearance >30 ml/min (see sections 4.2 and 5.2). Renal function and serum potassium should be closely monitored during treatment with valsartan. This applies particularly when valsartan is given in the presence of other conditions (fever, dehydration) likely to impair renal function.

Impaired hepatic function

As in adults, Valsartan tablets are contraindicated in paediatric patients with severe hepatic impairment, biliary cirrhosis and in patients with cholestasis (see sections 4.3 and 5.2). There is limited clinical experience with Valsartan in paediatric patients with mild to moderate hepatic impairment. The dose of valsartan should not exceed 80 mg in these patients.

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.

Paediatric population

In hypertension in children and adolescents, where underlying renal abnormalities are common, caution is recommended with the concomitant use of valsartan and other substances that inhibit the renin angiotensin aldosterone system which may increase serum potassium. Renal function and serum potassium should be closely monitored.

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 breast-feeding 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 (≥1/1000 to <1/100); rare (≥1/10,000 to <1/1000); 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**
  - **Blood and lymphatic system disorders**
    - Not known: Decrease in haemoglobin, Decrease in haematocrit, Neutropenia, Thrombocytopenia
  - **Immune system disorders**
    - Not known: Hypersensitivity including serum sickness
  - **Metabolism and nutrition disorders**
    - Not known: Increase of serum potassium
Ear and labyrinth system disorders
Uncommon Vertigo

Vascular disorders
Not known Vasculitis

Respiratory, thoracic and mediastinal disorders
Uncommon Cough

Gastrointestinal disorders
Uncommon Abdominal pain

Hepato-biliary Disorders
Not known Elevation of liver function values including increase of serum bilirubin.

Skin and subcutaneous tissue disorders
Not known Angioedema, Rash, Pruritus

Musculoskeletal and connective tissue disorders
Not known Myalgia

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

General disorders and administration site conditions
Uncommon: Fatigue

Paediatric population
Hypertension
The antihypertensive effect of valsartan has been evaluated in two randomised, double-blind clinical studies in 561 paediatric patients from 6 to 18 years of age. With the exception of isolated gastrointestinal disorders (like abdominal pain, nausea, vomiting) and dizziness, no relevant differences in terms of type, frequency and severity of adverse reactions were identified between the safety profile for paediatric patients aged 6 to 18 years and that previously reported for adult patients.

Neurocognitive and developmental assessment of paediatric patients aged 6 to 16 years of age revealed no overall clinically relevant adverse impact after treatment with valsartan for up to one year.

In a double-blind randomized study in 90 children aged 1 to 6 years, which was followed by a one-year open-label extension, two deaths and isolated cases of marked liver transaminases elevations were observed. These cases occurred in a population who had significant comorbidities. A causal relationship to valsartan has not been established. In a second study in which 75 children aged 1 to 6 years were randomised, no significant liver transaminase elevations or death occurred with valsartan treatment. Hyperkalaemia was more frequently observed in children and adolescents aged 6 to 18 years with underlying chronic kidney disease.
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**

**Blood and lymphatic system disorders**
- Not known: Thrombocytopenia

**Immune system disorders**
- Not known: Hypersensitivity including serum sickness

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

**Nervous system disorders**
- Common: Dizziness, Postural dizziness
- Uncommon: Syncope, Headache

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

**Cardiac disorders**
- Uncommon: Cardiac failure

**Vascular disorders**
- Common: Hypotension, Orthostatic hypotension
- Not known: Vasculitis

**Respiratory, thoracic and mediastinal disorders**
- Uncommon: Cough

**Gastrointestinal disorders**
- Uncommon: Nausea, Diarrhoea

**Hepatobiliary Disorders**
- Not known: Elevation of liver function values

**Skin and subcutaneous tissue disorders**
- Uncommon: Angioedema
- Not known: Rash, Pruritus

**Musculoskeletal and connective tissue disorders**
- Not known: Myalgia

**Renal and urinary disorders**
- Common: Renal failure and impairment
- Uncommon: Acute renal failure, Elevation of serum
creatinine
Not known Increase in Blood Urea Nitrogen

**General disorders and administration site conditions**

Uncommon Asthenia, Fatigue

### 4.9 Overdose

**Symptoms**

Overdose with Valsartan may result in marked hypotension, which could lead to depressed levels 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 groups: 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 AT\(_2\) receptor, which appears to counterbalance the effect of the AT\(_1\) receptor. Valsartan does not exhibit any partial agonist activity at the AT\(_1\) receptor and has much (about 20,000 fold) greater affinity for the AT\(_1\) receptor than for the AT\(_2\) receptor. Valsartan is not known to bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

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, and 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 patient’s post-myocardial infarction.

There was no difference in all-cause mortality or 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 LVIDDD significantly reduced from baseline at endpoint compared to placebo.

**Paediatric population**

**Hypertension**

The antihypertensive effect of valsartan have been evaluated in four randomized, double-blind clinical studies in 561 paediatric patients from 6 to 18 years of age and 165 paediatric patients 1 to 6 years of age. Renal and urinary disorders, and obesity were the most common underlying medical conditions potentially contributing to hypertension in the children enrolled in these studies.

**Clinical experience in children at or above 6 years of age**

In a clinical study involving 261 hypertensive paediatric patients 6 to 16 years of age, patients who weighed <35 kg received 10, 40 or 80 mg of valsartan daily (low, medium and high doses), and patients who weighed ≥35 kg received 20, 80, and 160 mg of valsartan daily (low, medium and high doses). At the end of 2 weeks, valsartan reduced both systolic and diastolic blood pressure in a dose-dependent manner. Overall, the three dose levels of valsartan (low, medium and high) significantly reduced systolic blood pressure by 8, 10, 12 mm Hg from the baseline, respectively. Patients were re-randomized to either continue receiving the same dose of valsartan or were switched to placebo. In patients who continued to receive the medium and high doses of valsartan, systolic blood pressure at trough was -4 and -7 mm Hg lower than patients who received the placebo treatment. In patients receiving the low dose of valsartan, systolic blood pressure at trough was similar to that of patients who received the placebo treatment. Overall, the dose-dependent antihypertensive effect of valsartan was consistent across all the demographic subgroups.

In another clinical study involving 300 hypertensive paediatric patients 6 to 18 years of age, eligible patients were randomized to receive valsartan or enalapril tablets for 12 weeks. Children weighing between ≥18 kg and <35 kg
received valsartan 80 mg or enalapril 10 mg; those between ≥35 kg and <80 kg received valsartan 160 mg or enalapril 20 mg; those ≥80 kg received valsartan 320 mg or enalapril 40 mg. Reductions in systolic blood pressure were comparable in patients receiving valsartan (15 mmHg) and enalapril (14 mmHg) (non-inferiority p-value <0.0001). Consistent results were observed for diastolic blood pressure with reductions of 9.1 mmHg and 8.5 mmHg with valsartan and enalapril, respectively.

Clinical experience in children less than 6 years of age
Two clinical studies were conducted in patients aged 1 to 6 years with 90 and 75 patients, respectively. No children below the age of 1 year were enrolled in these studies. In the first study, the efficacy of valsartan was confirmed compared to placebo but a dose-response could not be demonstrated. In the second study, higher doses of valsartan were associated with greater BP reductions, but the dose response trend did not achieve statistical significance and the treatment difference compared to placebo was not significant. Because of these inconsistencies, valsartan is not recommended in this age group (see section 4.8).

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 (C_max) by about 50%, although from about 8 h post dosing plasma valsartan concentrations are similar for the fed and fasted groups. This reduction in AUC is not, however, accompanied by a clinically significant reduction in the therapeutic effect, and valsartan can therefore be given either with or without food.

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

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

Excretion:
Valsartan shows multiexponential decay kinetics (t_1/α <1 h and t_1/β 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 C_max 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 concentrations 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).

**Paediatric population**

In a study of 26 paediatric hypertensive patients (aged 1 to 16 years) given a single dose of a suspension of valsartan (mean: 0.9 to 2 mg/kg, with a maximum dose of 80 mg), the clearance (litres/h/kg) of valsartan was comparable across the age range of 1 to 16 years and similar to that of adults receiving the same formulation.

**Impaired renal function**

Use in paediatric patients with a creatinine clearance <30 ml/min and paediatric patients undergoing dialysis has not been studied, therefore valsartan is not recommended in these patients. No dose adjustment is required for paediatric patients with a creatinine clearance >30 ml/min. Renal function and serum potassium should be closely monitored (see sections 4.2 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.

**Paediatric population**
Daily oral dosing of neonatal/juvenile rats (from a postnatal day 7 to postnatal day 70) with valsartan at doses as low as 1 mg/kg/day (about 10-35% of the maximum recommended paediatric dose of 4 mg/kg/day on systemic exposure basis) produced persistent, irreversible kidney damage. These effects above mentioned represent an expected exaggerated pharmacological effect of angiotensin converting enzyme inhibitors and angiotensin II type 1 blockers; such effects are observed if rats are treated during the first 13 days of life. This period coincides with 36 weeks of gestation in humans, which could occasionally extend up to 44 weeks after conception in humans. The rats in the juvenile valsartan study were dosed up to day 70, and effects on renal maturation (postnatal 4-6 weeks) cannot be excluded. Functional renal maturation is an ongoing process within the first year of life in humans. Consequently, a clinical relevance in children <1 year of age cannot be excluded, while preclinical data do not indicate a safety concern for children older than 1 year.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Lactose monohydrate
Cellulose, Microcrystalline
Maize starch
Crosopovidone (Type-A)
Povidone (PVP-K 30)
Silica, Colloidal anhydrous
Magnesium stearate

**Tablet Coating**
Hypermellose 6cP (E464)
Titanium dioxide (E171)
Macrogol
Talc (E553b)
Yellow Iron oxide (E172)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years

6.4 Special precautions for storage
Do not store above 30°C. Store in the original package.

6.5 Nature and contents of container
Aluminium-PVC/Aluminium/OPA blister in packs of 14,
Not all pack sizes may be marketed

6.6 Special precautions for disposal
None

7 MARKETING AUTHORISATION HOLDER
Dr. Reddy's Laboratories (UK) Ltd.
6 Riverview Road
Beverley
East Yorkshire
HU17 0LD
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 08553/0462

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE
AUTHORISATION
19/09/2011

10 DATE OF REVISION OF THE TEXT
19/09/2011
1 NAME OF THE MEDICINAL PRODUCT
Valsartan 80 mg film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 80 mg valsartan. Also contains 28.50 mg of lactose monohydrate.

3 PHARMACEUTICAL FORM
Film-coated tablet.
Pink coloured, round, film-coated tablet with beveled edge debossed with ‘V’ on one side of the tablet 80 and breakline on the other side.

The tablets can be divided in to two equal halves

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypertension
Treatment of essential hypertension in adults, children and adolescents 6 to 18 years of age

Heart Failure
Treatment of symptomatic heart failure in adult patients 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

Hypertension
The recommended dose of Valsartan is 80 mg once daily. The antihypertensive effect is substantially present within 2 weeks, and maximal effects are attained within 4 weeks. In some patients whose blood pressure is not adequately controlled, the dose can be increased to 160 mg and to a maximum of 320 mg.

Valsartan may also be administered with other antihypertensive agents. The addition of a diuretic such as hydrochlorothiazide will decrease blood pressure even further in these patients.

Heart failure
The recommended starting dose of Valsartan is 40 mg twice daily. Up titration 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.

**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 tablets are 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 80mg.

**Paediatric population**

**Paediatric hypertension**

**Children and adolescents 6 to 18 years of age**
The initial dose is 40 mg once daily for children weighing below 35 kg and 80 mg once daily for those weighing 35 kg or more. The dose should be adjusted based on blood pressure response. For maximum doses studied in clinical trials please refer to the table below.

Doses higher than those listed have not been studied and are therefore not recommended.

<table>
<thead>
<tr>
<th>Weight</th>
<th>Maximum dose studied in clinical trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥18 kg to &lt;35 kg</td>
<td>80 mg</td>
</tr>
<tr>
<td>≥35 kg to &lt;80 kg</td>
<td>160 mg</td>
</tr>
<tr>
<td>≥80 kg to ≤160 kg</td>
<td>320 mg</td>
</tr>
</tbody>
</table>

**Children less than 6 years of age**
Available data are described in sections 4.8, 5.1 and 5.2. However safety and efficacy of Valsartan in children aged 1 to 6 years have not been established.

**Use in paediatric patients aged 6 to 18 years with renal impairment**
Use in paediatric patients with a creatinine clearance <30 ml/min and paediatric patients undergoing dialysis has not been studied, therefore valsartan is not recommended in these patients. No dose adjustment is required for paediatric patients with a creatinine clearance >30 ml/min. Renal function and serum potassium should be closely monitored (see sections 4.4 and 5.2).

**Use in paediatric patients aged 6 to 18 years with hepatic impairment**
As in adults, Valsartan tablets are contraindicated in paediatric patients with severe hepatic impairment, biliary cirrhosis and in patients with cholestasis (see sections 4.3, 4.4 and 5.2). There is limited clinical experience with Valsartan in paediatric patients with mild to moderate hepatic impairment. The dose of valsartan should not exceed 80 mg in these patients.

**Paediatric heart failure and recent myocardial infarction**
Valsartan tablets are not recommended for the treatment of heart failure or recent myocardial infarction in children and adolescents below the age of 18 years due to the lack of data on safety and efficacy.
Method of administration
Valsartan tablets may be taken independently of a meal and should be administered with water.

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
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. No dosage adjustment is required for patients with a creatinine clearance>10 ml/min. (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.

Paediatric population

Impaired renal function

Use in paediatric patients with a creatinine clearance <30 ml/min and paediatric patients undergoing dialysis has not been studied, therefore valsartan is not recommended in these patients. No dose adjustment is required for paediatric patients with a creatinine clearance >30 ml/min (see sections 4.2 and 5.2). Renal function and serum potassium should be closely monitored during treatment with valsartan. This applies particularly when valsartan is given in the presence of other conditions (fever, dehydration) likely to impair renal function.
Impaired hepatic function
As in adults, Valsartan tablets are contraindicated in paediatric patients with severe hepatic impairment, biliary cirrhosis and in patients with cholestasis (see sections 4.3 and 5.2). There is limited clinical experience with Valsartan in paediatric patients with mild to moderate hepatic impairment. The dose of valsartan should not exceed 80 mg in these patients.

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.

Paediatric population
In hypertension in children and adolescents, where underlying renal abnormalities are common, caution is recommended with the concomitant use of valsartan and other substances that inhibit the renin angiotensin aldosterone system which may increase serum potassium. Renal function and serum potassium should be closely monitored.

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 breast-feeding 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 (≥1/1000 to <1/100); rare (≥1/10,000 to <1/1000); 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**
  
  **Blood and lymphatic system disorders**
  
  Not known: Decrease in haemoglobin, Decrease in haematocrit, Neutropenia, Thrombocytopenia

  **Immune system disorders**
  
  Not known: Hypersensitivity including serum sickness

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

  **Ear and labyrinth system disorders**
  
  Uncommon: Vertigo

  **Vascular disorders**
  
  Not known: Vasculitis

  **Respiratory, thoracic and mediastinal disorders**
  
  Uncommon: Cough

  **Gastrointestinal disorders**
  
  Uncommon: Abdominal pain

  **Hepato-biliary Disorders**
  
  Not known: Elevation of liver function values including increase of serum bilirubin.

  **Skin and subcutaneous tissue disorders**
  
  Not known: Angioedema, Rash, Pruritus

  **Musculoskeletal and connective tissue disorders**
  
  Not known: Myalgia

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

  **General disorders and administration site conditions**
  
  Uncommon: Fatigue

*Paediatric population*

**Hypertension**

The antihypertensive effect of valsartan has been evaluated in two randomised, double-blind clinical studies in 561 paediatric patients from 6 to 18 years of age. With the exception of isolated gastrointestinal disorders (like abdominal pain, nausea, vomiting) and dizziness, no relevant differences in terms of type, frequency and severity of adverse reactions were identified between the safety profile for paediatric patients aged 6 to 18 years and that previously reported for adult patients.
Neurocognitive and developmental assessment of paediatric patients aged 6 to 16 years of age revealed no overall clinically relevant adverse impact after treatment with valsartan for up to one year. In a double-blind randomized study in 90 children aged 1 to 6 years, which was followed by a one-year open-label extension, two deaths and isolated cases of marked liver transaminases elevations were observed. These cases occurred in a population who had significant comorbidities. A causal relationship to valsartan has not been established. In a second study in which 75 children aged 1 to 6 years were randomised, no significant liver transaminase elevations or death occurred with valsartan treatment. Hyperkalaemia was more frequently observed in children and adolescents aged 6 to 18 years with underlying chronic kidney disease. 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**
  - **Blood and lymphatic system disorders**
    - Not known: Thrombocytopenia
  - **Immune system disorders**
    - Not known: Hypersensitivity including serum sickness
  - **Metabolism and nutrition disorders**
    - Uncommon: Hyperkalaemia
    - Not known: Increase of serum potassium
  - **Nervous system disorders**
    - Common: Dizziness, Postural dizziness
    - Uncommon: Syncope, Headache
  - **Ear and labyrinth system disorders**
    - Uncommon: Vertigo
  - **Cardiac disorders**
    - Uncommon: Cardiac failure
  - **Vascular disorders**
    - Common: Hypotension, Orthostatic hypotension
    - Not known: Vasculitis
  - **Respiratory, thoracic and mediastinal disorders**
    - Uncommon: Cough
  - **Gastrointestinal disorders**
    - Uncommon: Nausea, Diarrhoea
  - **Hepatobiliary Disorders**
Not known  Elevation of liver function values

**Skin and subcutaneous tissue disorders**

Uncommon  Angioedema
Not known  Rash, Pruritus

**Musculoskeletal and connective tissue disorders**

Not known  Myalgia

**Renal and urinary disorders**

Common  Renal failure and impairment
Uncommon  Acute renal failure, Elevation of serum creatinine
Not known  Increase in Blood Urea Nitrogen

**General disorders and administration site conditions**

Uncommon  Asthenia, Fatigue

### 4.9 Overdose

**Symptoms**

Overdose with Valsartan may result in marked hypotension, which could lead to depressed levels 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 groups: 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 AT_2 receptor, which appears to counterbalance the effect of the AT_1 receptor. Valsartan does not exhibit any partial agonist activity at the AT_1 receptor and has much (about 20,000 fold) greater affinity for the AT_1 receptor than for the AT_2 receptor. Valsartan is not known to bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

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).

Hypertension
行政stration of valsartan to patients with hypertension results in reduction of blood pressure without affecting pulse rate.
In most patients, after administration of a single oral dose, onset of antihypertensive activity occurs within 2 hours, and the peak reduction of blood pressure is achieved within 4-6 hours. The antihypertensive effect persists over 24 hours after dosing. During repeated dosing, the antihypertensive effect is substantially present within 2 weeks, and maximal effects are attained within 4 weeks and persist during long-term therapy. Combined with hydrochlorothiazide, a significant additional reduction in blood pressure is achieved.
Abrupt withdrawal of valsartan has not been associated with rebound hypertension or other adverse clinical events.
In hypertensive patients with type 2 diabetes and microalbuminuria, valsartan has been shown to reduce the urinary excretion of albumin. The MARVAL (Micro Albuminuria Reduction with Valsartan) study assessed the reduction in urinary albumin excretion (UAE) with valsartan (80-160 mg/od) versus amlodipine (5-10 mg/od), in 332 type 2 diabetic patients (mean age: 58 years; 265 men) with microalbuminuria (valsartan: 58 µg/min; amlodipine: 55.4 µg/min), normal or high blood pressure and with preserved renal function (blood creatinine <120 µmol/l). At 24 weeks, UAE was reduced (p<0.001) by 42% (–24.2 µg/min; 95% CI: –40.4 to –19.1) with valsartan and approximately 3% (–1.7 µg/min; 95% CI: –5.6 to 14.9) with amlodipine despite similar rates of blood pressure reduction in both groups.
Furthermore another study examined that the efficacy of valsartan in reducing UAE in 391 hypertensive patients (BP=150/88 mmHg) with type 2 diabetes, albuminuria (mean=102 µg/min; 20-700 µg/min) and preserved renal function (mean serum creatinine = 80 µmol/l). Patients were randomized to one of 3 doses of valsartan (160, 320 and 640 mg/od) and treated for 30 weeks. The purpose of the study was to determine the optimal dose of valsartan for reducing UAE in hypertensive patients with type 2 diabetes. At 30 weeks, the percentage change in UAE was significantly reduced by 36% from baseline with valsartan 160 mg (95%CI: 22 to 47%), and by 44% with valsartan 320 mg (95%CI: 31 to 54%). It was concluded that 160-320 mg of valsartan produced clinically relevant reductions in UAE in hypertensive patients with type 2 diabetes.
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, and 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 patient’s post-myocardial infarction.

There was no difference in all-cause mortality or 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.

**Paediatric population**

**Hypertension**

The antihypertensive effect of valsartan have been evaluated in four randomized, double-blind clinical studies in 561 paediatric patients from 6 to 18 years of age and 165 paediatric patients 1 to 6 years of age. Renal and urinary disorders, and obesity were the most common underlying medical conditions potentially contributing to hypertension in the children enrolled in these studies.

**Clinical experience in children at or above 6 years of age**

In a clinical study involving 261 hypertensive paediatric patients 6 to 16 years of age, patients who weighed <35 kg received 10, 40 or 80 mg of valsartan daily (low, medium and high doses), and patients who weighed ≥35 kg received 20, 80, and 160 mg of valsartan daily (low, medium and high doses). At the end of 2 weeks, valsartan reduced both systolic and diastolic blood pressure in a dose-dependent manner. Overall, the three dose levels of valsartan (low, medium and high) significantly reduced systolic blood pressure by 8, 10, 12 mm Hg from the baseline, respectively. Patients were re-randomized to either continue receiving the same dose of valsartan or were switched to placebo. In patients who continued to receive the medium and high doses of valsartan, systolic blood pressure at trough was -4 and -7 mm Hg lower than patients who received the placebo treatment. In patients receiving the low dose of valsartan, systolic blood pressure at trough was similar to that of patients who received the placebo treatment. Overall, the dose-dependent antihypertensive effect of valsartan was consistent across all the demographic subgroups.

In another clinical study involving 300 hypertensive paediatric patients 6 to 18 years of age, eligible patients were randomized to receive valsartan or enalapril tablets for 12 weeks. Children weighing between ≥18 kg and <35 kg received valsartan 80 mg or enalapril 10 mg; those between ≥35 kg and <80 kg received valsartan 160 mg or enalapril 20 mg; those ≥80 kg received valsartan 320 mg or enalapril 40 mg. Reductions in systolic blood pressure
were comparable in patients receiving valsartan (15 mmHg) and enalapril (14 mmHg) (non-inferiority p-value <0.0001). Consistent results were observed for diastolic blood pressure with reductions of 9.1 mmHg and 8.5 mmHg with valsartan and enalapril, respectively.

Clinical experience in children less than 6 years of age
Two clinical studies were conducted in patients aged 1 to 6 years with 90 and 75 patients, respectively. No children below the age of 1 year were enrolled in these studies. In the first study, the efficacy of valsartan was confirmed compared to placebo but a dose-response could not be demonstrated. In the second study, higher doses of valsartan were associated with greater BP reductions, but the dose response trend did not achieve statistical significance and the treatment difference compared to placebo was not significant. Because of these inconsistencies, valsartan is not recommended in this age group (see section 4.8).

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 (C_max) by about 50%, although from about 8 h post dosing plasma valsartan concentrations are similar for the fed and fasted groups. This reduction in AUC is not, however, accompanied by a clinically significant reduction in the therapeutic effect, and valsartan can therefore be given either with or without food.

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

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

Excretion:
Valsartan shows multiexponential decay kinetics (t_1/2α <1 h and t_1/2β 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 C_max 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 concentrations 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).

**Paediatric population**
In a study of 26 paediatric hypertensive patients (aged 1 to 16 years) given a single dose of a suspension of valsartan (mean: 0.9 to 2 mg/kg, with a maximum dose of 80 mg), the clearance (litres/h/kg) of valsartan was comparable across the age range of 1 to 16 years and similar to that of adults receiving the same formulation.

**Impaired renal function**
Use in paediatric patients with a creatinine clearance <30 ml/min and paediatric patients undergoing dialysis has not been studied, therefore valsartan is not recommended in these patients. No dose adjustment is required for paediatric patients with a creatinine clearance >30 ml/min. Renal function and serum potassium should be closely monitored (see sections 4.2 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.

Paediatric population
Daily oral dosing of neonatal/juvenile rats (from a postnatal day 7 to
postnatal day 70) with valsartan at doses as low as 1 mg/kg/day (about
10-35% of the maximum recommended paediatric dose of 4 mg/kg/day on
systemic exposure basis) produced persistent, irreversible kidney damage.
These effects above mentioned represent an expected exaggerated
pharmacological effect of angiotensin converting enzyme inhibitors and
angiotensin II type 1 blockers; such effects are observed if rats are treated
during the first 13 days of life. This period coincides with 36 weeks of
gestation in humans, which could occasionally extend up to 44 weeks after
conception in humans. The rats in the juvenile valsartan study were dosed
up to day 70, and effects on renal maturation (postnatal 4-6 weeks) cannot
be excluded. Functional renal maturation is an ongoing process within the
first year of life in humans. Consequently, a clinical relevance in children
<1 year of age cannot be excluded, while preclinical data do not indicate a
safety concern for children older than 1 year

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Lactose monohydrate
Cellulose, Microcrystalline
Maize starch
Crospovidone (Type-A)
Povidone (PVP-K 30)
Silica, Colloidal anhydrous
Magnesium stearate

Tablet coating
Hypropomellose (E464)
Titanium dioxide (E171)
Macrogol
Iron oxide Yellow (E172)
Iron oxide Black (E172)
Iron oxide Red (E172)
6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years

6.4 Special precautions for storage
Do not store above 30°C. Store in the original package.

6.5 Nature and contents of container
Aluminum-PVC/Aluminum/OPA blister in packs of 28 tablets
Not all pack sizes may be marketed

6.6 Special precautions for disposal
No specific instructions for use/handling.

7 MARKETING AUTHORISATION HOLDER
Dr. Reddy’s Laboratories (UK) Ltd.
6 Riverview Road
Beverley
East Yorkshire
HU17 0LD
United Kingdom

8 MARKETING AUTHORITY NUMBER(S)
PL 08553/0463

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORITY
19/09/2011

10 DATE OF REVISION OF THE TEXT
19/09/2011
1 NAME OF THE MEDICINAL PRODUCT
Valsartan 160 mg film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
One tablet contains 160 mg valsartan. Also contains 57.00 mg of lactose monohydrate

3 PHARMACEUTICAL FORM
Film-coated tablet.

Grey-orange coloured, oval shaped, film-coated tablet with beveled edge debossed ‘V160’ on one side of the tablet and breakline on the other side.

The tablets can be divided into two equal halves

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Hypertension
Treatment of essential hypertension in adults, children and adolescents 6 to 18 years of age
Heart Failure
Treatment of symptomatic heart failure in adult patients 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
Hypertension
The recommended dose of Valsartan is 80 mg once daily. The antihypertensive effect is substantially present within 2 weeks, and maximal effects are attained within 4 weeks. In some patients whose blood pressure is not adequately controlled, the dose can be increased to 160 mg and to a maximum of 320 mg.
Valsartan may also be administered with other antihypertensive agents. The addition of a diuretic such as hydrochlorothiazide will decrease blood pressure even further in these patients.
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.

**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 tablets are 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 80mg.

**Paediatric population**

**Paediatric hypertension**

*Children and adolescents 6 to 18 years of age*

The initial dose is 40 mg once daily for children weighing below 35 kg and 80 mg once daily for those weighing 35 kg or more. The dose should be adjusted based on blood pressure response. For maximum doses studied in clinical trials please refer to the table below.

Doses higher than those listed have not been studied and are therefore not recommended.

<table>
<thead>
<tr>
<th>Weight</th>
<th>Maximum dose studied in clinical trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥18 kg to &lt;35 kg</td>
<td>80 mg</td>
</tr>
<tr>
<td>≥35 kg to &lt;80 kg</td>
<td>160 mg</td>
</tr>
<tr>
<td>≥80 kg to ≤160 kg</td>
<td>320 mg</td>
</tr>
</tbody>
</table>

*Children less than 6 years of age*

Available data are described in sections 4.8, 5.1 and 5.2. However safety and efficacy of Valsartan in children aged 1 to 6 years have not been established.

**Use in paediatric patients aged 6 to 18 years with renal impairment**

Use in paediatric patients with a creatinine clearance <30 ml/min and paediatric patients undergoing dialysis has not been studied, therefore valsartan is not recommended in these patients. No dose adjustment is required for paediatric patients with a creatinine clearance >30 ml/min. Renal function and serum potassium should be closely monitored (see sections 4.4 and 5.2).

**Use in paediatric patients aged 6 to 18 years with hepatic impairment**

As in adults, Valsartan tablets are contraindicated in paediatric patients with severe hepatic impairment, biliary cirrhosis and in patients with cholestasis (see sections 4.3, 4.4 and 5.2). There is limited clinical experience with Valsartan in paediatric patients with mild to moderate hepatic impairment. The dose of valsartan should not exceed 80 mg in these patients.

**Paediatric heart failure and recent myocardial infarction**

Valsartan tablets are not recommended for the treatment of heart failure or recent myocardial infarction in children and adolescents below the age of 18 years due to the lack of data on safety and efficacy.

**Method of administration**

Valsartan tablets may be taken independently of a meal and should be administered with water.
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
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. No dosage adjustment is required for patients with a creatinine clearance>10 ml/min.(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 AII RAs 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.

Paediatric population

Impaired renal function

Use in paediatric patients with a creatinine clearance <30 ml/min and paediatric patients undergoing dialysis has not been studied, therefore valsartan is not recommended in these patients. No dose adjustment is required for paediatric patients with a creatinine clearance >30 ml/min (see sections 4.2 and 5.2). Renal function and serum potassium should be closely monitored during treatment with valsartan. This applies particularly when valsartan is given in the presence of other conditions (fever, dehydration) likely to impair renal function.

Impaired hepatic function

As in adults, Valsartan tablets are contraindicated in paediatric patients with severe hepatic impairment, biliary cirrhosis and in patients with cholestasis (see sections 4.3 and 5.2). There is limited clinical experience with Valsartan
in paediatric patients with mild to moderate hepatic impairment. The dose of valsartan should not exceed 80 mg in these patients.

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.

Paediatric population
In hypertension in children and adolescents, where underlying renal abnormalities are common, caution is recommended with the concomitant use of valsartan and other substances that inhibit the renin angiotensin aldosterone system which may increase serum potassium. Renal function and serum potassium should be closely monitored.

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.
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 breast-feeding 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 (≥1/1000 to <1/100); rare (≥1/10,000 to <1/1000); 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**

**Blood and lymphatic system disorders**
Not known Decrease in haemoglobin, Decrease in haematocrit, Neutropenia, Thrombocytopenia

**Immune system disorders**
Not known Hypersensitivity including serum sickness

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

**Ear and labyrinth system disorders**
Uncommon Vertigo

**Vascular disorders**
Not known Vasculitis

**Respiratory, thoracic and mediastinal disorders**
Uncommon Cough

**Gastrointestinal disorders**
Uncommon Abdominal pain

**Hepato-biliary Disorders**
Not known Elevation of liver function values including increase of serum bilirubin.

**Skin and subcutaneous tissue disorders**
Not known Angioedema, Rash, Pruritus

**Musculoskeletal and connective tissue disorders**
Not known Myalgia

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

**General disorders and administration site conditions**
Uncommon Fatigue

*Paediatric population*

**Hypertension**
The antihypertensive effect of valsartan has been evaluated in two randomised, double-blind clinical studies in 561 paediatric patients from 6 to 18 years of age. With the exception of isolated gastrointestinal disorders (like abdominal pain, nausea, vomiting) and dizziness, no relevant differences in terms of type, frequency and severity of adverse reactions were identified between the safety profile for paediatric patients aged 6 to 18 years and that previously reported for adult patients.

Neurocognitive and developmental assessment of paediatric patients aged 6 to 16 years of age revealed no overall clinically relevant adverse impact after treatment with valsartan for up to one year.
In a double-blind randomized study in 90 children aged 1 to 6 years, which was followed by a one-year open-label extension, two deaths and isolated cases of marked liver transaminases elevations were observed. These cases occurred in a population who had significant comorbidities. A causal relationship to valsartan has not been established. In a second study in which 75 children aged 1 to 6 years were randomised, no significant liver transaminase elevations or death occurred with valsartan treatment. Hyperkalaemia was more frequently observed in children and adolescents aged 6 to 18 years with underlying chronic kidney disease.

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**

  **Blood and lymphatic system disorders**
  - Not known Thrombocytopenia

  **Immune system disorders**
  - Not known Hypersensitivity including serum sickness

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

  **Nervous system disorders**
  - Common Dizziness, Postural dizziness
  - Uncommon Syncope, Headache

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

  **Cardiac disorders**
  - Uncommon Cardiac failure

  **Vascular disorders**
  - Common Hypotension, Orthostatic hypotension
  - Not known Vasculitis

  **Respiratory, thoracic and mediastinal disorders**
  - Uncommon Cough

  **Gastrointestinal disorders**
  - Uncommon Nausea, Diarrhoea

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

  **Skin and subcutaneous tissue disorders**
Uncommon Angioedema
Not known Rash, Pruritus

**Musculoskeletal and connective tissue disorders**
Not known Myalgia

**Renal and urinary disorders**
Common Renal failure and impairment
Uncommon Acute renal failure, Elevation of serum creatinine
Not known Increase in Blood Urea Nitrogen

**General disorders and administration site conditions**
Uncommon Asthenia, Fatigue

4.9 **Overdose**

**Symptoms**
Overdose with Valsartan may result in marked hypotension, which could lead to depressed levels 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 groups: 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).

Hypertension

Administration of Valsartan tablets to patients with hypertension results in reduction of blood pressure without affecting pulse rate.

In most patients, after administration of a single oral dose, onset of antihypertensive activity occurs within 2 hours, and the peak reduction of blood pressure is achieved within 4-6 hours. The antihypertensive effect persists over 24 hours after dosing. During repeated dosing, the antihypertensive effect is substantially present within 2 weeks, and maximal effects are attained within 4 weeks and persist during long-term therapy. Combined with hydrochlorothiazide, a significant additional reduction in blood pressure is achieved.

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

In hypertensive patients with type 2 diabetes and microalbuminuria, valsartan has been shown to reduce the urinary excretion of albumin. The MARVAL (Micro Albuminuria Reduction with Valsartan) study assessed the reduction in urinary albumin excretion (UAE) with valsartan (80-160 mg/od) versus amlodipine (5-10 mg/od), in 332 type 2 diabetic patients (mean age: 58 years; 265 men) with microalbuminuria (valsartan: 58 µg/min; amlodipine: 55.4 µg/min), normal or high blood pressure and with preserved renal function (blood creatinine <120 µmol/l). At 24 weeks, UAE was reduced (p<0.001) by 42% (–24.2 µg/min; 95% CI: –40.4 to –19.1) with valsartan and approximately 3% (–1.7 µg/min; 95% CI: –5.6 to 14.9) with amlodipine despite similar rates of blood pressure reduction in both groups.

Furthermore a valsartan tablets study examined that the efficacy of valsartan in reducing UAE in 391 hypertensive patients (BP=150/88 mmHg) with type 2 diabetes, albuminuria (mean=102 µg/min; 20-700 µg/min) and preserved renal function (mean serum creatinine = 80 µmol/l). Patients were randomized to one of 3 doses of valsartan (160, 320 and 640 mg/od) and treated for 30 weeks. The purpose of the study was to determine the optimal dose of valsartan for reducing UAE in hypertensive patients with type 2 diabetes. At 30 weeks, the percentage change in UAE was significantly reduced by 36% from baseline with valsartan 160 mg (95%CI: 22 to 47%), and by 44% with valsartan 320 mg (95%CI: 31 to 54%). It was concluded that 160-320 mg of valsartan produced clinically relevant reductions in UAE in hypertensive patients with type 2 diabetes.

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, and 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 patient’s post-myocardial infarction.

There was no difference in all-cause mortality or 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.

**Paediatric population**

**Hypertension**

The antihypertensive effect of valsartan have been evaluated in four randomized, double-blind clinical studies in 561 paediatric patients from 6 to 18 years of age and 165 paediatric patients 1 to 6 years of age. Renal and urinary disorders, and obesity were the most common underlying medical conditions potentially contributing to hypertension in the children enrolled in these studies.

**Clinical experience in children at or above 6 years of age**

In a clinical study involving 261 hypertensive paediatric patients 6 to 16 years of age, patients who weighed <35 kg received 10, 40 or 80 mg of valsartan daily (low, medium and high doses), and patients who weighed ≥35 kg received 20, 80, and 160 mg of valsartan daily (low, medium and high doses). At the end of 2 weeks, valsartan reduced both systolic and diastolic blood pressure in a dose-dependent manner. Overall, the three dose levels of valsartan (low, medium and high) significantly reduced systolic blood pressure by 8, 10, 12 mm Hg from the baseline, respectively. Patients were re-randomized to either continue receiving the same dose of valsartan or were switched to placebo. In patients who continued to receive the medium and high doses of valsartan, systolic blood pressure at trough was -4 and -7 mm Hg lower than patients who received the placebo treatment. In patients receiving the low dose of valsartan, systolic blood pressure at trough was similar to that of patients who received the placebo treatment. Overall, the dose-dependent antihypertensive effect of valsartan was consistent across all the demographic subgroups.

In another clinical study involving 300 hypertensive paediatric patients 6 to 18 years of age, eligible patients were randomized to receive valsartan or enalapril tablets for 12 weeks. Children weighing between ≥18 kg and <35 kg received valsartan 80 mg or enalapril 10 mg; those between ≥35 kg and <80 kg received valsartan 160 mg or enalapril 20 mg; those ≥80 kg received valsartan 320 mg or enalapril 40 mg. Reductions in systolic blood pressure were comparable in patients receiving valsartan (15 mmHg) and enalapril (14 mm Hg) (non-inferiority p-value <0.0001). Consistent results were
observed for diastolic blood pressure with reductions of 9.1 mmHg and 8.5 mmHg with valsartan and enalapril, respectively.

Clinical experience in children less than 6 years of age
Two clinical studies were conducted in patients aged 1 to 6 years with 90 and 75 patients, respectively. No children below the age of 1 year were enrolled in these studies. In the first study, the efficacy of valsartan was confirmed compared to placebo but a dose-response could not be demonstrated. In the second study, higher doses of valsartan were associated with greater BP reductions, but the dose response trend did not achieve statistical significance and the treatment difference compared to placebo was not significant. Because of these inconsistencies, valsartan is not recommended in this age group (see section 4.8).

The European Medicines Agency has waived the obligation to submit the results of studies with valsartan tablets in all subsets of the paediatric population in heart failure and heart failure after recent myocardial infarction. See section 4.2 for information on paediatric use.

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 (C_max) by about 50%, although from about 8 h post dosing plasma valsartan concentrations are similar for the fed and fasted groups. This reduction in AUC is not, however, accompanied by a clinically significant reduction in the therapeutic effect, and valsartan can therefore be given either with or without food.

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

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

Excretion:
Valsartan shows multiexponential decay kinetics (t_1/2α <1 h and t_1/2β 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 C_max 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 concentrations versus degree of hepatic dysfunction. Valsartan tablets have not been studied in patients with severe hepatic dysfunction (see sections 4.2, 4.3 and 4.4).

**Paediatric population**
In a study of 26 paediatric hypertensive patients (aged 1 to 16 years) given a single dose of a suspension of valsartan (mean: 0.9 to 2 mg/kg, with a maximum dose of 80 mg), the clearance (litres/h/kg) of valsartan was comparable across the age range of 1 to 16 years and similar to that of adults receiving the same formulation.

**Impaired renal function**
Use in paediatric patients with a creatinine clearance < 30 ml/min and paediatric patients undergoing dialysis has not been studied, therefore valsartan is not recommended in these patients. No dose adjustment is required for paediatric patients with a creatinine clearance > 30 ml/min. Renal function and serum potassium should be closely monitored (see sections 4.2 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.

**Paediatric population**

Daily oral dosing of neonatal/juvenile rats (from a postnatal day 7 to postnatal day 70) with valsartan at doses as low as 1 mg/kg/day (about 10-35% of the maximum recommended paediatric dose of 4 mg/kg/day on systemic exposure basis) produced persistent, irreversible kidney damage. These effects above mentioned represent an expected exaggerated pharmacological effect of angiotensin converting enzyme inhibitors and angiotensin II type 1 blockers; such effects are observed if rats are treated during the first 13 days of life. This period coincides with 36 weeks of gestation in humans, which could occasionally extend up to 44 weeks after conception in humans. The rats in the juvenile valsartan study were dosed up to day 70, and effects on renal maturation (postnatal 4-6 weeks) cannot be excluded. Functional renal maturation is an ongoing process within the first year of life in humans. Consequently, a clinical relevance in children <1 year of age cannot be excluded, while preclinical data do not indicate a safety concern for children older than 1 year.

### 6 PHARMACEUTICAL PARTICULARS

#### 6.1 List of excipients

- Lactose Monohydrate
- Cellulose, Microcrystalline
- Maize starch
- Crospovidone (Type-A)
- Povidone
- Silica, Colloidal anhydrous
- Magnesium stearate

**Coating**

- Hypromellose (E464)
- Titanium dioxide (E171)
- Macrogol
Iron oxide Yellow (E172)
Iron oxide Black (E172)
Iron oxide Red (E172)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years

6.4 Special precautions for storage
Do not store above 30°C. Store in the original package.

6.5 Nature and contents of container
Aluminium-PVC/Aluminium/OPA blisters in packs of 28 tablets
Not all pack sizes may be marketed

6.6 Special precautions for disposal
No specific instructions for use/handling.

7 MARKETING AUTHORISATION HOLDER
Dr. Reddy’s Laboratories (UK) Ltd.
6 Riverview Road
Beverley
East Yorkshire
HU17 0LD
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 08553/0464

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
19/09/2011

10 DATE OF REVISION OF THE TEXT
19/09/2011
1 NAME OF THE MEDICINAL PRODUCT
Valsartan 320 mg film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
One tablet contains 320 mg valsartan. Also contains 114.00 mg of lactose monohydrate.

3 PHARMACEUTICAL FORM
Film-coated tablet.
Light brown coloured, oval shaped, film-coated tablet with beveled edge debossed with ‘V’ 320 on one side of the tablet and breakline on the other side.
The tablets can be divided into two equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypertension
Treatment of essential hypertension in adults, children and adolescents 6 to 18 years of age.

4.2 Posology and method of administration

Posology
Hypertension
The recommended dose of Valsartan is 80 mg once daily. The antihypertensive effect is substantially present within 2 weeks, and maximal effects are attained within 4 weeks. In some patients whose blood pressure is not adequately controlled, the dose can be increased to 160 mg and to a maximum of 320 mg.
Valsartan may also be administered with other antihypertensive agents. The addition of a diuretic such as hydrochlorothiazide will decrease blood pressure even further in these patients.

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 tablets are 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
Paediatric hypertension
Children and adolescents 6 to 18 years of age
The initial dose is 40 mg once daily for children weighing below 35 kg and 80 mg once daily for those weighing 35 kg or more. The dose should be adjusted based on blood pressure response. For maximum doses studied in clinical trials please refer to the table below.

Doses higher than those listed have not been studied and are therefore not recommended.

<table>
<thead>
<tr>
<th>Weight</th>
<th>Maximum dose studied in clinical trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥18 kg to &lt;35 kg</td>
<td>80 mg</td>
</tr>
<tr>
<td>≥35 kg to &lt;80 kg</td>
<td>160 mg</td>
</tr>
<tr>
<td>≥80 kg to ≤160 kg</td>
<td>320 mg</td>
</tr>
</tbody>
</table>

Children less than 6 years of age

Available data are described in sections 4.8, 5.1 and 5.2. However safety and efficacy of Valsartan in children aged 1 to 6 years have not been established.

Use in paediatric patients aged 6 to 18 years with renal impairment

Use in paediatric patients with a creatinine clearance <30 ml/min and paediatric patients undergoing dialysis has not been studied, therefore valsartan is not recommended in these patients. No dose adjustment is required for paediatric patients with a creatinine clearance ≥30 ml/min. Renal function and serum potassium should be closely monitored (see sections 4.4 and 5.2).

Use in paediatric patients aged 6 to 18 years with hepatic impairment

As in adults, Valsartan tablets are contraindicated in paediatric patients with severe hepatic impairment, biliary cirrhosis and in patients with cholestasis (see sections 4.3, 4.4 and 5.2). There is limited clinical experience with Valsartan in paediatric patients with mild to moderate hepatic impairment. The dose of valsartan should not exceed 80 mg in these patients.

Paediatric heart failure and recent myocardial infarction

Valsartan tablets are not recommended for the treatment of heart failure or recent myocardial infarction in children and adolescents below the age of 18 years due to the lack of data on safety and efficacy.

Method of administration

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

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**

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. No dosage adjustment is required for patients with a creatinine clearance>10 ml/min. (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).

**Other conditions with stimulation of the renin-angiotensin system**

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.

**Paediatric population**
Impaired renal function
Use in paediatric patients with a creatinine clearance <30 ml/min and paediatric patients undergoing dialysis has not been studied, therefore valsartan is not recommended in these patients. No dose adjustment is required for paediatric patients with a creatinine clearance >30 ml/min (see sections 4.2 and 5.2). Renal function and serum potassium should be closely monitored during treatment with valsartan. This applies particularly when valsartan is given in the presence of other conditions (fever, dehydration) likely to impair renal function.

Impaired hepatic function
As in adults, Valsartan tablets are contraindicated in paediatric patients with severe hepatic impairment, biliary cirrhosis and in patients with cholestasis (see sections 4.3 and 5.2). There is limited clinical experience with Valsartan in paediatric patients with mild to moderate hepatic impairment. The dose of valsartan should not exceed 80 mg in these patients.

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.

Paediatric population
In hypertension in children and adolescents, where underlying renal abnormalities are common, caution is recommended with the concomitant use of valsartan and other substances that inhibit the renin angiotensin aldosterone system which may increase serum potassium. Renal function and serum potassium should be closely monitored.
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 breast-feeding 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 (≥1/1000 to <1/100); rare (≥1/10,000 to <1/1000); 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**

  **Blood and lymphatic system disorders**
  Not known  Decrease in haemoglobin, Decrease in haematocrit, Neutropenia, Thrombocytopenia

  **Immune system disorders**
  Not known  Hypersensitivity including serum sickness

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

  **Ear and labyrinth system disorders**
  Uncommon  Vertigo

  **Vascular disorders**
  Not known  Vasculitis

  **Respiratory, thoracic and mediastinal disorders**
  Uncommon  Cough

  **Gastrointestinal disorders**
  Uncommon  Abdominal pain

  **Hepato-biliary Disorders**
  Not known  Elevation of liver function values including increase of serum bilirubin.

  **Skin and subcutaneous tissue disorders**
  Not known  Angioedema, Rash, Pruritus

  **Musculoskeletal and connective tissue disorders**
  Not known  Myalgia

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

  **General disorders and administration site conditions**
  Uncommon:  Fatigue

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**Paediatric population**

**Hypertension**

The antihypertensive effect of valsartan has been evaluated in two randomised, double-blind clinical studies in 561 paediatric patients from 6 to 18 years of age.
With the exception of isolated gastrointestinal disorders (like abdominal pain, nausea, vomiting) and dizziness, no relevant differences in terms of type, frequency and severity of adverse reactions were identified between the safety profile for paediatric patients aged 6 to 18 years and that previously reported for adult patients. Neurocognitive and developmental assessment of paediatric patients aged 6 to 16 years of age revealed no overall clinically relevant adverse impact after treatment with valsartan for up to one year.

In a double-blind randomized study in 90 children aged 1 to 6 years, which was followed by a one-year open-label extension, two deaths and isolated cases of marked liver transaminases elevations were observed. These cases occurred in a population who had significant comorbidities. A causal relationship to valsartan has not been established. In a second study in which 75 children aged 1 to 6 years were randomised, no significant liver transaminase elevations or death occurred with valsartan treatment. Hyperkalaemia was more frequently observed in children and adolescents aged 6 to 18 years with underlying chronic kidney disease.

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

**Blood and lymphatic system disorders**

Not known Thrombocytopenia

**Immune system disorders**

Not known Hypersensitivity including serum sickness

**Metabolism and nutrition disorders**

Uncommon Hyperkalaemia

Not known Increase of serum potassium

**Nervous system disorders**

Common Dizziness, Postural dizziness

Uncommon Syncope, Headache

**Ear and labyrinth system disorders**

Uncommon Vertigo

**Cardiac disorders**

Uncommon Cardiac failure

**Vascular disorders**

Common Hypotension, Orthostatic hypotension

Not known Vasculitis

**Respiratory, thoracic and mediastinal disorders**

Uncommon Cough
Gastrointestinal disorders
Uncommon Nausea, Diarrhoea

Hepatobiliary Disorders
Not known Elevation of liver function values

Skin and subcutaneous tissue disorders
Uncommon Angioedema
Not known Rash, Pruritus

Musculoskeletal and connective tissue disorders
Not known Myalgia

Renal and urinary disorders
Common Renal failure and impairment
Uncommon Acute renal failure, Elevation of serum creatinine
Not known Increase in Blood Urea Nitrogen

General disorders and administration site conditions
Uncommon Asthenia, Fatigue

4.9 Overdose

Symptoms
Overdose with Valsartan may result in marked hypotension, which could lead to depressed levels 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 groups: 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).

**Hypertension**

Administration of Valsartan tablets to patients with hypertension results in reduction of blood pressure without affecting pulse rate.

In most patients, after administration of a single oral dose, onset of antihypertensive activity occurs within 2 hours, and the peak reduction of blood pressure is achieved within 4-6 hours. The antihypertensive effect persists over 24 hours after dosing. During repeated dosing, the antihypertensive effect is substantially present within 2 weeks, and maximal effects are attained within 4 weeks and persist during long-term therapy. Combined with hydrochlorothiazide, a significant additional reduction in blood pressure is achieved.

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

In hypertensive patients with type 2 diabetes and microalbuminuria, valsartan has been shown to reduce the urinary excretion of albumin. The MARVAL (Micro Albuminuria Reduction with Valsartan) study assessed the reduction in urinary albumin excretion (UAE) with valsartan (80-160 mg/od) versus amlodipine (5-10 mg/od), in 332 type 2 diabetic patients (mean age: 58 years; 265 men) with microalbuminuria (valsartan: 58 µg/min; amlodipine: 55.4 µg/min), normal or high blood pressure and with preserved renal function (blood creatinine <120 µmol/l). At 24 weeks, UAE was reduced (p<0.001) by 42% (~24.2 µg/min; 95% CI: –40.4 to –19.1) with valsartan and approximately 3% (~1.7 µg/min; 95% CI: –5.6 to 14.9) with amlodipine despite similar rates of blood pressure reduction in both groups.

Furthermore a valsartan tablets study examined that the efficacy of valsartan in reducing UAE in 391 hypertensive patients (BP=150/88 mmHg) with type 2 diabetes, albuminuria (mean=102 µg/min; 20-700 µg/min) and preserved renal function (mean serum creatinine = 80 µmol/l). Patients were randomized to one of 3 doses of valsartan (160, 320 and 640 mg/od) and treated for 30 weeks. The purpose of the study was to determine the optimal dose of valsartan for reducing UAE in hypertensive patients with type 2 diabetes. At 30 weeks, the percentage change in UAE was significantly reduced by 36% from baseline with valsartan 160 mg (95%CI: 22 to 47%), and by 44% with valsartan 320 mg (95%CI: 31 to 54%). It was concluded that 160-320 mg of valsartan produced clinically relevant reductions in UAE in hypertensive patients with type 2 diabetes.
**Paediatric population**

**Hypertension**

The antihypertensive effect of valsartan have been evaluated in four randomized, double-blind clinical studies in 561 paediatric patients from 6 to 18 years of age and 165 paediatric patients 1 to 6 years of age. Renal and urinary disorders, and obesity were the most common underlying medical conditions potentially contributing to hypertension in the children enrolled in these studies.

**Clinical experience in children at or above 6 years of age**

In a clinical study involving 261 hypertensive paediatric patients 6 to 16 years of age, patients who weighed <35 kg received 10, 40 or 80 mg of valsartan daily (low, medium and high doses), and patients who weighed ≥35 kg received 20, 80, and 160 mg of valsartan daily (low, medium and high doses). At the end of 2 weeks, valsartan reduced both systolic and diastolic blood pressure in a dose-dependent manner. Overall, the three dose levels of valsartan (low, medium and high) significantly reduced systolic blood pressure by 8, 10, 12 mm Hg from the baseline, respectively. Patients were re-randomized to either continue receiving the same dose of valsartan or were switched to placebo. In patients who continued to receive the medium and high doses of valsartan, systolic blood pressure at trough was -4 and -7 mm Hg lower than patients who received the placebo treatment. In patients receiving the low dose of valsartan, systolic blood pressure at trough was similar to that of patients who received the placebo treatment. Overall, the dose-dependent antihypertensive effect of valsartan was consistent across all the demographic subgroups.

In another clinical study involving 300 hypertensive paediatric patients 6 to 18 years of age, eligible patients were randomized to receive valsartan or enalapril tablets for 12 weeks. Children weighing between ≥18 kg and <35 kg received valsartan 80 mg or enalapril 10 mg; those between ≥35 kg and <80 kg received valsartan 160 mg or enalapril 20 mg; those ≥80 kg received valsartan 320 mg or enalapril 40 mg. Reductions in systolic blood pressure were comparable in patients receiving valsartan (15 mmHg) and enalapril (14 mm Hg) (non-inferiority p-value <0.0001). Consistent results were observed for diastolic blood pressure with reductions of 9.1 mmHg and 8.5 mmHg with valsartan and enalapril, respectively.

**Clinical experience in children less than 6 years of age**

Two clinical studies were conducted in patients aged 1 to 6 years with 90 and 75 patients, respectively. No children below the age of 1 year were enrolled in these studies. In the first study, the efficacy of valsartan was confirmed compared to placebo but a dose-response could not be demonstrated. In the second study, higher doses of valsartan were associated with greater BP reductions, but the dose response trend did not achieve statistical significance and the treatment difference compared to placebo was not significant. Because of these inconsistencies, valsartan is not recommended in this age group (see section 4.8).

The European Medicines Agency has waived the obligation to submit the results of studies with valsartan tablets in all subsets of the paediatric population in heart failure and heart failure after recent myocardial infarction. See section 4.2 for information on paediatric use.
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 (C_max) by about 50%, although from about 8 h post dosing plasma valsartan concentrations are similar for the fed and fasted groups. This reduction in AUC is not, however, accompanied by a clinically significant reduction in the therapeutic effect, and valsartan can therefore be given either with or without food.

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

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

Excretion:
Valsartan shows multiexponential decay kinetics (t_1/2α <1 h and t_1/2β 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 halflife of valsartan is 6 hours.

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 concentrations versus degree of hepatic dysfunction. Valsartan tablets have not been studied in patients with severe hepatic dysfunction (see sections 4.2, 4.3
and 4.4).

**Paediatric population**
In a study of 26 paediatric hypertensive patients (aged 1 to 16 years) given a single dose of a suspension of valsartan (mean: 0.9 to 2 mg/kg, with a maximum dose of 80 mg), the clearance (litres/h/kg) of valsartan was comparable across the age range of 1 to 16 years and similar to that of adults receiving the same formulation.

**Impaired renal function**
Use in paediatric patients with a creatinine clearance <30 ml/min and paediatric patients undergoing dialysis has not been studied, therefore valsartan is not recommended in these patients. No dose adjustment is required for paediatric patients with a creatinine clearance >30 ml/min. Renal function and serum potassium should be closely monitored (see sections 4.2 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.

**Paediatric population**
Daily oral dosing of neonatal/juvenile rats (from a postnatal day 7 to postnatal day 70) with valsartan at doses as low as 1 mg/kg/day (about 10-35% of the maximum recommended paediatric dose of 4 mg/kg/day on systemic exposure basis) produced persistent, irreversible kidney damage. These effects above mentioned represent an expected exaggerated pharmacological effect of angiotensin converting enzyme inhibitors and angiotensin II type 1 blockers; such effects are observed if rats are treated during the first 13 days of life. This
period coincides with 36 weeks of gestation in humans, which could occasionally extend up to 44 weeks after conception in humans. The rats in the juvenile valsartan study were dosed up to day 70, and effects on renal maturation (postnatal 4-6 weeks) cannot be excluded. Functional renal maturation is an ongoing process within the first year of life in humans. Consequently, a clinical relevance in children <1 year of age cannot be excluded, while preclinical data do not indicate a safety concern for children older than 1 year.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Lactose monohydrate
Cellulose, Microcrystalline
Maize starch
Crospovidone (Type-A)
Povidone (PVP-K 30)
Silica, Colloidal anhydrous
Magnesium stearate

Tablet Coating
Hypromellose
Titanium dioxide
Macrogol
Iron oxide Yellow (E172)
Iron oxide Black (E172)
Iron oxide Red (E172)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years

6.4 Special precautions for storage
Do not store above 30°C. Store in the original package

6.5 Nature and contents of container
Aluminium-PVC/Aluminium/OPA blister packs of 28 tablets
Not all pack sizes may be marketed

6.6 Special precautions for disposal
No specific instructions for use/handling.

7 MARKETING AUTHORISATION HOLDER
Dr. Reddy’s Laboratories (UK) Ltd.
6 Riverview Road
Beverley
8 MARKETING AUTHORISATION NUMBER(S)
PL 08553/0465

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
19/09/2011

10 DATE OF REVISION OF THE TEXT
19/09/2011
Module 3

Product Information Leaflet

The following texts are the approved Product Information Leaflet (PIL) texts for PL 08553/0394-0397. No PIL mock-ups have been provided. In accordance with medicines legislation, the products shall not be marketed in the UK until approval of the PIL mock-ups has been obtained.
PACKAGE LEAFLET Information for the User
Valsartan 40 mg film-coated Tablets

Valsartan

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your 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 get 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 called angiotensin II receptor antagonists, which
help to control high blood pressure. Angiotensin II is a substance in the body that causes
blood vessels to tighten, thus causing an increase in blood pressure. Valsartan works by
blocking the effect of angiotensin II. As a result, blood vessels relax and blood pressure is
lowered.

Valsartan Tablets are used to treat:

- high blood pressure in adults, children and adolescents (age 6 to 18 years of age).
  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
or kidney failure and increases the risk of heart attacks. Lowering your blood pressure to
normal reduces the risk of developing these disorders.
- adult patients who have symptomatic heart failure.

  Valsartan is used when a group of medicines called Angiotensin Converting Enzyme
  (ACE) inhibitors (another medication to treat heart failure) cannot be used or Valsartan
  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 buildup. It is caused when the heart muscle
cannot pump blood strongly enough to supply all the blood needed throughout the body.

Valsartan Tablets may also be authorised to treat other conditions which are not mentioned in
this leaflet. Ask your doctor or pharmacist if you have further questions.

2. Before you take Valsartan

Do not take Valsartan if you
- are allergic to valsartan or to any of the other ingredients in the tablets (see section 6)
- have **severe liver disease**
- 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 Tablets.

**Take special care and check with your doctor before taking Valsartan if you**
- have **liver disease**
- have severe **kidney disease** or are having **dialysis**
- have **narrowing of the kidney artery**
- have recently had a **kidney transplant**
- are **already being treated after a heart attack or for heart failure** (Your doctor may need to check your kidney function)
- have **other severe heart disease** other than heart failure or heart attack.
- suffer from **aldosteronism** (when you produce too much of the hormone aldosterone) as the use of Valsartan is not recommended
- are taking **medicines that increase the amount of potassium** in your blood such as potassium supplements, salt substitutes containing potassium, potassium-sparing medicines and heparin. (As it may be necessary to do regular checks of the amount of potassium in your blood)
- are **dehydrated** (have lost a lot of fluid) caused by diarrhoea, vomiting, or due to high doses of ’water’ tablets (diuretics)
- think you are or **(might become) pregnant** (as 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 the late stage (see pregnancy section)
- are **below 18 years of age and take Valsartan in combination with other medicines** that inhibit the rennin angiotensin aldosterone system (medicines that lower blood pressure). Your doctor may check your kidney function and the amount of potassium in your blood at regular intervals.

**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, especially:
- **other medicines that lower blood pressure** especially water pills (diuretics)
- **medicines that increase the amount of potassium** in the blood such as potassium supplements, or salt substitutes containing potassium, potassium-sparing medicines and heparin
- **certain type of pain killers non-steroidal anti-inflammatory medicines** (NSAIDs)
- **lithium** (to treat some types of mental illness)

In addition:
- if you are being **treated after a heart attack**, a combination with **ACE inhibitors** (a medication to treat heart attack) is not recommended.
• 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 Tablets with or without food.

Pregnancy and breastfeeding

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 tablets before you become pregnant or as soon as you know you are pregnant and will advise you to take a different medicine. 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 the baby if 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 your ability to concentrate.

Important information about some of the ingredients
This medicine contains a sugar called lactose. If your doctor has told you that you have intolerance to some sugars, contact your doctor before taking this medicine.

3. How to take Valsartan

Always use Valsartan exactly as your doctor has told you in order to get the best results and reduce the risk of side effects. If you are not sure, check with your doctor or pharmacist.
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 are feeling well.

Children and adolescents (6 to 18 years of age) with high blood pressure: In patients who weigh less than 35 kg the usual dose is 40 mg of Valsartan once daily. In patients who weigh 35 kg or more the usual starting dose is 80 mg of Valsartan once daily. In some cases your doctor may prescribe higher doses (the dose can be increased to 160 mg and to a maximum of 320 mg).

Adult patients with heart failure: Treatment usually starts with 40 mg twice a day. Your doctor will increase the dose gradually over several weeks to a maximum of 160 mg twice a
day. The final dose depends on what you as 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.

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

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

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

If you stop taking Valsartan
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.

Some symptoms need immediate medical attention:
You may experience symptoms of angioedema (severe allergic reaction) such as
• swelling of the face, tongue, lips or throat
• difficulty in breathing or swallowing
• hives, itching.
If you get any of these, see your doctor immediately.

Other side effects are shown below.
If any of the following side effects gets serious, or if you notice any effects not listed in this leaflet, tell your doctor or pharmacist.

Common: affects 1 to 10 users in 100
• dizziness
• low blood pressure with or without symptoms, such as dizziness or fainting on standing up
• decreased kidney function (signs of renal impairment)

Uncommon: affects 1 to 10 users in 1,000
• headache
• angioedema (see “Some symptoms need immediate medical attention”)
• sudden loss of consciousness
• spinning sensation (vertigo)
• severely 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)
• cough
• abdominal pain
• diarrhoea
• nausea
• tiredness
• weakness

Not known: frequency cannot be estimated from available data
• 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 (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 levels of white blood cells called neutropenia)
• decreased level of haemoglobin and decrease of the percentage of red blood cells (which can lead to anaemia in severe cases)
• increased level of potassium in the blood (which can trigger muscle spasms and abnormal heart rhythm in severe cases)
• elevation of liver function values (which can indicate liver damage) including an increase of bilirubin in the blood (which in severe cases can cause yellow skin and eyes)
• increased levels of blood urea nitrogen and 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 for high blood pressure than in patients treated for heart failure or after a recent heart attack.

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

5. How to store Valsartan

Keep out of the reach and sight of children.
Do not use Valsartan if you notice that the pack is damaged or shows signs of tampering.
Store in the original package below 30°C

Do not use Valsartan after the expiry date which is stated on the carton. The expiry date refers to the last day of that month.
Medicines should not be disposed of via waste water or household waste. Ask your pharmacist how to dispose of medicines no longer required. This will help to protect the environment.

6. Further information

What Valsartan Tablets contain
The active substance (which makes the medicine work) is valsartan. Each tablet contains 40 mg of valsartan.

The other ingredients are lactose monohydrate, cellulose, microcrystalline, maize starch, crospovidone, povidone, colloidal anhydrous silica, magnesium stearate in the tablet core, and hypromellose, titanium dioxide (E171), macrogol, tcalc and yellow iron oxide (E172) in the tablet coating.

What Valsartan Tablets look like and contents of the pack
Each tablet is a yellow, oval shaped, film-coated tablet with beveled edge debossed ‘V’ on one side and ‘4’ and ‘0’ on either side of the breakline on the other side. The tablets can be divided into two equal halves.

Available pack sizes: 14, 28, 30, 50, 56, 60, 98 or 100 tablets. Not all pack sizes may be available.

Marketing Authorisation Holder and Manufacturer
Dr. Reddy’s Laboratories (UK) Ltd., 6 Riverview Road, Beverley, HU17 0LD, United Kingdom

This leaflet was last updated in 09/2011
PACKAGE LEAFLET Information for the User  
Valsartan 80 mg & 160 mg film-coated Tablets

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your 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 get 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 called angiotensin II receptor antagonists, which help to control high blood pressure. Angiotensin II is a substance in the body that causes blood vessels to tighten, thus causing an increase in blood pressure. Valsartan works by blocking the effect of angiotensin II. As a result, blood vessels relax and blood pressure is lowered.

Valsartan Tablets are used to treat:
- **high blood pressure in adults, children and adolescents (age 6 to 18 years of age).**
  - 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 or kidney failure and increases the risk of heart attacks. Lowering your blood pressure to normal reduces the risk of developing these disorders.
- **adult patients who have symptomatic heart failure.**
  - Valsartan is used when a group of medicines called Angiotensin Converting Enzyme (ACE) inhibitors (another medication to treat heart failure) cannot be used or Valsartan 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 buildup. It is caused when the heart muscle cannot pump blood strongly enough to supply all the blood needed throughout the body.

Valsartan tablets may also be authorised to treat other conditions which are not mentioned in this leaflet. Ask your doctor or pharmacist if you have further questions.

2. Before you take Valsartan

Do not take Valsartan if you
- are **allergic** to valsartan or to any of the other ingredients in the tablets (see section 6)
- have **severe liver disease**
• 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 Tablets.

Take special care and check with your doctor before taking Valsartan if you
• have liver disease
• have severe kidney disease or are having dialysis
• have narrowing of the kidney artery
• have recently had a kidney transplant
• are already being treated after a heart attack or for heart failure (Your doctor may need to check your kidney function)
• have other severe heart disease other than heart failure or heart attack.
• suffer from aldosteronism (when you produce too much of the hormone aldosterone) as the use of Valsartan is not recommended
• are taking medicines that increase the amount of potassium in your blood such as potassium supplements, salt substitutes containing potassium, potassium-sparing medicines and heparin. (As it may be necessary to do regular checks of the amount of potassium in your blood)
• are dehydrated (have lost a lot of fluid) caused by diarrhoea, vomiting, or due to high doses of ‘water’ tablets (diuretics)
• think you are or (might become) pregnant (as 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 the late stage (see pregnancy section)
• are below 18 years of age and take Valsartan in combination with other medicines that inhibit the rennin angiotensin aldosterone system (medicines that lower blood pressure). Your doctor may check your kidney function and the amount of potassium in your blood at regular intervals.

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, especially:
• other medicines that lower blood pressure especially water pills (diuretics)
• medicines that increase the amount of potassium in the blood such as potassium supplements, or salt substitutes containing potassium, potassium-sparing medicines and heparin
• certain type of pain killers non-steroidal anti-inflammatory medicines (NSAIDs)
• lithium (to treat some types of mental illness)

In addition:
• if you are being treated after a heart attack, a combination with ACE inhibitors (a medication to treat heart attack) is not recommended.
• 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 Tablets with or without food.

Pregnancy and breastfeeding

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 tablets before you become pregnant or as soon as you know you are pregnant and will advise you to take a different medicine. 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 the baby if 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 your ability to concentrate.

Important information about some of the ingredients
This medicine contains a sugar called lactose. If your doctor has told you that you have intolerance to some sugars, contact your doctor before taking this medicine.

3. How to take Valsartan

Always use Valsartan exactly as your doctor has told you in order to get the best results and reduce the risk of side effects. If you are not sure, check with your doctor or pharmacist.

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 are feeling well.

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

Children and adolescents (6 to 18 years of age) with high blood pressure: In patients who weigh less than 35 kg the usual dose is 40 mg of Valsartan once daily. In patients who weigh 35 kg or more the usual starting dose is 80 mg of Valsartan once daily. In some cases your doctor may prescribe higher doses (the dose can be increased to 160 mg and to a maximum of 320 mg).
**Adult patients with heart failure:** Treatment usually starts with 40 mg twice a day. Your doctor will increase the dose gradually over several weeks to a maximum of 160 mg twice a day. The final dose depends on what you as 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.

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

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

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

**If you stop taking Valsartan**
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.

Some symptoms need immediate medical attention:
You may experience symptoms of angioedema (severe allergic reaction) such as:
- swelling of the face, tongue, lips or throat
- difficulty in breathing or swallowing
- hives, itching.
If you get any of these, see your doctor immediately.

Other side effects are shown below.

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

**Common: affects 1 to 10 users in 100**
- dizziness
- low blood pressure with or without symptoms, such as dizziness or fainting on standing up
- decreased kidney function (signs of renal impairment)

**Uncommon: affects 1 to 10 users in 1,000**
- headache
- angioedema (see “Some symptoms need immediate medical attention”)

MHRA PAR; VALSARTAN 40 MG, 80 MG, 160 MG AND 320 MG FILM-COATED TABLETS, PL 08553/0394-0397 AND PL 08553/0462-0465
• sudden loss of consciousness.
• spinning sensation (vertigo)
• severely 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)
• cough
• abdominal pain
• diarrhoea
• nausea
• tiredness
• weakness

**Not known: frequency cannot be estimated from available data**

• 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 (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 levels of white blood cells called neutropenia)
• decreased level of haemoglobin and decrease of the percentage of red blood cells (which can lead to anaemia in severe cases)
• increased level of potassium in the blood (which can trigger muscle spasms and abnormal heart rhythm in severe cases)
• elevation of liver function values (which can indicate liver damage) including an increase of bilirubin in the blood (which in severe cases can cause yellow skin and eyes)
• increased levels of blood urea nitrogen and 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 for high blood pressure than in patients treated for heart failure or after a recent heart attack.

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

5. **How to store Valsartan**

**Keep out of the reach and sight of children.**

Do not use Valsartan if you notice that the pack is damaged or shows signs of tampering.

Store in the original package below 30°C

Do not use Valsartan after the expiry date which is stated on the carton. The expiry date refers to the last day of that month.

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

6. Further information

What Valsartan Tablets contain
The active substance (which makes the medicine work) is valsartan. Each tablet contains 80mg or 160mg of valsartan.

The other ingredients are lactose monohydrate, cellulose, microcrystalline, maize starch, crospovidone, povidone, colloidal anhydrous silica, magnesium stearate, hypromellose, titanium dioxide (E171), macrogol, iron oxides (yellow, black and red).

What Valsartan Tablets look like and contents of the pack
Valsartan 80 mg tablets are pink coloured, round, film-coated tablet with beveled edge debossed with ‘V and 80’ on one side of the tablet, and a breakline on the other side.

Valsartan 160 mg tablets are grey-orange coloured, oval shaped, film-coated tablet with beveled edge debossed ‘V160’ on one side of the tablet and breakline on the other side.

The tablets can be divided in to two equal halves

Available pack sizes: 14, 28, 30, 50, 56, 60, 98 or 100 tablets. Not all pack sizes may be available.

Marketing Authorisation Holder and Manufacturer
Dr. Reddy’s Laboratories (UK) Ltd., 6 Riverview Road, Beverley, HU17 0LD, United Kingdom

This leaflet was last updated in 09/2011
PACKAGE LEAFLET Information for the User
Valsartan 320 mg film-coated Tablets

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your 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 get 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 called angiotensin II receptor antagonists, which help to control high blood pressure. Angiotensin II is a substance in the body that causes blood vessels to tighten, thus causing an increase in blood pressure. Valsartan works by blocking the effect of angiotensin II. As a result, blood vessels relax and blood pressure is lowered.

Valsartan Tablets are used to treat:
high blood pressure in adults, children and adolescents (age 6 to 18 years of age). 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 or kidney failure and increases the risk of heart attacks. Lowering your blood pressure to normal reduces the risk of developing these disorders.

2. Before you take Valsartan

Do not take Valsartan if you
- are allergic to valsartan or to any of the other ingredients in the tablets (see section 6)
- have severe liver disease
- 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 Tablets.

Take special care and check with your doctor before taking Valsartan if you
- have liver disease
- have severe kidney disease or are having dialysis
• have **narrowing of the kidney artery**
• have recently had a **kidney transplant**
• are **already being treated after a heart attack or for heart failure** (Your doctor may need to check your kidney function)
• have **other severe heart disease** other than heart failure or heart attack.
• suffer from **aldosteronism** (when you produce too much of the hormone aldosterone) as the use of Valsartan is not recommended
• are taking **medicines that increase the amount of potassium** in your blood such as potassium supplements, salt substitutes containing potassium, potassium-sparing medicines and heparin. (As it may be necessary to do regular checks of the amount of potassium in your blood)
• are **dehydrated** (have lost a lot of fluid) caused by diarrhoea, vomiting, or due to high doses of ’water’ tablets (diuretics)
• think you are or **(might become) pregnant** (as 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 the late stage (see pregnancy section)
• are **below 18 years of age** and take **Valsartan in combination with other medicines** that inhibit the rennin angiotensin aldosterone system (medicines that lower blood pressure). Your doctor may check your kidney function and the amount of potassium in your blood at regular intervals.

**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, especially:
• **other medicines that lower blood pressure** especially water pills (diuretics)
• **medicines that increase the amount of potassium** in the blood such as potassium supplements, or salt substitutes containing potassium, potassium-sparing medicines and heparin
• certain type of pain killers **non-steroidal anti-inflammatory medicines** (NSAIDs)
• **lithium** (to treat some types of mental illness)

In addition:
• if you are being treated after a heart attack, a combination with ACE inhibitors (a medication to treat heart attack) is not recommended.
• 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 Tablets with or without food.

**Pregnancy and breastfeeding**

**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 tablets
before you become pregnant or as soon as you know you are pregnant and will advise you to take a different medicine. 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 the baby if 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 your ability to concentrate.

**Important information about some of the ingredients**
This medicine contains a sugar called lactose. If your doctor has told you that you have intolerance to some sugars, contact your doctor before taking this medicine.

### 3. How to take Valsartan

Always use Valsartan exactly as your doctor has told you in order to get the best results and reduce the risk of side effects. If you are not sure, check with your doctor or pharmacist.

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 are feeling well.

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

**Children and adolescents (6 to 18 years of age) with high blood pressure:** In patients who weigh less than 35 kg the usual dose is 40 mg of Valsartan once daily. In patients who weigh 35 kg or more the usual starting dose is 80 mg of Valsartan once daily. In some cases your doctor may prescribe higher doses (the dose can be increased to 160 mg and to a maximum of 320 mg).

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

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

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

**If you stop taking Valsartan**
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.

Some symptoms need immediate medical attention:
You may experience symptoms of angioedema (**severe allergic reaction**) such as
- swelling of the face, tongue, lips or throat
- difficulty in breathing or swallowing
- hives, itching.

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

Other side effects are shown below.

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

**Common: affects 1 to 10 users in 100**
- dizziness
- low blood pressure with or without symptoms, such as dizziness or fainting on standing up
- decreased kidney function (signs of renal impairment)

**Uncommon: affects 1 to 10 users in 1,000**
- headache
- angioedema (see “Some symptoms need immediate medical attention”)
- sudden loss of consciousness
- spinning sensation (vertigo)
- severely 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)
- cough
- abdominal pain
- diarrhoea
- nausea
- tiredness
- weakness

**Not known: frequency cannot be estimated from available data**
• 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 (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 levels of white blood cells called neutropenia)
• decreased level of haemoglobin and decrease of the percentage of red blood cells (which can lead to anaemia in severe cases)
• increased level of potassium in the blood (which can trigger muscle spasms and abnormal heart rhythm in severe cases)
• elevation of liver function values (which can indicate liver damage) including an increase of bilirubin in the blood (which in severe cases can cause yellow skin and eyes)
• increased levels of blood urea nitrogen and 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 for high blood pressure than in patients treated for heart failure or after a recent heart attack.

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

5. How to store Valsartan

Keep out of the reach and sight of children.
Do not use Valsartan if you notice that the pack is damaged or shows signs of tampering.
Store in the original package below 30°C

Do not use Valsartan after the expiry date which is stated on the carton. The expiry date refers to the last day of that month.
Medicines should not be disposed of via waste water or household waste. Ask your pharmacist how to dispose of medicines no longer required. This will help to protect the environment.

6. Further information

What Valsartan Tablets contain
The active substance (which makes the medicine work) is valsartan. Each tablet contains 320 mg of valsartan.

The other ingredients are lactose monohydrate, cellulose, microcrystalline, maize starch, croscavidgeone, povidone, colloidal anhydrous silica, magnesium stearate in the tablet core, and hypromellose, titanium dioxide (E171), macrogol and iron oxides (yellow, black and red; E172) in the tablet coating.

What Valsartan Tablets look like and contents of the pack
Valsartan 320 mg tablets are light brown coloured, oval shaped, film-coated tablets with bevelled edge debossed with ‘V and 320’ on one side of the tablet and breakline on the other side.

The tablets can be divided into two equal halves.

Available pack sizes: 14, 28, 30, 50, 56, 60, 98 or 100 tablets. Not all pack sizes may be available.

Marketing Authorisation Holder and Manufacturer
Dr. Reddy’s Laboratories (UK) Ltd., 6 Riverview Road, Beverley, HU17 0LD, United Kingdom

This leaflet was last updated in 09/2011
The following texts are the approved Product Information Leaflet (PIL) texts for PL 08553/0462-0465. No PIL mock-ups have been provided. In accordance with medicines legislation, the products shall not be marketed in the UK until approval of the PIL mock-ups has been obtained.
Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your 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 get 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 called angiotensin II receptor antagonists, which help to control high blood pressure. Angiotensin II is a substance in the body that causes blood vessels to tighten, thus causing an increase in blood pressure. Valsartan works by blocking the effect of angiotensin II. As a result, blood vessels relax and blood pressure is lowered.

Valsartan Tablets are used to treat:
- **high blood pressure in adults, children and adolescents (age 6 to 18 years of age).** 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 or kidney failure and increases the risk of heart attacks. Lowering your blood pressure to normal reduces the risk of developing these disorders.
- **adult patients who have symptomatic heart failure.** Valsartan is used when a group of medicines called Angiotensin Converting Enzyme (ACE) inhibitors (another medication to treat heart failure) cannot be used or Valsartan 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 buildup. It is caused when the heart muscle cannot pump blood strongly enough to supply all the blood needed throughout the body.

Valsartan Tablets may also be authorised to treat other conditions which are not mentioned in this leaflet. Ask your doctor or pharmacist if you have further questions.

2. Before you take Valsartan

**Do not take Valsartan if you**
- are allergic to valsartan or to any of the other ingredients in the tablets (see section 6)
• have severe liver disease
• 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 Tablets.

Take special care and check with your doctor before taking Valsartan if you
• have liver disease
• have severe kidney disease or are having dialysis
• have narrowing of the kidney artery
• have recently had a kidney transplant
• are already being treated after a heart attack or for heart failure (Your doctor may need to check your kidney function)
• have other severe heart disease other than heart failure or heart attack.
• suffer from aldosteronism (when you produce too much of the hormone aldosterone) as the use of Valsartan is not recommended
• are taking medicines that increase the amount of potassium in your blood such as potassium supplements, salt substitutes containing potassium, potassium-sparing medicines and heparin. (As it may be necessary to do regular checks of the amount of potassium in your blood)
• are dehydrated (have lost a lot of fluid) caused by diarrhoea, vomiting, or due to high doses of ‘water’ tablets (diuretics)
• think you are or might become pregnant (as 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 the late stage (see pregnancy section)
• are below 18 years of age and take Valsartan in combination with other medicines that inhibit the rennin angiotensin aldosterone system (medicines that lower blood pressure). Your doctor may check your kidney function and the amount of potassium in your blood at regular intervals.

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, especially:
• other medicines that lower blood pressure especially water pills (diuretics)
• medicines that increase the amount of potassium in the blood such as potassium supplements, or salt substitutes containing potassium, potassium-sparing medicines and heparin
• certain type of pain killers non-steroidal anti-inflammatory medicines (NSAIDs)
• lithium (to treat some types of mental illness)

In addition:
• if you are being treated after a heart attack, a combination with ACE inhibitors (a medication to treat heart attack) is not recommended.
• 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 Tablets with or without food.

Pregnancy and breastfeeding

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 tablets before you become pregnant or as soon as you know you are pregnant and will advise you to take a different medicine. 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 the baby if 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 your ability to concentrate.

Important information about some of the ingredients
This medicine contains a sugar called lactose. If your doctor has told you that you have intolerance to some sugars, contact your doctor before taking this medicine

3. How to take Valsartan

Always use Valsartan exactly as your doctor has told you in order to get the best results and reduce the risk of side effects. If you are not sure, check with your doctor or pharmacist. 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 are feeling well.

Children and adolescents (6 to 18 years of age) with high blood pressure: In patients who weigh less than 35 kg the usual dose is 40 mg of Valsartan once daily. In patients who weigh 35 kg or more the usual starting dose is 80 mg of Valsartan once daily. In some cases your doctor may prescribe higher doses (the dose can be increased to 160 mg and to a maximum of 320 mg).

Adult patients with heart failure: Treatment usually starts with 40 mg twice a day. Your doctor will increase the dose gradually over several weeks to a maximum of 160 mg twice a
day. The final dose depends on what you as 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.

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

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

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

If you stop taking Valsartan
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.

Some symptoms need immediate medical attention:

You may experience symptoms of angioedema (severe allergic reaction) such as
• swelling of the face, tongue, lips or throat
• difficulty in breathing or swallowing
• hives, itching.

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

Other side effects are shown below.

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

Common: affects 1 to 10 users in 100
• dizziness
• low blood pressure with or without symptoms, such as dizziness or fainting on standing up
• decreased kidney function (signs of renal impairment)

Uncommon: affects 1 to 10 users in 1,000
• headache
• angioedema (see “Some symptoms need immediate medical attention”)
- sudden loss of consciousness
- spinning sensation (vertigo)
- severely 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)
- cough
- abdominal pain
- diarrhoea
- nausea
- tiredness
- weakness

Not known: frequency cannot be estimated from available data
- 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 (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 levels of white blood cells called neutropenia)
- decreased level of haemoglobin and decrease of the percentage of red blood cells (which can lead to anaemia in severe cases)
- increased level of potassium in the blood (which can trigger muscle spasms and abnormal heart rhythm in severe cases)
- elevation of liver function values (which can indicate liver damage) including an increase of bilirubin in the blood (which in severe cases can cause yellow skin and eyes)
- increased levels of blood urea nitrogen and 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 for high blood pressure than in patients treated for heart failure or after a recent heart attack.

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

5. How to store Valsartan

Keep out of the reach and sight of children.
Do not use Valsartan if you notice that the pack is damaged or shows signs of tampering.
Store in the original package below 30°C

Do not use Valsartan after the expiry date which is stated on the carton. The expiry date refers to the last day of that month.
Medicines should not be disposed of via waste water or household waste. Ask your pharmacist how to dispose of medicines no longer required. This will help to protect the environment.

6. Further information

**What Valsartan Tablets contain**
The active substance (which makes the medicine work) is valsartan. Each tablet contains 40 mg of valsartan.

The other ingredients are lactose monohydrate, cellulose, microcrystalline, maize starch, crospovidone, povidone, colloidal anhydrous silica, magnesium stearate in the tablet core, and hypromellose, titanium dioxide (E171), macrogol, talc and yellow iron oxide (E172) in the tablet coating.

**What Valsartan Tablets look like and contents of the pack**

Each tablet is a yellow, oval shaped, film-coated tablet with bevelled edge debossed ‘V’ on one side and ‘4’ and ‘0’ on either side of the breakline on the other side. The tablets can be divided into two equal halves.

Available pack sizes: 14 tablets.

**Marketing Authorisation Holder and Manufacturer**

Dr. Reddy's Laboratories (UK) Ltd., 6 Riverview Road, Beverley, HU17 0LD, United Kingdom

This leaflet was last updated in 09/2011
PACKAGE LEAFLET Information for the User
Valsartan 80 mg & 160 mg film-coated Tablets

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your 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 get 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 called angiotensin II receptor antagonists, which
help to control high blood pressure. Angiotensin II is a substance in the body that causes
blood vessels to tighten, thus causing an increase in blood pressure. Valsartan works by
blocking the effect of angiotensin II. As a result, blood vessels relax and blood pressure is
lowered.

Valsartan Tablets are used to treat:
• high blood pressure in adults, children and adolescents (age 6 to 18 years of age).
  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
or kidney failure and increases the risk of heart attacks. Lowering your blood pressure to
normal reduces the risk of developing these disorders.
• adult patients who have symptomatic heart failure.
  Valsartan is used when a group of medicines called Angiotensin Converting Enzyme
(ACE) inhibitors (another medication to treat heart failure) cannot be used or Valsartan
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 buildup. It is caused when the heart muscle
cannot pump blood strongly enough to supply all the blood needed throughout the body.

Valsartan tablets may also be authorised to treat other conditions which are not mentioned in
this leaflet. Ask your doctor or pharmacist if you have further questions.

2. Before you take Valsartan

Do not take Valsartan if you
• are allergic to valsartan or to any of the other ingredients in the tablets (see section 6)
• have severe liver disease
• 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 Tablets.

Take special care and check with your doctor before taking Valsartan if you
• have liver disease
• have severe kidney disease or are having dialysis
• have narrowing of the kidney artery
• have recently had a kidney transplant
• are already being treated after a heart attack or for heart failure (Your doctor may need to check your kidney function)
• have other severe heart disease other than heart failure or heart attack.
• suffer from aldosteronism (when you produce too much of the hormone aldosterone) as the use of Valsartan is not recommended
• are taking medicines that increase the amount of potassium in your blood such as potassium supplements, salt substitutes containing potassium, potassium-sparing medicines and heparin. (As it may be necessary to do regular checks of the amount of potassium in your blood)
• are dehydrated (have lost a lot of fluid) caused by diarrhoea, vomiting, or due to high doses of 'water' tablets (diuretics)
• think you are or (might become) pregnant (as 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 the late stage (see pregnancy section)
• are below 18 years of age and take Valsartan in combination with other medicines that inhibit the rennin angiotensin aldosterone system (medicines that lower blood pressure). Your doctor may check your kidney function and the amount of potassium in your blood at regular intervals.

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, especially:
• other medicines that lower blood pressure especially water pills (diuretics)
• medicines that increase the amount of potassium in the blood such as potassium supplements, or salt substitutes containing potassium, potassium-sparing medicines and heparin
• certain type of pain killers non-steroidal anti-inflammatory medicines (NSAIDs)
• lithium (to treat some types of mental illness)

In addition:
• if you are being treated after a heart attack, a combination with ACE inhibitors (a medication to treat heart attack) is not recommended.
• 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 Tablets with or without food.

Pregnancy and breastfeeding

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 tablets before you become pregnant or as soon as you know you are pregnant and will advise you to take a different medicine. 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 the baby if 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 your ability to concentrate.

Important information about some of the ingredients
This medicine contains a sugar called lactose. If your doctor has told you that you have intolerance to some sugars, contact your doctor before taking this medicine.

3. How to take Valsartan

Always use Valsartan exactly as your doctor has told you in order to get the best results and reduce the risk of side effects. If you are not sure, check with your doctor or pharmacist.

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 are feeling well.

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

**Children and adolecens (6 to 18 years of age) with high blood pressure:** In patients who weigh less than 35 kg the usual dose is 40 mg of Valsartan once daily. In patients who weigh 35 kg or more the usual starting dose is 80 mg of Valsartan once daily. In some cases your doctor may prescribe higher doses (the dose can be increased to 160 mg and to a maximum of 320 mg).
**Adult patients with heart failure:** Treatment usually starts with 40 mg twice a day. Your doctor will increase the dose gradually over several weeks to a maximum of 160 mg twice a day. The final dose depends on what you as 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.

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

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

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

**If you stop taking Valsartan**
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.

Some symptoms need immediate medical attention:
You may experience symptoms of angioedema (severe allergic reaction) such as
• swelling of the face, tongue, lips or throat
• difficulty in breathing or swallowing
• hives, itching.
If you get any of these, see your doctor immediately.

Other side effects are shown below.
**If any of the following side effects gets serious, or if you notice any effects not listed in this leaflet, tell your doctor or pharmacist.**

**Common: affects 1 to 10 users in 100**
• dizziness
• low blood pressure with or without symptoms, such as dizziness or fainting on standing up
• decreased kidney function (signs of renal impairment)

**Uncommon: affects 1 to 10 users in 1,000**
• headache
• angioedema (see “Some symptoms need immediate medical attention”)
• sudden loss of consciousness.
• spinning sensation (vertigo)
• severely 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)
• cough
• abdominal pain
• diarrhoea
• nausea
• tiredness
• weakness

Not known: frequency cannot be estimated from available data
• 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 (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 levels of white blood cells called neutropenia)
• decreased level of haemoglobin and decrease of the percentage of red blood cells (which can lead to anaemia in severe cases)
• increased level of potassium in the blood (which can trigger muscle spasms and abnormal heart rhythm in severe cases)
• elevation of liver function values (which can indicate liver damage) including an increase of bilirubin in the blood (which in severe cases can cause yellow skin and eyes)
• increased levels of blood urea nitrogen and 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 for high blood pressure than in patients treated for heart failure or after a recent heart attack.

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

5. How to store Valsartan

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

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

6. Further information

What Valsartan Tablets contain
The active substance (which makes the medicine work) is valsartan. Each tablet contains 80mg or 160mg of valsartan.

The other ingredients are lactose monohydrate, cellulose, microcrystalline, maize starch, crospovidone, povidone, colloidal anhydrous silica, magnesium stearate, hypromellose, titanium dioxide (E171), macrogol, iron oxides (yellow, black and red).

What Valsartan Tablets look like and contents of the pack
Valsartan 80 mg tablets are pink coloured, round, film-coated tablet with beveled edge debossed with ‘V and 80’ on one side of the tablet, and a breakline on the other side.

Valsartan 160 mg tablets are grey-orange coloured, oval shaped, film-coated tablet with beveled edge debossed ‘V160’ on one side of the tablet and breakline on the other side.

The tablets can be divided in to two equal halves

Available pack sizes: 28 tablets.

Marketing Authorisation Holder and Manufacturer
Dr. Reddy’s Laboratories (UK) Ltd., 6 Riverview Road, Beverley, HU17 0LD, United Kingdom

This leaflet was last updated in 09/2011
PACKAGE LEAFLET Information for the User
Valsartan 320 mg film-coated Tablets
Valsartan

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your 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 get 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 called angiotensin II receptor antagonists, which help to control high blood pressure. Angiotensin II is a substance in the body that causes blood vessels to tighten, thus causing an increase in blood pressure. Valsartan works by blocking the effect of angiotensin II. As a result, blood vessels relax and blood pressure is lowered.

Valsartan Tablets are used to treat:
**high blood pressure in adults, children and adolescents (age 6 to 18 years of age).** 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 or kidney failure and increases the risk of heart attacks. Lowering your blood pressure to normal reduces the risk of developing these disorders.

2. Before you take Valsartan

Do not take Valsartan if you
- are allergic to valsartan or to any of the other ingredients in the tablets (see section 6)
- have severe liver disease
- 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 Tablets.

Take special care and check with your doctor before taking Valsartan if you
- have liver disease
- have severe kidney disease or are having dialysis
• have narrowing of the kidney artery
• have recently had a kidney transplant
• are already being treated after a heart attack or for heart failure (Your doctor may need to check your kidney function)
• have other severe heart disease other than heart failure or heart attack.
• suffer from aldosteronism (when you produce too much of the hormone aldosterone) as the use of Valsartan is not recommended
• are taking medicines that increase the amount of potassium in your blood such as potassium supplements, salt substitutes containing potassium, potassium-sparing medicines and heparin. (As it may be necessary to do regular checks of the amount of potassium in your blood)
• are dehydrated (have lost a lot of fluid) caused by diarrhoea, vomiting, or due to high doses of ‘water’ tablets (diuretics)
• think you are or (might become) pregnant (as 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 the late stage (see pregnancy section)
• are below 18 years of age and take Valsartan in combination with other medicines that inhibit the rennin angiotensin aldosterone system (medicines that lower blood pressure). Your doctor may check your kidney function and the amount of potassium in your blood at regular intervals.

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, especially:
• other medicines that lower blood pressure especially water pills (diuretics)
• medicines that increase the amount of potassium in the blood such as potassium supplements, or salt substitutes containing potassium, potassium-sparing medicines and heparin
• certain type of pain killers non-steroidal anti-inflammatory medicines (NSAIDs)
• lithium (to treat some types of mental illness)

In addition:
• if you are being treated after a heart attack, a combination with ACE inhibitors (a medication to treat heart attack) is not recommended.
• 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 Tablets with or without food.

Pregnancy and breastfeeding

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 tablets
before you become pregnant or as soon as you know you are pregnant and will advise you to take a different medicine. 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 the baby if 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 your ability to concentrate.

**Important information about some of the ingredients**
This medicine contains a sugar called lactose. If your doctor has told you that you have intolerance to some sugars, contact your doctor before taking this medicine.

### 3. How to take Valsartan

Always use Valsartan exactly as your doctor has told you in order to get the best results and reduce the risk of side effects. If you are not sure, check with your doctor or pharmacist.

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 are feeling well.

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

**Children and adolescents (6 to 18 years of age) with high blood pressure:** In patients who weigh less than 35 kg the usual dose is 40 mg of Valsartan once daily. In patients who weigh 35 kg or more the usual starting dose is 80 mg of Valsartan once daily. In some cases your doctor may prescribe higher doses (the dose can be increased to 160 mg and to a maximum of 320 mg).

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

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

**If you forget to take Valsartan**

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MHRA PAR; VALSARTAN 40 MG, 80 MG, 160 MG AND 320 MG FILM-COATED TABLETS, PL 08553/0394-0397 AND PL 08553/0462-0465
If you forget to take a dose, take it as soon as you remember. However, if it is almost time for next dose, skip the dose you missed. **Do not take a double dose** to make up for a forgotten dose.

**If you stop taking Valsartan**
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.

Some symptoms need immediate medical attention:
You may experience symptoms of angioedema (severe allergic reaction) such as
- swelling of the face, tongue, lips or throat
- difficulty in breathing or swallowing
- hives, itching.
If you get any of these, see your doctor immediately.

Other side effects are shown below.

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

**Common: affects 1 to 10 users in 100**
- dizziness
- low blood pressure with or without symptoms, such as dizziness or fainting on standing up
- decreased kidney function (signs of renal impairment)

**Uncommon: affects 1 to 10 users in 1,000**
- headache
- angioedema (see “Some symptoms need immediate medical attention”)
- sudden loss of consciousness
- spinning sensation (vertigo)
- severely 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)
- cough
- abdominal pain
- diarrhoea
- nausea
- tiredness
- weakness

**Not known: frequency cannot be estimated from available data**
• 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 (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 levels of white blood cells called neutropenia)
• decreased level of haemoglobin and decrease of the percentage of red blood cells (which can lead to anaemia in severe cases)
• increased level of potassium in the blood (which can trigger muscle spasms and abnormal heart rhythm in severe cases)
• elevation of liver function values (which can indicate liver damage) including an increase of bilirubin in the blood (which in severe cases can cause yellow skin and eyes)
• increased levels of blood urea nitrogen and 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 for high blood pressure than in patients treated for heart failure or after a recent heart attack.

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

5. How to store Valsartan

Keep out of the reach and sight of children.
Do not use Valsartan if you notice that the pack is damaged or shows signs of tampering. Store in the original package below 30°C

Do not use Valsartan after the expiry date which is stated on the carton. The expiry date refers to the last day of that month. Medicines should not be disposed of via waste water or household waste. Ask your pharmacist how to dispose of medicines no longer required. This will help to protect the environment.

6. Further information

What Valsartan Tablets contain
The active substance (which makes the medicine work) is valsartan. Each tablet contains 320 mg of valsartan.

The other ingredients are lactose monohydrate, cellulose, microcrystalline, maize starch, crospovidone, povidone, colloidal anhydrous silica, magnesium stearate in the tablet core, and hypromellose, titanium dioxide (E171), macrogol and iron oxides (yellow, black and red; E172) in the tablet coating.

What Valsartan Tablets look like and contents of the pack
Valsartan 320 mg tablets are light brown coloured, oval shaped, film-coated tablets with beveled edge debossed with ‘V and 320’ on one side of the tablet and breakline on the other side.
The tablets can be divided into two equal halves

Available pack sizes: 28 tablets.

**Marketing Authorisation Holder and Manufacturer**
Dr. Reddy’s Laboratories (UK) Ltd., 6 Riverview Road, Beverley, HU17 0LD, United Kingdom

This leaflet was last updated in 09/2011
Module 4

Labelling

The following text is the approved label text for PL 08553/0394-0397. No label mock-ups have been provided. In accordance with medicines legislation, the products shall not be marketed in the UK until approval of the label mock-ups has been obtained.
PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Valsartan 40 mg film-coated Tablets

Valsartan 80 mg film-coated Tablets

Valsartan 160 mg film-coated Tablets

Valsartan 320 mg film-coated Tablets

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 40 mg, 80 mg, 160 mg, 320 mg of valsartan.

3. LIST OF EXCIPIENTS

Contains Lactose. Read the package leaflet before use.

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets
28 film-coated tablets
30 film-coated tablets
50 film-coated tablets
56 film-coated tablets
60 film-coated tablets
98 film-coated tablets
100 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.
7. OTHER SPECIAL WARNING(S), IF NECESSARY
n/a

8. EXPIRY DATE
EXP

9. SPECIAL STORAGE CONDITIONS
Do not store above 30°C. Store in the original package.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE
No specific instructions for use/handling

11. NAME AND ADDRESS OF THE MARKETING AUTHORIZATION HOLDER
Dr. Reddy’s Laboratories (UK) Ltd., 6 Riverview Road, Beverley, HU17 0LD

12. MARKETING AUTHORIZATION NUMBER(S)
PL 08553/0394
PL 08553/0395
PL 08553/0396
PL 08553/0397

13. BATCH NUMBER
BN

14. GENERAL CLASSIFICATION FOR SUPPLY
POM

15. INSTRUCTIONS ON USE
Take as directed by your physician.

16. INFORMATION IN BRAILLE
Valsartan 40 mg film-coated tablets
Valsartan 80 mg film-coated tablets
Valsartan 160 mg film-coated tablets
Valsartan 320 mg film-coated tablets
MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER LABEL

1. NAME OF THE MEDICINAL PRODUCT

Valsartan 40 mg film-coated Tablets
Valsartan 80 mg film-coated Tablets
Valsartan 160 mg film-coated Tablets
Valsartan 320 mg film-coated Tablets

2. NAME OF THE MARKETING AUTHORITY
   (MARKETING AUTHORISATION HOLDER)

Dr. Reddy’s Laboratories (UK) Ltd.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

BN

5. OTHER

u/a
The following text is the approved label text for PL 08553/0462-0465. No label mock-ups have been provided. In accordance with medicines legislation, the products shall not be marketed in the UK until approval of the label mock-ups has been obtained.
PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Valsartan 40 mg film-coated Tablets
Valsartan 80 mg film-coated Tablets
Valsartan 160 mg film-coated Tablets
Valsartan 320 mg film-coated Tablets

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 40 mg / 80 mg / 160 mg / 320 mg of valsartan.

3. LIST OF EXCIPIENTS

Contains Lactose. Read the package leaflet before use.

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets
28 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

n/a

8. EXPIRY DATE

EXP
9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C. Store in the original package.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

No specific instructions for use/handling

11. NAME AND ADDRESS OF THE MARKETING AUTHORIZATION HOLDER

Dr. Reddy's Laboratories (UK) Ltd., 6 Riverview Road, Beverley, HU17 0LD

12. MARKETING AUTHORIZATION NUMBER(S)

PL 08553/0462
PL 08553/0463
PL 08553/0464
PL 08553/0465

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

Take as directed by your physician.

16. INFORMATION IN BRAILLE

Valsartan 40 mg film-coated tablets
Valsartan 80 mg film-coated tablets
Valsartan 160 mg film-coated tablets
Valsartan 320 mg film-coated tablets
MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER LABEL

1. NAME OF THE MEDICINAL PRODUCT

Valsartan 40 mg film-coated Tablets

Valsartan 80 mg film-coated Tablets

Valsartan 160 mg film-coated Tablets

Valsartan 320 mg film-coated Tablets

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Dr. Reddy’s Laboratories (UK) Ltd.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

BN

5. OTHER

n/a
Module 5

Scientific Discussion

RECOMMENDATION
Based on the review of the data on quality, safety and efficacy, the RMS (UK) considers that the applications for Valsartan 40 mg, 80 mg, 160 mg and 320 mg film-coated Tablets in the treatment of essential hypertension and/or heart failure and/or recent myocardial infarction could be approved.

EXECUTIVE SUMMARY

Problem statement
These Decentralised applications were submitted under Article 10.1 of Directive 2001/83/EC, as amended. The applicant claims that that the proposed products are generic versions of the products Diovan 40mg, 80mg, 160 mg and 320mg film-coated tablets (Novartis Pharmaceuticals UK). Diovan 40mg, 80mg and 160 mg film-coated tablets (PL 00101/0599-0601) were licensed in the UK on 22 March 2002 and Diovan 320mg film-coated tablets (PL 00101/0726) were licensed in the UK on 17 September 2007. Diovan Capsules were authorised prior to this, therefore the legal basis of these applications is acceptable.

With the UK as the Reference Member State in this Decentralised Procedure, Dr. Reddy’s Laboratories (UK) Ltd. applied for Marketing Authorisations for Valsartan 40 mg, 80 mg, 160 mg and 320 mg film-coated Tablets in the following Concerned Member States through the procedures indicated:

UK/H/2636/001-004/DC: DE, IT, RO
UK/H/4641/001-004/DC: IT

About the product
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 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.

Valsartan is used in the treatment of recent myocardial infarction, heart failure and essential hypertension. Its indications depend on the strength of the tablet.

General comments on the submitted dossier
The submitted documentation in relation to the proposed type of product is considered to be of sufficient quality and is consistent with the current EU regulatory
requirements. Satisfactory overall summaries of the dossiers regarding the quality, non-clinical and clinical parts have been submitted.

**General comments on compliance with GMP, GLP, GCP and agreed ethical principles**

**GMP**
The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of these products.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP certificates of satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

**GLP**
No new non-clinical studies were submitted in support of these applications, and none are needed for applications of this type.

**GCP**
Statements have been provided confirming that the submitted bioequivalence study was conducted in compliance with Good Clinical Practices (GCP), as referenced in the ICH guidelines (ICH E6), local regulatory requirements, and the principles enunciated in the Declaration of Helsinki.

**SCIENTIFIC OVERVIEW AND DISCUSSION**

**Quality aspects**

**Drug substance**

**General Information**

rINN/USAN/BAN: Valsartan
Chemical name: \((2S)-3\text{-Methyl-2-}[pentanoyl][2\text{'}-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]amino]butanoic acid\)
Chemical structure:

![Chemical structure diagram]

Molecular formula: $C_{24}H_{29}N_5O_3$
Molecular weight: 435.5

**General properties**
White or almost white, hygroscopic powder. Practically insoluble in water, freely soluble in anhydrous ethanol, sparingly soluble in methylene chloride.

All aspects of the manufacture and control of the hydrochlorothiazide are supported by an EDQM Certificate of Suitability. This certificate is accepted as confirmation of the suitability of this drug substance for inclusion in this medicinal product.

Appropriate stability data have been generated, supporting a suitable retest period when the drug substance is stored in the packaging proposed.

**Drug product**

**Description and composition**
The four different tablet strengths can be differentiated from each other by colour and identification markings.

Valsartan 40 mg film-coated Tablets are yellow coloured, oval shaped, film-coated tablets with a beveled edge, debossed with ‘V’ on one side and ‘4’ and ‘0’ on either side of the breakline on the other side; Valsartan 80 mg film-coated Tablets are pink coloured, round, film-coated tablets with a beveled edge, debossed with ‘V 80’ on one side of the tablet and a breakline on the other side; Valsartan 160 mg film-coated Tablets are grey-orange coloured, oval shaped, film-coated tablets with a beveled edge, debossed with ‘V160’ on one side of the tablet and a breakline on the other side and Valsartan 320 mg film-coated Tablets are light brown coloured, oval shaped, film-coated tablet with a beveled edge, debossed with ‘V 320’ on one side of the tablet and a breakline on the other side. The tablets can be divided into two equal halves.

The cores of all four tablet strengths contain lactose monohydrate, microcrystalline cellulose, maize starch, crospovidone (Type-A), povidone (PVP-K 30), colloidal anhydrous silica and magnesium stearate. The coating of all four tablet strengths contains hypromellose, titanium dioxide, macrogol and iron oxide yellow (E172). In addition, the coating of the 40 mg tablets contains talc (E553b) and the coating of the three higher strength tablets contain iron oxide black (E172) and iron oxide red (E172).
The excipients used in the tablets comply with current Ph. Eur. requirements, with the exception of iron oxide yellow (E172), iron oxide black (E172) and iron oxide red (E172) which comply with Directive 95/45/EC. In the absence of Ph. Eur. Monographs for these excipients this is satisfactory.

Suitable declarations issued by suppliers of the excipients to confirm compliance with the requirements of the relevant guideline and Directives with regard to TSE are provided. Lactose used in the manufacture of tablets is sourced from milk collected for human consumption and, thus, poses no concerns with respect to TSE/BSE.

**Pharmaceutical development**

The objective of the development programme was to develop a formulation similar to the innovator products, Diovan 40mg, 80mg, 160 mg and 320mg film-coated tablets. A satisfactory account of the pharmaceutical development has been provided.

**Manufacturing process**

A satisfactory batch formula has been provided, along with an appropriate account of the manufacturing process. The manufacturing process has been validated using pilot-scale batches and has shown satisfactory results. A commitment has been provided that validation data from production-scale batches will be provided once they are available.

**Finished product specification**

The finished product specifications are acceptable. Test methods have been described and have been adequately validated. Batch data have been provided and comply with the release specifications. Certificates of analysis have been provided for all working standards used.

**Container-closure system**

The tablets are stored in aluminium-PVC/aluminium/OPA blisters. PLs 08553/0394-0397 may be available in packs of 14, 28, 30, 50, 56, 60, 98 and 100 tablets; PL 08553/0462 may be available in packs of 14 tablets; and PL 08553/0463-0465 may be available in packs of 28 tablets, although not all pack sizes may be marketed.

Satisfactory specifications and certificates of analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with foodstuffs.

**Stability of the product**

Stability studies were performed in accordance with current guidelines on the finished product in the packaging proposed for marketing. The data from these studies support a shelf-life of 2 years for these products when the storage precautions ‘Store in the original package’ and ‘Do not store above 30°C’ are applied.

**Product literature**

The SmPCs, PIL and labels are pharmaceutically acceptable.

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

**Marketing Authorisation Application (MAA) forms**
The MAA forms are pharmaceutically satisfactory.

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

**Quality conclusion**
There are no objections to the approval of Valsartan 40 mg, 80 mg, 160 mg and 320 mg film-coated Tablets from a quality point of view.

**Non-clinical aspects**

**Non-clinical overview**
The pharmacological, pharmacokinetic and toxicological properties of valsartan are well known. As valsartan is a well known drug substance, no further studies are required and the applicant has provided none. An overview based on the literature is thus appropriate.

**Expert report**
In view of the fact that the pharmaco-toxicological properties of valsartan are well known, the expert report is acceptable.

**Environmental risk assessment**
A suitable justification for the absence of a formal environmental risk assessment has been provided, based on the expectation that introduction of this generic product onto the market is unlikely to result in an increase in the combined sales of all valsartan-containing products, which in turn is unlikely to increase exposure of the environment to valsartan.

**Product literature**
The product literature is acceptable from a non-clinical point of view.

**Non-clinical conclusion**
There are no objections to the approval of Valsartan 40 mg, 80 mg, 160 mg and 320 mg film-coated Tablets from a non-clinical point of view.

**Clinical aspects**

**Pharmacokinetics**
To support the application, the applicant has submitted a balanced, randomised, open label, two-sequence, two-treatment, two-period, cross-over, single-dose bioequivalence study of Valsartan 320 mg film-coated Tablets and Diovan 320mg...
film-coated tablets in normal, healthy, adult, male and female human subjects under fasting conditions.

Satisfactory justification is provided for a bio-waiver for the 40 mg, 80 mg and 160 mg tablets. As Valsartan 40 mg, 80 mg, 160 mg and 320 mg film-coated Tablets meet the criteria specified in the “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98 rev. 1/Corr), the results and conclusions of the bioequivalence study on the 320 mg strength tablets can be extrapolated to the lower strength tablets.

60 healthy adult male volunteers were enrolled and 58 subjects completed the study. The reference product was from the EU market and is appropriate.

**Results**

**Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, $t_{\text{max}}$ median, range)**

<table>
<thead>
<tr>
<th>PK Parameters</th>
<th>Test</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td>7016.793 ± 2323.9527</td>
<td>7080.0043 ± 2414.5693</td>
</tr>
<tr>
<td>AUC_{0-t} (ng.hr/mL)</td>
<td>45820.8676 ± 17331.1311</td>
<td>46908.5964 ± 18018.1635</td>
</tr>
<tr>
<td>AUC_{0-}\infty (ng.hr/mL)</td>
<td>46494.7831 ± 17465.5778</td>
<td>47646.2332 ± 18183.2718</td>
</tr>
<tr>
<td>$\text{AUC}<em>{\text{0-}}/\text{AUC}</em>{\text{0-\infty}}$ (%)</td>
<td>98.425 ± 0.8295</td>
<td>98.263 ± 0.6909</td>
</tr>
<tr>
<td>$t_{\text{max}}$ (hr)</td>
<td>6.4602 ± 2.8220</td>
<td>6.0207 ± 2.3335</td>
</tr>
<tr>
<td>$K_{\text{e}}$(hr$^{-1}$)</td>
<td>0.1229 ± 0.0410</td>
<td>0.1279 ± 0.0409</td>
</tr>
<tr>
<td><strong>Median (Range)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$t_{\text{max}}$ (hr)</td>
<td>3.670 (1.33 – 5.00)</td>
<td>3.670 (1.00 – 5.00)</td>
</tr>
</tbody>
</table>

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
AUC_{0-}\infty area under the plasma concentration-time curve from time zero to infinity
$C_{\text{max}}$ maximum plasma concentration
$T_{\text{max}}$ time for maximum concentration
$T_{1/2}$ half-life

The geometric mean and 90% confidence interval based on least squares mean obtained from ANOVA for the pharmacokinetic parameters $C_{\text{max}}$, AUC_{0-4} and AUC_{0-}\infty are summarised in the following table:

**Table 2: results of log transformed pharmacokinetic parameters**

<table>
<thead>
<tr>
<th>PK Parameter</th>
<th>Geometric Least Square Means</th>
<th>T/R Ratio (%)</th>
<th>90% Confidence Interval</th>
<th>Power (%)</th>
<th>ISCV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$</td>
<td>6587.5430</td>
<td>6706.1887</td>
<td>98.23</td>
<td>90.51</td>
<td>106.61</td>
</tr>
<tr>
<td>AUC_{0-t}</td>
<td>42732.0833</td>
<td>43695.0432</td>
<td>97.80</td>
<td>90.80</td>
<td>105.33</td>
</tr>
<tr>
<td>AUC_{0-}\infty</td>
<td>43417.8954</td>
<td>44422.4561</td>
<td>97.74</td>
<td>98.81</td>
<td>105.19</td>
</tr>
</tbody>
</table>

The ratio AUC_{0-4}/AUC_{0-}\infty was greater than 80% for each subject.
Results of $C_{\text{max}}$, $T_{\text{max}}$ and $T_{1/2}$ for the reference product were in accordance with results provided in the SmPC of the originator.

When PK parameters of the test product were compared with those of the reference product, 90% geometric confidence intervals of the ratio (A/B) of least-squares means from the ANOVA of the Log-transformed AUC$_{0-t}$ and $C_{\text{max}}$ were within 80% to 125%.

Therefore, criteria used to assess bioequivalence between test and reference formulations were fulfilled for $C_{\text{max}}$ and AUC$_{0-t}$.

**Safety results**
A total of two adverse events were reported during the study and both were assessed as probably related to the study drug. There were no serious adverse events. There were no safety concerns.

**Conclusion**
Based on the submitted bioequivalence study Valsartan 320 mg film-coated Tablets are considered bioequivalent to Diovan 320mg film-coated tablets in healthy subjects under fasting conditions. As Valsartan 40 mg, 80 mg, 160 mg and 320 mg film-coated Tablets meet the criteria specified in the “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98 rev. 1/Corr), the results and conclusions of the bioequivalence study on the 320 mg strength tablets can be extrapolated to the 40 mg, 80 mg and 160 mg strength tablets.

**Pharmacodynamics**
The pharmacodynamic characteristics of valsartan have been well-studied in the past. There would be no particular concerns for a generic medicinal product. No new data have been submitted and none are required.

**Clinical efficacy and safety**
No new efficacy data are presented and none is required. A comprehensive review of the published literature has been provided by the applicant, citing the well established clinical pharmacology, efficacy and safety of valsartan.

**Pharmacovigilance system**
The RMS considers that the pharmacovigilance system fulfils the requirements. The applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the collection and notification of any adverse reaction suspected of occurring in the Community or in a third country.

**Risk management plan**
No safety concerns requiring additional risk minimization activities have been identified. A detailed RMP is not considered necessary for these applications.

**Expert report**
A clinical overall summary, written by an appropriately qualified physician, has been provided and is a satisfactory, non-critical summary of the clinical part of the dossier.
Product literature
All product literature (SmPCs, PIL and labelling) is medically satisfactory.

Clinical conclusion
There are no objections to the approval of Valsartan 40 mg, 80 mg, 160 mg and 320 mg film-coated Tablets from a clinical point of view.
OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Valsartan 40 mg, 80 mg, 160 mg and 320 mg film-coated Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL
No new non-clinical data were submitted and none are required for applications of these type.

EFFICACY
The use of valsartan in the treatment of essential hypertension and/or heart failure and/or recent myocardial infarction is well established. Bioequivalence has been demonstrated between the applicant’s Valsartan 40 mg, 80 mg, 160 mg and 320 mg film-coated Tablets and the reference products. New efficacy data is, therefore, not needed.

SAFETY
No new or unexpected safety concerns arise from these applications.

The SmPCs and PIL are satisfactory and consistent with those of the reference products. Satisfactory labelling has also been submitted.

BENEFIT-RISK ASSESSMENT
The quality of the products is acceptable and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with valsartan is considered to have demonstrated the therapeutic value of the compound. The benefit-risk balance is, therefore, considered to be positive. Marketing Authorisations should be granted.