Public Assessment Report

Decentralised Procedure

Valsartan 40, 80 and 160mg Capsules

Valsartan

UK/H/3958/001-3/DC

UK licence no: PL 18909/0305-7

Arrow Generics Limited
LAY SUMMARY

On 9th March 2011, the Reference Member State (RMS) and the Concerned Member States (CMSs) agreed to grant Marketing Authorisations to Arrow Generics Limited for the medicinal products Valsartan 40, 80 and 160mg Capsules. The marketing authorisations were granted via the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS). After the national phase, a licence was granted in the UK on 6th April 2011. These medicines are only available on prescription from your doctor.

The active ingredient in Valsartan Capsules is valsartan. Valsartan belongs to a class of medicines known as “angiotensin II receptor antagonists”. Valsartan helps blood vessels relax and so reduces strain on the heart.

Valsartan 40mg, 80mg and 160mg Capsules can be used to treat:

- Symptomatic heart failure in adults
- High blood pressure in children and adolescents aged 6 to 18 years

Valsartan 80mg and 160mg Capsules can be used to treat:

- High blood pressure in adults

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Valsartan 40, 80 and 160mg Capsules outweigh the risks, hence Marketing Authorisations have been granted.
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## Module 1

<table>
<thead>
<tr>
<th><strong>Product Name</strong></th>
<th>Valsartan 40, 80 and 160mg Capsules</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of Application</strong></td>
<td>Generic, Article 10.1</td>
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<td><strong>Active Substance</strong></td>
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<td><strong>Form</strong></td>
<td>Capsules</td>
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<tr>
<td><strong>Strength</strong></td>
<td>40, 80 and 160mg Capsules</td>
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<tr>
<td><strong>MA Holder</strong></td>
<td>Arrow Generics Limited, Unit 2, Eastman Way, Stevenage, Hertfordshire, SG1 4SZ, U.K.</td>
</tr>
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<td><strong>RMS</strong></td>
<td>UK</td>
</tr>
<tr>
<td><strong>CMS</strong></td>
<td>Cyprus and Malta</td>
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<tr>
<td><strong>Procedure Numbers</strong></td>
<td>UK/H/3958/001-3/DC</td>
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<tr>
<td><strong>Timetable</strong></td>
<td>Day 210 – 9th March 2011</td>
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</tbody>
</table>
Module 2
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Valsartan 40mg Capsules

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

3 PHARMACEUTICAL FORM
Capsules, hard

Valsartan 40mg Capsules are a hard gelatin, light grey opaque / light grey opaque capsule with ‘VS3’ over ‘©’ on the cap and no markings on the body.

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 Capsules is 40mg twice daily. Uptitration to 80mg and 160mg 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 Capsules 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.

Weight Maximum dose studied in clinical trials
≥18 kg to <35 kg 80 mg
≥35 kg to <80 kg 160 mg
≥80 kg to ≤160 kg 320 mg

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 is 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
Valsartan is not recommended for the treatment of heart failure in children and adolescents below the age of 18 years due to the lack of data on safety and efficacy.

Method of administration
Valsartan Capsules 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.

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 dose adjustment is required for adult patients with 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).

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 Diovan (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).

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 section 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.

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.

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 is 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 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”.

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.
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** (≥ 1/1,000 to < 1/100)
- **Rare** (≥ 1/10,000 to < 1/1,000)
- **Very rare** (< 1/10,000), including isolated reports

Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.

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

**Hypertension**

<table>
<thead>
<tr>
<th>Blood and lymphatic system disorders</th>
<th>Not known</th>
<th>Decrease in haemoglobin, Decrease in haematocrit, Neutropenia, Thrombocytopenia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Immune system disorders</strong></td>
<td>Not known</td>
<td>Hypersensitivity including serum sickness</td>
</tr>
<tr>
<td><strong>Metabolism and nutrition disorders</strong></td>
<td>Not known</td>
<td>Increase of serum potassium, hyponatraemia</td>
</tr>
<tr>
<td><strong>Ear and labyrinth system disorders</strong></td>
<td>Uncommon</td>
<td>Vertigo</td>
</tr>
<tr>
<td><strong>Vascular disorders</strong></td>
<td>Not known</td>
<td>Vasculitis</td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders</strong></td>
<td>Uncommon</td>
<td>Cough</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td>Uncommon</td>
<td>Abdominal pain</td>
</tr>
<tr>
<td><strong>Hepato-biliary disorders</strong></td>
<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>
<td></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 Diovan (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**

<table>
<thead>
<tr>
<th>Blood and lymphatic system disorders</th>
<th>Thrombocytopenia</th>
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<tr>
<td>Immune system disorders</td>
<td>Hypersensitivity including serum sickness</td>
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<tr>
<td>Metabolism and nutrition disorders</td>
<td>Hyperkalaemia</td>
</tr>
<tr>
<td></td>
<td>Increase of serum potassium, hyponatraemia</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Dizziness, Postural dizziness</td>
</tr>
<tr>
<td></td>
<td>Syncope, Headache</td>
</tr>
<tr>
<td>Ear and labyrinth system disorders</td>
<td>Vertigo</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Cardiac failure</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Hypotension, Orthostatic hypotension</td>
</tr>
<tr>
<td></td>
<td>Vasculitis</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
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<tr>
<td>-----------------------------------------------</td>
<td>---</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Cough</td>
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</table>

<table>
<thead>
<tr>
<th>Gastrointestinal disorders</th>
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</thead>
<tbody>
<tr>
<td>Uncommon</td>
<td>Nausea, Diarrhoea</td>
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<table>
<thead>
<tr>
<th>Hepato-biliary disorders</th>
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<tbody>
<tr>
<td>Not known</td>
<td>Elevation of liver function values</td>
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</table>

<table>
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<th>Skin and subcutaneous tissue disorders</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Uncommon</td>
<td>Angioedema</td>
</tr>
<tr>
<td>Not known</td>
<td>Rash, Pruritis</td>
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<table>
<thead>
<tr>
<th>Musculoskeletal and connective tissue disorders</th>
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<tbody>
<tr>
<td>Not known</td>
<td>Myalgia</td>
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<table>
<thead>
<tr>
<th>Renal and urinary disorders</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>Renal failure and impairment</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Acute renal failure, Elevation of serum creatinine</td>
</tr>
<tr>
<td>Not known</td>
<td>Increase in Blood Urea Nitrogen</td>
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</table>

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

### 4.9 Overdose

#### Symptoms

Overdose with valsartan may result in marked hypotension, which could lead to depressed level of consciousness, circulatory collapse and/or shock.

#### Treatment

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

### 5 PHARMACOLOGICAL PROPERTIES

#### 5.1 Pharmacodynamic properties

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

Valsartan is an orally active, potent, and specific angiotensin II (Ang II) receptor antagonist. It acts selectively on the AT\(_1\) receptor subtype, which is responsible for the known actions of angiotensin II. The increased plasma levels of Ang II following AT\(_1\) receptor blockade with valsartan may stimulate the unblocked 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 randomised within 12 hours to 10 days after the onset of myocardial infarction symptoms to valsartan, captopril, or the combination of both. The mean treatment duration was two years. The primary endpoint was time to all-cause mortality.

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

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

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

Heart failure

Val-HeFT was a randomised, controlled, multinational clinical trial of valsartan compared with placebo on morbidity and mortality in 5,010 NYHA class II (62%), III (36%) and IV (2%) heart failure patients receiving usual therapy with LVEF <40% and left ventricular internal diastolic diameter (LVIDD) >2.9 cm/m². Baseline therapy included ACE inhibitors (93%), diuretics (86%), digoxin (67%) and beta blockers (36%). The mean duration of follow-up was nearly two years. The mean daily dose of Diovan (valsartan) in Val-HeFT was 254mg. 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.
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 (80-160mg/od) versus amlodipine (5-10mg/od), in 332 type 2 diabetic patients (mean age: 58 years; 265 men) with microalbuminuria (valsartan: 58 μg/min; amlodipine: 55.4 μg/min), normal or high blood pressure and with preserved renal function (blood creatinine <120 μmol/l). At 24 weeks, UAE was reduced (p<0.001) by 42% (–24.2 μg/min; 95% CI: –40.4 to –19.1) with valsartan and approximately 3% (–1.7 μg/min; 95% CI: –5.6 to 14.9) with amlodipine despite similar rates of blood pressure reduction in both groups.

The Diovan Reduction of Proteinuria (DROP) study further examined the efficacy of valsartan in reducing UAE in 391 hypertensive patients (BP=150/88 mmHg) with type 2 diabetes, albuminuria (mean=102 μg/min; 20-700 μg/min) and preserved renal function (mean serum creatinine = 80 μmol/l). Patients were randomized to one of 3 doses of valsartan (160, 320 and 640mg/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 160mg (95%CI: 22 to 47%), and by 44% with valsartan 320mg (95%CI: 31 to 54%). It was concluded that 160-320mg of valsartan produced clinically relevant reductions in UAE in hypertensive patients with type 2 diabetes.

Paediatric population
Hypertension
The antihypertensive effect of valsartan has 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 tablets daily (low, medium and high doses), and patients who weighed ≥35kg received 20, 80, and 160 mg of valsartan tablets 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 (t1/2α <1 h and t1/2β about 9 h). Valsartan is primarily eliminated by biliary excretion in faeces (about 83% of dose) and renally in urine (about 13% of dose), mainly as unchanged drug. Following intravenous administration, plasma clearance of valsartan is about 2 l/h and its renal clearance is 0.62 l/h (about 30% of total clearance). The half-life of valsartan is 6 hours.

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

Special populations

Elderly
A somewhat higher systemic exposure to valsartan was observed in some elderly subjects than in young subjects; however, this has not been shown to have any clinical significance.

Impaired renal function
As expected for a compound where renal clearance accounts for only 30% of total plasma clearance, no correlation was seen between renal function and systemic exposure to valsartan. Dose adjustment is therefore not required in patients with renal impairment (creatinine clearance >10 ml/min). There is currently no experience on the safe use in patients with a creatinine clearance <10 ml/min and patients undergoing dialysis, therefore valsartan should be used with caution in these patients (see sections 4.2 and 4.4). Valsartan is highly bound to plasma protein and is unlikely to be removed by dialysis.
**Hepatic impairment**
Approximately 70% of the dose absorbed is eliminated in the bile, essentially in the unchanged form. Valsartan does not undergo any noteworthy biotransformation. A doubling of exposure (AUC) was observed in patients with mild to moderate hepatic impairment compared to healthy subjects. However, no correlation was observed between plasma valsartan concentration versus degree of hepatic dysfunction. Diovan (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 (600mg/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 (600mg/kg/day) are approximately 18 times the maximum recommended human dose on a mg/m² basis (calculations assume an oral dose of 320mg/day and a 60-kg patient).

In non-clinical safety studies, high doses of valsartan (200 to 600mg/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 600mg/kg/day) are approximately 6 and 18 times the maximum recommended human dose on a mg/m² basis (calculations assume an oral dose of 320mg/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
Microcrystalline cellulose (101), Croscarmellose Sodium, Sodium laurilsulfate, Povidone (K30), Magnesium stearate.

*Capsule Body and Cap Composition:*

Titanium dioxide (E171)
Red iron oxide (E172(ii))
Black iron oxide (E172(i))
Gelatin

*Black Printing Ink:*

Shellac
Ethanol
Isopropanol
Butanol
Propylene glycol
Water, purified
Strong ammonia solution
Potassium hydroxide
Black iron oxide (E172)

6.2 Incompatibilities
None known

6.3 Shelf life
24 months

6.4 Special precautions for storage
Store below 30°C.

6.5 Nature and contents of container
The capsules are packed in Aluminium lidding foil/ PVC-PVDC blister packs.

Pack sizes:

7, 28 and 98 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Arrow Generics Limited, Unit 2, Eastman Way, Stevenage, Hertfordshire, SG1 4SZ, U.K.

8 MARKETING AUTHORISATION NUMBER(S)
PL 18909/0305

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
06/04/2011

10 DATE OF REVISION OF THE TEXT
06/04/2011
1 NAME OF THE MEDICINAL PRODUCT
Valsartan 80mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each capsule contains 80mg Valsartan.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Capsules, hard

Valsartan 80mg Capsules are a hard gelatin, light grey opaque / flesh opaque capsule with ‘VS2’ over ‘☐’ on the cap and no markings on the body.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypertension
Treatment of essential hypertension in adults, and 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 Capsules is 40mg twice daily. Uptitration to 80mg and 160mg 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.

Hypertension
The recommended starting dose of Valsartan Capsules is 80mg 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 160mg and to a maximum of 320mg.

Valsartan Capsules 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 Capsules 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 is 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

Valsartan is not recommended for the treatment of heart failure in children and adolescents below the age of 18 years due to the lack of data on safety and efficacy.

Method of administration

Valsartan Capsules 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.

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 dose adjustment is required for adult patients with 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).

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 Diovan (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).

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 section 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.

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.

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 is 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 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 (≥ 1/1,000 to < 1/100)
- Rare (≥ 1/10,000 to < 1/1,000)
- Very rare (< 1/10,000), including isolated reports

Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.

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

**Hypertension**

<table>
<thead>
<tr>
<th>Blood and lymphatic system disorders</th>
<th>Decrease in haemoglobin, Decrease in haematocrit, Neutropenia, Thrombocytopenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune system disorders</td>
<td>Hypersensitivity including serum sickness</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Increase of serum potassium, hyponatraemia</td>
</tr>
<tr>
<td>Ear and labyrinth system disorders</td>
<td>Vertigo</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Vasculitis</td>
</tr>
</tbody>
</table>

21
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 Diovan (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

<table>
<thead>
<tr>
<th>Blood and lymphatic system disorders</th>
<th>Not known</th>
<th>Thrombocytopenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune system disorders</td>
<td>Not known</td>
<td>Hypersensitivity including serum sickness</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Uncommon</td>
<td>Hyperkalaemia</td>
</tr>
<tr>
<td></td>
<td>Not known</td>
<td>Increase of serum potassium, hyponatraemia</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Common</td>
<td>Dizziness, Postural dizziness</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Syncope, Headache</td>
</tr>
<tr>
<td>Disorder Category</td>
<td>Frequency</td>
<td>Symptoms</td>
</tr>
<tr>
<td>-------------------------------------------------------</td>
<td>-----------</td>
<td>---------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Ear and labyrinth system disorders</td>
<td>Uncommon</td>
<td>Vertigo</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Uncommon</td>
<td>Cardiac failure</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Common</td>
<td>Hypotension, Orthostatic hypotension</td>
</tr>
<tr>
<td></td>
<td>Not known</td>
<td>Vasculitis</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Uncommon</td>
<td>Cough</td>
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<tr>
<td>Gastrointestinal disorders</td>
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<td>Nausea, Diarrhoea</td>
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<tr>
<td></td>
<td>Not known</td>
<td>Elevation of liver function values</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Uncommon</td>
<td>Angioedema</td>
</tr>
<tr>
<td></td>
<td>Not known</td>
<td>Rash, Pruritus</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Not known</td>
<td>Myalgia</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Common</td>
<td>Renal failure and impairment</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Acute renal failure, Elevation of serum creatinine</td>
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<tr>
<td></td>
<td>Not known</td>
<td>Increase in Blood Urea Nitrogen</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Uncommon</td>
<td>Asthenia, Fatigue</td>
</tr>
</tbody>
</table>

4.9 Overdose

**Symptoms**

Overdose with valsartan may result in marked hypotension, which could lead to depressed level of consciousness, circulatory collapse and/or shock.

**Treatment**

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

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

Valsartan is unlikely to be removed by haemodialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Valsartan is an orally active, potent, and specific angiotensin II (Ang II) receptor antagonist. It acts selectively on the AT\textsubscript{1} receptor subtype, which is responsible for the known actions of angiotensin II. The increased plasma levels of Ang II following AT\textsubscript{1} receptor blockade with valsartan may stimulate the unblocked AT\textsubscript{2} receptor, which appears to counterbalance the effect of the AT\textsubscript{1} receptor. Valsartan does not exhibit any partial agonist activity at the AT\textsubscript{1} receptor and has much (about 20,000 fold) greater affinity for the AT\textsubscript{1} receptor than for the AT\textsubscript{2} receptor. Valsartan is not known to bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

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 randomised within 12 hours to 10 days after the onset of myocardial infarction symptoms to valsartan, captopril, or the combination of both. The mean treatment duration was two years. The primary endpoint was time to all-cause mortality.

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

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

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

Heart failure
Val-HeFT was a randomised, controlled, multinational clinical trial of valsartan compared with placebo on morbidity and mortality in 5,010 NYHA class II (62%), III (36%) and IV (2%) heart failure patients receiving usual therapy with LVEF <40% and left ventricular internal diastolic diameter (LVIDD) >2.9 cm/m². Baseline therapy included ACE inhibitors (93%), diuretics (86%), digoxin (67%) and beta blockers (36%). The mean duration of follow-up was nearly two years. The mean daily dose of Diovan (valsartan) in Val-HeFT was 254mg. 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.

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.
A 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 (80-160mg/od) versus amlodipine (5-10mg/od), in 332 type 2 diabetic patients (mean age: 58 years; 265 men) with microalbuminuria (valsartan: 58 μg/min; amlodipine: 55.4 μg/min), normal or high blood pressure and with preserved renal function (blood creatinine <120 μmol/l). At 24 weeks, UAE was reduced (p<0.001) by 42% (−24.2 μg/min; 95% CI: −40.4 to −19.1) with valsartan and approximately 3% (−1.7 μg/min; 95% CI: −5.6 to 14.9) with amlodipine despite similar rates of blood pressure reduction in both groups.

The Diovan Reduction of Proteinuria (DROP) study further examined the efficacy of valsartan in reducing UAE in 391 hypertensive patients (BP=150/88 mmHg) with type 2 diabetes, albuminuria (mean=102 μg/min; 20-700 μg/min) and preserved renal function (mean serum creatinine = 80 μmol/l). Patients were randomized to one of 3 doses of valsartan (160, 320 and 640mg/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 160mg (95%CI: 22 to 47%), and by 44% with valsartan 320mg (95%CI: 31 to 54%). It was concluded that 160-320mg of valsartan produced clinically relevant reductions in UAE in hypertensive patients with type 2 diabetes.

Paediatric population
Hypertension
The antihypertensive effect of valsartan has 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 tablets daily (low, medium and high doses), and patients who weighed ≥35kg received 20, 80, and 160 mg of valsartan tablets 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 (Cmax) by about 50%, although from about 8 h post dosing plasma valsartan concentrations are similar for the fed and fasted groups. This reduction in AUC is not, however, accompanied by a clinically significant reduction in the therapeutic effect, and valsartan can therefore be given either with or without food.

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

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

Excretion:
Valsartan shows multiexponential decay kinetics (t1/2α <1 h and t1/2β about 9 h). Valsartan is primarily eliminated by biliary excretion in faeces (about 83% of dose) and renally in urine (about 13% of dose), mainly as unchanged drug. Following intravenous administration, plasma clearance of valsartan is about 2 l/h and its renal clearance is 0.62 l/h (about 30% of total clearance). The half-life of valsartan is 6 hours.

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

Special populations

Elderly
A somewhat higher systemic exposure to valsartan was observed in some elderly subjects than in young subjects; however, this has not been shown to have any clinical significance.

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

**Hepatic impairment**
Approximately 70% of the dose absorbed is eliminated in the bile, essentially in the unchanged form. Valsartan does not undergo any noteworthy biotransformation. A doubling of exposure (AUC) was observed in patients with mild to moderate hepatic impairment compared to healthy subjects. However, no correlation was observed between plasma valsartan concentration versus degree of hepatic dysfunction. Diovan (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 (600mg/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 (600mg/kg/day) are approximately 18 times the maximum recommended human dose on a mg/m² basis (calculations assume an oral dose of 320mg/day and a 60-kg patient).

In non-clinical safety studies, high doses of valsartan (200 to 600mg/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 600mg/kg/day) are approximately 6 and 18 times the maximum recommended human dose on a mg/m² basis (calculations assume an oral dose of 320mg/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
Microcrystalline cellulose (101), Croscarmellose Sodium, Sodium laurilsulfate, Povidone (K30), Magnesium stearate.

Capsule Body and Cap Composition:
- Titanium dioxide (E171)
- Red iron oxide (E172(ii))
- Black iron oxide (E172(i))
- Gelatin

Black Printing Ink:
- Shellac
- Ethanol
- Isopropanol
- Butanol
- Propylene glycol
- Water, purified
- Strong ammonia solution
- Potassium hydroxide
- Black iron oxide (E172)

6.2 Incompatibilities
None known

6.3 Shelf life
24 months

6.4 Special precautions for storage
Store below 30°C.

6.5 Nature and contents of container
The capsules are packed in Aluminium lidding foil/ PVC-PVDC blister packs.

Pack sizes:
- 7, 28 and 98 capsules.

Not all pack sizes may be marketed

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Arrow Generics Limited, Unit 2, Eastman Way, Stevenage, Hertfordshire, SG1 4SZ, U.K.

8 MARKETING AUTHORISATION NUMBER(S)
PL 18909/0306

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
06/04/2011

10 DATE OF REVISION OF THE TEXT
06/04/2011
1 NAME OF THE MEDICINAL PRODUCT
Valsartan 160mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each capsule contains 160mg Valsartan.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Capsules, hard

Valsartan 160mg Capsules are a hard gelatin, dark grey opaque / flesh opaque capsule with ‘VS1’ over ‘ Dover’ on the cap and no markings on the body.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications

Hypertension
Treatment of essential hypertension in adults, and 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 Capsules is 40mg twice daily. Uptitration to 80mg and 160mg 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.

Hypertension
The recommended starting dose of Valsartan Capsules is 80mg 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 160mg and to a maximum of 320mg.

Valsartan Capsules 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 Capsules 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 is 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
Valsartan is not recommended for the treatment of heart failure in children and adolescents below the age of 18 years due to the lack of data on safety and efficacy.

Method of administration
Valsartan Capsules 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.

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 dose adjustment is required for adult patients with 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).
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 Diovan (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).

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 section 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.

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.

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 is 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 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 (≥ 1/1,000 to < 1/100)
- Rare (≥ 1/10,000 to < 1/1,000)
- Very rare (< 1/10,000), including isolated reports

Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.

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

**Hypertension**

<table>
<thead>
<tr>
<th>Blood and lymphatic system disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Not known</td>
<td>Decrease in haemoglobin, Decrease in haematocrit, Neutropenia, Thrombocytopenia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Immune system disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Not known</td>
<td>Hypersensitivity including serum sickness</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Metabolism and nutrition disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Not known</td>
<td>Increase of serum potassium, hyponatraemia</td>
</tr>
</tbody>
</table>

| Ear and labyrinth system disorders | |
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 Diovan (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

<table>
<thead>
<tr>
<th>Blood and lymphatic system disorders</th>
<th>Not known</th>
<th>Thrombocytopenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune system disorders</td>
<td>Not known</td>
<td>Hypersensitivity including serum sickness</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Uncommon</td>
<td>Hyperkalaemia</td>
</tr>
<tr>
<td></td>
<td>Not known</td>
<td>Increase of serum potassium, hyponatraemia</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
4.9 Overdose

Symptoms
Overdose with valsartan may result in marked hypotension, which could lead to depressed level of consciousness, circulatory collapse and/or shock.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Angiotensin II Antagonists, plain, ATC code: C09CA03

Valsartan is an orally active, potent, and specific angiotensin II (Ang II) receptor antagonist. It acts selectively on the 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 \( \leq 40\% \) by radionuclide ventriculography or \( \leq 35\% \) by echocardiography or ventricular contrast angiography). Patients were randomised within 12 hours to 10 days after the onset of myocardial infarction symptoms to valsartan, captopril, or the combination of both. The mean treatment duration was two years. The primary endpoint was time to all-cause mortality.

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

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

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

**Heart failure**

Val-HeFT was a randomised, controlled, multinational clinical trial of valsartan compared with placebo on morbidity and mortality in 5,010 NYHA class II (62%), III (36%) and IV (2%) heart failure patients receiving usual therapy with LVEF <40% and left ventricular internal diastolic diameter (LVIDD) >2.9 cm/m². Baseline therapy included ACE inhibitors (93%), diuretics (86%), digoxin (67%) and beta blockers (36%). The mean duration of follow-up was nearly two years. The mean daily dose of Diovan (valsartan) in Val-HeFT was 254mg. 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 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.

**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.

A 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 (80-160mg/od) versus amlodipine (5-10mg/od), in 332 type 2 diabetic patients (mean age: 58 years; 265 men) with microalbuminuria (valsartan: 58 μg/min; amlodipine: 55.4 μg/min), normal or high blood pressure and with preserved renal function (blood creatinine <120 μmol/l). At 24 weeks, UAE was reduced (p<0.001) by 42% (–24.2 μg/min; 95% CI: –40.4 to –19.1) with valsartan and approximately 3% (–1.7 μg/min; 95% CI: –5.6 to 14.9) with amlodipine despite similar rates of blood pressure reduction in both groups.

The Diovan Reduction of Proteinuria (DROP) study further examined the efficacy of valsartan in reducing UAE in 391 hypertensive patients (BP=150/88 mmHg) with type 2 diabetes, albuminuria (mean=102 μg/min; 20-700 μg/min) and preserved renal function (mean serum creatinine = 80 μmol/l). Patients were randomized to one of 3 doses of valsartan (160, 320 and 640mg/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 160mg (95%CI: 22 to 47%), and by 44% with valsartan 320mg (95%CI: 31 to 54%). It was concluded that 160-320mg of valsartan produced clinically relevant reductions in UAE in hypertensive patients with type 2 diabetes.

**Paediatric population**

**Hypertension**

The antihypertensive effect of valsartan has 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 tablets daily (low, medium and high doses), and patients who weighed ≥35 kg received 20, 80, and 160 mg of valsartan tablets 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$_{1/2a}$ <1 h and t$_{1/2b}$ 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 160mg twice a day). The average accumulation factor is about 1.7. The apparent clearance of valsartan following oral administration is approximately 4.5 l/h. Age does not affect the apparent clearance in heart failure patients.

**Special populations**

**Elderly**
A somewhat higher systemic exposure to valsartan was observed in some elderly subjects than in young subjects; however, this has not been shown to have any clinical significance.

**Impaired renal function**
As expected for a compound where renal clearance accounts for only 30% of total plasma clearance, no correlation was seen between renal function and systemic exposure to valsartan. Dose adjustment is therefore not required in patients with renal impairment (creatinine clearance >10 ml/min). There is currently no experience on the safe use in patients with a creatinine clearance <10 ml/min and patients undergoing dialysis, therefore valsartan should be used with caution in these patients (see sections 4.2 and 4.4). Valsartan is highly bound to plasma protein and is unlikely to be removed by dialysis.
Hepatic impairment
Approximately 70% of the dose absorbed is eliminated in the bile, essentially in the unchanged form. Valsartan does not undergo any noteworthy biotransformation. A doubling of exposure (AUC) was observed in patients with mild to moderate hepatic impairment compared to healthy subjects. However, no correlation was observed between plasma valsartan concentration versus degree of hepatic dysfunction. Diovan (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 (600mg/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 (600mg/kg/day) are approximately 18 times the maximum recommended human dose on a mg/m² basis (calculations assume an oral dose of 320mg/day and a 60-kg patient).
In non-clinical safety studies, high doses of valsartan (200 to 600mg/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 600mg/kg/day) are approximately 6 and 18 times the maximum recommended human dose on a mg/m² basis (calculations assume an oral dose of 320mg/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
Microcrystalline cellulose (101), Croscarmellose Sodium, Sodium laurilsulfate, Povidone (K30),
Magnesium stearate.

Capsule Body and Cap Composition:
Titanium dioxide (E171)
Red iron oxide (E172(ii))
Black iron oxide (E172(i))
Gelatin

Black Printing Ink:
Shellac
Ethanol
Isopropanol
Butanol
Propylene glycol
Water, purified
Strong ammonia solution
Potassium hydroxide
Black iron oxide (E172)

6.2 Incompatibilities
None known

6.3 Shelf life
24 months

6.4 Special precautions for storage
Store below 30°C.

6.5 Nature and contents of container
The capsules are packed in Aluminium lidding foil/ PVC-PVDC blister packs.

Pack sizes:
7, 28 and 98 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Arrow Generics Limited, Unit 2, Eastman Way, Stevenage, Hertfordshire, SG1 4SZ, U.K.

8 MARKETING AUTHORISATION NUMBER(S)
PL 18909/0307

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
06/04/2011

10 DATE OF REVISION OF THE TEXT
06/04/2011
Module 3

PACKAGE LEAFLET: INFORMATION FOR THE USER

Valsartan 40/80/160mg Capsules

(par Valsartan 40, 80 and 160mg Capsules UK/H/3958/001-3/DC)

Read all of this leaflet carefully before you start taking this medicine.

1. WHAT VALSARTAN CAPSULES ARE AND WHAT THEY ARE USED FOR

The active ingredient of Valsartan Capsules is valsartan. Valsartan belongs to a class of medicines known as "angiotensin II receptor antagonists." Valsartan helps blood vessels relax and so reduces strain on the heart.

Valsartan 40mg, 80mg & 160mg Capsules can be used to treat:

(i) symptomatic heart failure in adults.

Heart failure occurs when the heart muscles cannot pump blood strong enough to carry all the blood needed throughout the body.

Heart failure symptoms include shortness of breath and swelling of the body, often worsening after exercise.

Valsartan Capsules are used for heart failure when a group of medicines called Angiotensin Converting Enzyme (ACE) inhibitors (a medication that treats heart failure) cannot be used or Valsartan Capsules may be used in addition to ACE inhibitors when beta blockers (another medication to treat heart failure) cannot be used.

(ii) high blood pressure in children and adolescents aged 6 to 18 years.

High blood pressure may damage the body's blood vessels and may result in a stroke, heart failure or kidney failure. Lowering blood pressure reduces the risk of developing these conditions.

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

Valsartan 40mg, 80mg & 160mg Capsules can also be used to treat:

(iii) high blood pressure in adults.

High blood pressure may damage the body's blood vessels and may result in a stroke, heart failure or kidney failure. Lowering blood pressure reduces the risk of developing these conditions.

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

Valsartan, which is contained in Valsartan Capsules, is also authorised to treat other conditions that are not mentioned in this leaflet.

Ask your doctor or pharmacist if you have further questions.

2. BEFORE YOU TAKE VALSARTAN CAPSULES

Do not take Valsartan Capsules if you:

- are allergic (hypersensitive) to valsartan or any of the other ingredients of Valsartan Capsules.
- have severe liver disease.
- are more than 3 months pregnant (it is also better to avoid Valsartan Capsules in early pregnancy - see pregnancy section).
- If any of these apply to you, do not take Valsartan Capsules.

Take special care with Valsartan Capsules if you:

- have liver disease.
- have severe kidney disease or if you are undergoing dialysis.
- are known to be suffering from the kidney disease.
- have recently had kidney transplantation.
- are receiving treatment after a heart attack or for heart failure that your doctor may have ordered that you are taking.
- have severe heart disease other than heart failure or heart attack.

- are taking medicines that increase the amount of potassium in your blood, these include potassium supplements, potassium-sparing medicines and heparin. It may be necessary to check the amount of potassium in your blood at regular intervals.
- are likely to have 'primary aldosteronism', a hormone imbalance. If this applies to you than the use of Valsartan Capsules is not recommended.
- have lived a lot of fluid balance, vomiting, or high levels of water (diabetes).

In addition:

- if you are below the age of 18 years and you take Valsartan Capsules with other medicines then your doctor may request tests to check your blood balance and how your kidneys are working.
- you must tell your doctor if you think you are or might be pregnant. Valsartan Capsules are not recommended in early pregnancy, and must not be taken if you are more than 3 months pregnant, as it may cause serious harm to your baby if used at that stage (see pregnancy section).
- If any of the above applies to you, tell your doctor before you take Valsartan Capsules.

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 Capsules are taken together with certain other medicines. It may be necessary to change the dose, to take other medicines or to stop taking any of the medicines. This applies to both prescription and non-prescription medicines, especially:

- medicines that lower blood pressure, especially "water tablets" (diuretics).
- medicines that increase the amount of potassium in your blood. These include potassium supplements, potassium-sparing medicines and heparin.
- corticosteroids used to treat other conditions.

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

In addition:

- if you are being treated after a heart attack, a combination with ACE inhibitors (medicines used to treat heart attack) is not recommended.
- if you are being treated for heart failure, a triple combination with ACE inhibitors and beta blockers is used and Valsartan Capsules may be used to treat heart failure is not recommended.

Taking Valsartan Capsules with food and drink

You can take Valsartan Capsules 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 Capsules before you become pregnant or as soon as you know you are pregnant, and will advise you to take another medicine instead of Valsartan Capsules. Valsartan Capsules are 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 it is used after the third month of pregnancy.

Tell your doctor if you are breastfeeding as it may be necessary to start breastfeeding (Valsartan Capsules are not recommended for mothers who are breastfeeding, 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 Capsules affect you. Like many other medicines used to treat high blood pressure, Valsartan Capsules may cause dizziness and affect the ability to concentrate.

3. HOW TO TAKE VALSARTAN CAPSULES

Always take Valsartan Capsules exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Adults

(iii) Heart failure: Treatment starts generally with 40 mg twice daily. Your doctor will increase the dose gradually over several weeks to a maximum of 100 mg twice daily. The final dose depends on what you can tolerate as an individual patient. Valsartan Capsules can be given together with other treatment for heart failure: your doctor will decide which treatment is suitable for you.

(ii) High blood pressure: The usual dose is 80 mg daily. In some cases your doctor may prescribe higher doses (e.g. 160mg or 320mg). He may also combine Valsartan Capsules with an additional medicine e.g. a diuretic (“water tablet”).

Children and adolescents (ages 6 to 18 years) with high blood pressure

In patients who weigh less than 35 kg the usual dose is 40 mg of Valsartan Capsules once daily.

In patients who weigh 35 kg or more the usual starting dose is 80 mg of Valsartan Capsules once daily.

In some cases your doctor may prescribe higher doses (the dose can be increased to 100 mg and to a maximum of 200 mg).

You can take Valsartan Capsules with or without food.

Swallow Valsartan Capsules with a glass of water.

Take Valsartan Capsules at the same time each day.

If you take more Valsartan Capsules than you should

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

If you forget to take Valsartan Capsules

Don't take a double dose to make up for a forgotten dose.

If you have forgotten your dose, take it as soon as you remember. However, if it is almost time for your next dose, skip the dose you missed.

If you stop taking Valsartan Capsules

Stopping your treatment with Valsartan Capsules 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 Capsules can cause side effects, although not everybody gets them. The frequency of some side effects may vary depending on your condition.

The following side effects are important and will require immediate action if you experience them. You should stop taking Valsartan Capsules and see your doctor immediately if the following symptoms occur:

Frequency not known:

• swelling of the face, tongue and windpipe which can cause great difficulty in breathing.

The following side effects have also been reported:

Common, affecting up to 1 in 10 people:

• dizziness, diziness in standing
• low blood pressure
• kidney problems that may become severe
• changes in blood test results that show how the kidneys are working.

Uncommon, affecting fewer than 1 in 100 people:

• feeling faint, feeling sick
• rash (causing breathlessness, fluid retention)
• headache
• cough
• abdominal pain, nausea, diarrhea
• tiredness, fatigue
• increase in blood potassium levels affect the heart and cause muscle symptoms.

5. HOW TO STORE VALSARTAN CAPSULES

Store below 30°C.

Keep out of the reach and sight of children.

Do not use Valsartan Capsules after the expiry date which is stated on the pack after 56E. The expiry date refers to the last day of that month.

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

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

6. FURTHER INFORMATION

What Valsartan Capsules contain

The active substance is Valsartan.

Each capsule contains 80mg Valsartan.

Each capsule contains 160mg Valsartan.

Each of the ingredients in capsules is micronized cellulose (101), croscarmellose sodium, sodium lauryl sulphate, povidone (K36), magnesium stearate, gelatin, titanium dioxide (E171), iron oxide (E172) and black iron oxide (E172).

The blank printing ink contains shellac, ethanols, isopropyl alcohol, propylene glycol, purified water, strong ammonia solution, potassium hydroxide and black iron oxide (E172).

What Valsartan Capsules look like and contents of the pack

Valsartan 80 mg capsules are a hard gelatin, light grey opaque / light grey opaque capsule with ‘VS’ over ‘>’ on the cap and no markings on the body.

Valsartan 160 mg capsules are a hard gelatin, light grey opaque / flesh opaque capsule with ‘VS’ over ‘>’ on the cap and no markings on the body.

The capsules are packaged in aluminium foil blister packs.

Pack sizes: 7, 28, 30.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

Aurobindo Pharma, Limited, 162, Harl N Industrial Estate, Karewadi, Indore, India.

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

This leaflet was last approved in March 2011.

L701/1AA
Module 4
Labelling
Module 5
Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Reference Member State (RMS) and Concerned Member States (CMSs) consider that the applications for Valsartan 40, 80 and 160mg Capsules in the treatment of hypertension in adults, children and adolescents (6 to 18 years of age) and 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, could be approved.

These applications are for Valsartan 40, 80 and 160mg Capsules submitted under Article 10.1 of Directive 2001/83/EC as amended. The reference products are Diovan 40, 80 and 160mg Capsules (PL 00101/0524-6), which were first licensed to Novartis Pharmaceuticals Ltd, UK, on 31st October 1997.

With the UK as the RMS in these Decentralised Procedures (UK/H/3958/001-3/DC), Arrow Generics Limited applied for the Marketing Authorisations for Valsartan 40, 80 and 160mg Capsules in Cyprus and Malta.

Valsartan is an orally active, potent, and specific angiotensin II (Ang II) receptor antagonist. It acts selectively on the AT\textsubscript{1} receptor subtype, which is responsible for the known actions of angiotensin II. The increased plasma levels of Angiotensin II following AT\textsubscript{1} receptor blockade with valsartan may stimulate the unblocked AT\textsubscript{2} receptor, which appears to counterbalance the effect of the AT\textsubscript{1} receptor. Valsartan does not exhibit any partial agonist activity at the AT\textsubscript{1} receptor and has much (about 20,000 fold) greater affinity for the AT\textsubscript{1} receptor than for the AT\textsubscript{2} receptor. Valsartan is not known to bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

No new preclinical and clinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years. A bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

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

The RMS considers that the Pharmacovigilance System as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country. A suitable justification has been provided for non-submission of a Risk Management Plan.

All Member States agreed to grant a licence for the above products at the end of procedure (Day 210 – 9\textsuperscript{th} March 2011). After a subsequent national phase, the UK granted a licence for these products on 6\textsuperscript{th} April 2011 (PL 18909/0305-7).
## II. ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th><strong>Name of the product in the Reference Member State</strong></th>
<th>Valsartan 40, 80 and 160mg Capsules</th>
</tr>
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<tbody>
<tr>
<td><strong>Name(s) of the active substance(s) (INN)</strong></td>
<td>Valsartan</td>
</tr>
<tr>
<td><strong>Pharmacotherapeutic classification (ATC code)</strong></td>
<td>C09CA03 - Angiotensin II Antagonists</td>
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<td><strong>Pharmaceutical form and strength(s)</strong></td>
<td>40, 80 and 160mg Capsules</td>
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<tr>
<td><strong>Reference numbers for the Decentralised Procedures</strong></td>
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<td><strong>Reference Member State</strong></td>
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<td><strong>Concerned Member States</strong></td>
<td>Cyprus and Malta</td>
</tr>
<tr>
<td><strong>Marketing Authorisation Number(s)</strong></td>
<td>PL 18909/0305-7</td>
</tr>
<tr>
<td><strong>Name and address of the authorisation holder</strong></td>
<td>Arrow Generics Limited,</td>
</tr>
<tr>
<td></td>
<td>Unit 2, Eastman Way,</td>
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<tr>
<td></td>
<td>Stevenage,</td>
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<td></td>
<td>Hertfordshire,</td>
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<td>SG1 4SZ, U.K.</td>
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</table>
III  SCIENTIFIC OVERVIEW AND DISCUSSION
III.1  QUALITY ASPECTS
DRUG SUBSTANCE

INN:  Valsartan
Chemical Name: N-(1-Oxypentyl)-N-[[2-(1H-tetrazole-5-yl)phenyl]phenylmethyl]-L-valine

Structure:

\[\text{Molecular Formula: } C_{24}H_{29}N_5O_3 \]
\[\text{Molecular Weight: } 435.5 \]
Appearance: is a white or almost white crystalline powder.
Solubility: It is freely soluble in methanol and ethanol, sparingly soluble in ethyl acetate, slightly soluble in dichloromethane and practically insoluble in water.

Synthesis of the drug substance from the designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant certificates of analysis. Appropriate proof-of-structure data have been supplied. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the drug substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Certificates of Analysis for all working standards have been provided.

Batch analysis data are provided and comply with the proposed specification.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging used to store the drug substance. Confirmation has been provided that the primary packaging complies with current guidelines concerning materials in contact with food.

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

DRUG PRODUCT
Other Ingredients
Other ingredients consist of the pharmaceutical excipients microcrystalline cellulose (101), croscarmellose sodium, sodium laurilsulfate, povidone (K30), magnesium stearate making up the tablet core. Capsule body and cap (titanium dioxide (E171), red iron oxide (E172(ii)) black iron oxide (E172(ii)) and gelatin) and Black Printing Ink (shellac, ethanol, isopropanol, butanol, propylene glycol, water, purified, strong ammonia solution, potassium hydroxide and black iron oxide (E172)).
All excipients comply with their respective European Pharmacopoeia monographs with the exception of the capsule shells which comply with an in house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

The applicant has confirmed that magnesium stearate is of vegetable origin and gelatin capsules of animal origin. Satisfactory TSE declarations/certificates are provided.

**Pharmaceutical Development**

The objective of the development programme was to formulate robust, stable tablets that contain the same active ingredient as Diovan 40, 80 and 160mg Capsules.

Comparative impurity and dissolution profiles have been presented for test and reference products.

**Manufacture**

A satisfactory batch formula has been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. Process validation data has been provided for three consecutive commercial scale batches. The results are satisfactory.

**Finished Product Specification**

The finished product specification is satisfactory. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for any working standards used.

**Container-Closure System**

The finished product is packed in Aluminium lidding foil/ PVC-PVDC blister packs. Pack sizes are 7, 28 and 98 capsules.

Specifications and Certificates of Analysis for all packaging materials have been provided. These are satisfactory. All primary packaging complies with EU legislation regarding contact with food.

**Stability**

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 24 months with a storage condition of ‘Store below 30°C’ is set. This is satisfactory.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling**

The SmPC, PIL and labels are pharmaceutically acceptable.

A package leaflet has been submitted to the MHRA together with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. 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.

The proposed artwork complies with the relevant statutory requirements. In line with current legislation the applicant has also included the name of the product in Braille on the outer packaging and has included sufficient space for a standard UK pharmacy dispensing label.
The MAH has stated that not all licensed pack sizes may be marketed. They have committed to submitting mock-ups for unmarketed pack sizes to the relevant regulatory authorities for approval before those packs are commercially marketed.

**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 aspects of the dossier.

**Conclusion**
There are no objections to the approval of these products from a pharmaceutical point of view.

**III.2 PRE-CLINICAL ASPECTS**
Pharmacodynamic, pharmacokinetic and toxicological properties of valsartan are well known. As valsartan is widely used and well-known, the applicant has not provided additional studies in support of their application. Overview based on literature review is, thus, appropriate.

No new preclinical data have been supplied with these applications and none are required for applications of this type. The pre-clinical expert report has been written by an appropriately qualified person and is a suitable summary of the pre-clinical aspects of the dossier.

A suitable justification has been provided for non-submission of environmental risk assessment.

There are no objections to the approval of these products from a preclinical point of view.

**III.3 CLINICAL ASPECTS**

**Clinical Pharmacology**

**Pharmacokinetics**

In support of this application, the marketing authorisation holder has submitted the following bioequivalence study:

**Study 1**
This is a randomised, two-sequence, two-period, single dose, crossover bioavailability study of Valsartan 160mg Capsules (test) and Diovan 160mg Capsules (reference) in healthy, male and female volunteers under fasting conditions.

Blood was collected prior to administration of drug and then at 0.33, 0.67, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.5, 5, 6, 8, 12, 16, 24, 36 and 48 hours after drug administration. A washout period of 7 days was used between testing.
Results

Statistical Summary of Ln-transformed Pharmacokinetic Parameters of Valsartan

<table>
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<tr>
<th>Parameter</th>
<th>Test</th>
<th>Reference</th>
<th>Ratio (%)</th>
<th>90% Confidence Limits (%)</th>
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<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>C.V(%)</td>
<td>Mean</td>
<td>C.V(%)</td>
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<tr>
<td>Cmax (ng/ml)</td>
<td>4095.4</td>
<td>36.5</td>
<td>4063.9</td>
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<td>AUC_t (ng.h/ml)</td>
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<td>36.1</td>
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<tr>
<td>AUC_∞ (ng.h/ml)</td>
<td>25760.8</td>
<td>36.1</td>
<td>26049.1</td>
<td>32.1</td>
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<tr>
<td>T_max (hours)*</td>
<td>3.33</td>
<td>35.2</td>
<td>3.33</td>
<td>34.0</td>
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</table>

The 90% confidence intervals for Cmax and AUC were within the pre-defined limits (80-125%). Bioequivalence has been shown for the test formulation (Valsartan 160mg Capsules) and the reference formulation (Diovan 160mg Capsules). Satisfactory justification is provided for a bio-waiver according to the Committee for Proprietary Medicinal Products Notes for Guidance on “Guideline on the Investigation of Bioequivalence” (CHMP/EWP/QWP/1401/98 Rev.1 Corr**). The results of the study for 160mg formulation can therefore be extrapolated to the other strengths i.e 40 and 80mg Capsules.

Pharmacodynamics
No new data have been submitted and none are required for these generic applications.

Clinical Efficacy
No new data have been submitted and none are required.

Clinical Safety
No new data have been submitted and none are required.

Expert Report
A clinical overall summary, written by an appropriately qualified physician, has been provided. This is a satisfactory, non-critical summary of Module 5.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling
The SmPCs, PIL and labelling are medically satisfactory and consistent with those for the reference products.

Clinical Expert Report
The clinical expert report is written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Marketing Authorisation Application (MAA) Forms
The MAA forms are medically satisfactory.

Clinical Conclusion
There are no objections to the approval of these products from a clinical point of view.
IV. OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

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

PRECLINICAL
No new preclinical data were submitted and none are required for applications of this type.

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

No new or unexpected safety concerns arise from these applications.

The SmPC and PIL are satisfactory and consistent with that of the reference product. Satisfactory labelling has also been submitted.

RISK-BENEFIT ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with valsartan is considered to have demonstrated the therapeutic value of the compound. The risk-benefit is, therefore, considered to be positive.
## Module 6

### STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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