SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Valsartan 80 mg film-coated tablets
Valsartan 160 mg film-coated tablets
Valsartan 320 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL form

Film-coated tablets.

80 mg: Pale red, round with bevelled edges, scored on one side; with debossing “D/V” on the scored side and “NVR” on the other side.

160 mg: Grey-orange, ovaloid, scored on one side; with debossing “DX/DX” on the scored side and “NVR” on the other side.

320 mg: Dark grey-violet, ovaloid with bevelled edges with debossing “DXL” on one side and “NVR” on the other side.

Not all strengths may be marketed.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypertension
Treatment of hypertension in children, adolescents and adults (see section 4.2).

Heart failure
Treatment of heart failure (NYHA class II-IV) in adult patients receiving standard therapy such as diuretics, digitalis and either angiotensin-converting enzyme (ACE) inhibitors or beta-blockers but not both; presence of all these standard therapies is not mandatory.

Valsartan improves morbidity in these patients, primarily via reduction in hospitalization for heart failure. Valsartan also slows the progression of heart failure, improves NYHA functional class, ejection fraction and signs and symptoms of heart failure and improves quality of life versus placebo (see section 5.1).

Post-myocardial infarction
Valsartan is indicated to improve survival following myocardial infarction in clinically stable adult patients with signs, symptoms or radiological evidence of left ventricular failure and/or with left ventricular systolic dysfunction (see section 5.1).

Hypertensive adult patients with Impaired Glucose Tolerance at cardiovascular risk
Valsartan is indicated in addition to lifestyle modifications to delay the progression to type 2 diabetes in hypertensive adult patients with impaired glucose tolerance at cardiovascular risk (see section 5.1).

4.2 Posology and method of administration

Posology

Hypertension
The recommended dose of Valsartan is 80 mg or 160 mg film-coated tablet once daily, irrespective of race, age, or gender. The antihypertensive effect is substantially present within 2 weeks and maximal effects are seen after 4 weeks. In patients whose blood pressure is not adequately controlled, the daily dose may be increased to 320 mg film-coated tablet, or a diuretic may be added.

Valsartan may also be administered with other antihypertensive agents.

Heart failure
The recommended starting dose of Valsartan is 40 mg film-coated tablet twice daily. Up-titration to 80 mg and 160 mg twice daily should be done to the highest dose 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.

Evaluation of patients with heart failure should always include assessment of renal function.

Post-myocardial infarction
Therapy may be initiated as early as 12 hours after a myocardial infarction. After an initial dose of 20 mg twice daily, valsartan therapy should be titrated to 40 mg, 80 mg, and 160 mg film-coated tablet twice daily over the next few weeks. The starting dose is provided by the 40 mg divisible tablet.

The target maximum dose is 160 mg twice daily. In general, it is recommended that patients achieve a dose level of 80 mg twice daily by two weeks after treatment initiation and that the target maximum dose be achieved by three months, based on the patient's tolerability to valsartan during titration. If symptomatic hypotension or renal dysfunction occurs, consideration should be given to a dosage reduction.

Valsartan may be used in patients treated with other post-myocardial infarction therapies, e.g. thrombolytics, acetylsalicylic acid, beta-blockers or statins.

Evaluation of post-myocardial infarction patients should always include assessment of renal function.

Hypertensive adult patients with Impaired Glucose Tolerance at cardiovascular risk
The recommended starting dose of Valsartan is 80 or 160 mg film-coated tablet once daily. For those patients starting on 80 mg, up-titration to 160 mg once daily should be done, as tolerated by the patient. If hypertension remains uncontrolled, please refer to section 4.2.

NOTE for all indications: No dosage adjustment is required for patients with renal impairment or for patients with hepatic impairment of non-biliary origin and without cholestasis.

Special populations
Pediatric population (Pediatric Hypertension)
Children and adolescents 6 to less than 18 years of age
The initial dose is a 40 mg tablet once daily for children and adolescents below 35 kg of weight 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 below 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 1 year of age
The safety and efficacy of Valsartan in children less than 1 year of age have not been established. Children less than 1 year of age must not receive Valsartan.

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

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

4.3 Contraindications

- Known hypersensitivity to valsartan or to any of the excipients listed in section 6.1.
- Pregnancy (see section 4.6)
- Concomitant use of angiotensin receptor antagonists (ARBs) - including Valsartan - or of angiotensin-converting-enzyme inhibitors (ACEIs) with aliskiren in patients with Type 2 diabetes (see section 4.5).

4.4 Special warnings and precautions for use

Patients with sodium- and/or volume-depletion
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.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, given an intravenous (i.v.) infusion of normal saline. Treatment can be continued once blood pressure has been stabilized.

Patients with renal artery stenosis
Short-term administration of Valsartan to twelve patients with reno-vascular hypertension secondary to unilateral renal artery stenosis did not induce any significant changes in renal hemodynamics, serum creatinine, or blood urea nitrogen (BUN). However, since other drugs that affect the renin-angiotensin-aldosterone system (RAAS) may increase blood urea and serum creatinine in patients with bilateral or unilateral renal artery stenosis, monitoring of both parameters is recommended as a safety measure.

Patients with impaired renal function
No dosage adjustment is required for patients with renal impairment. However, no data is available for severe cases (creatinine clearance < 10 mL/min.), and caution is therefore advised.

The use of ARBs - including Valsartan - or of ACEIs with aliskiren should be avoided in patients with severe renal impairment (GFR < 30 mL/min) (see section 4.5).

Patients with hepatic impairment
No dosage adjustment is required for patients with hepatic impairment. Valsartan is mostly eliminated unchanged in the bile, and patients with biliary obstructive disorders showed lower valsartan clearance (see section 5.1). Particular caution should be exercised when administering valsartan to patients with biliary obstructive disorders.

Patients with heart failure / post-myocardial infarction

Use of Valsartan in patients with heart failure or post-myocardial infarction commonly results in some reduction in blood pressure, but discontinuation of Valsartan therapy because of continuing symptomatic hypotension is not usually necessary provided dosing instructions are followed.

Caution should be observed when initiating therapy in patients with heart failure or post-myocardial infarction (see section 4.2).

As a consequence of the inhibition of the RAAS, changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the RAAS, treatment with ACE inhibitors or angiotensin receptor antagonists has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. Evaluation of patients with heart failure or post-myocardial infarction should always include assessment of renal function.

In patients with heart failure, caution should be observed with the triple combination of an ACE inhibitor, a beta-blocker and valsartan (see section 5.1).

Angioedema
Angioedema, including swelling of the larynx and glottis, causing airway obstruction and/or swelling of the face, lips, pharynx, and/or tongue has been reported in patients treated with valsartan; some of these patients previously experienced angioedema with other drugs including ACE inhibitors. Valsartan should be immediately discontinued in patients who develop angioedema, and Valsartan should not be re-administered.

Dual Blockade of the Renin-Angiotensin System (RAS)
Caution is required while co-administering ARBs, including Valsartan, with other agents blocking the RAS such as ACEIs or aliskiren (see section 4.5).

Pediatric population
Patients with impaired renal function
Use in pediatric patients with a glomerular filtration rate <30 mL/min/1.73 m2 and pediatric patients undergoing dialysis has not been studied, therefore valsartan is not recommended in these patients. No dose adjustment is required for pediatric patients with a glomerular filtration rate >30 mL/min/1.73 m2 (see section 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 (e.g. fever, dehydration) likely to impair renal function.

Patients with impaired hepatic function
As in adults, particular caution should be exercised when administering valsartan to pediatric patients with biliary obstructive disorders (see section 5.2). There is limited clinical experience with Valsartan in pediatric patients with mild to moderate hepatic impairment.

4.5 Interaction with other medicinal products and other forms of interaction

Dual blockade of the Renin-Angiotensin- System (RAS) with ARBs, ACEIs, or aliskiren
The concomitant use of ARBs, including Valsartan, with other agents acting on the RAS is associated with an increased incidence of hypotension, hyperkalemia, and changes in renal function compared to monotherapy. It is recommended to monitor blood pressure, renal function and electrolytes in patients on Valsartan and other agents that affect the RAS (see section 4.4).

The concomitant use of ARBs - including Valsartan - or of ACEIs with aliskiren, should be avoided in patients with severe renal impairment (GFR < 30 ml/min) (see section 4.4).
The concomitant use of ARBs - including Valsartan - or ACEIs with aliskiren is contraindicated in patients with Type 2 diabetes (see section 4.3).

Potassium

Concomitant use of potassium-sparing diuretics (e.g. spironolactone, triamterene, amiloride), potassium supplements, salt substitutes containing potassium or other drugs that may increase potassium levels (heparin, etc.) may lead to increases in serum potassium and in heart failure patients to increases in serum creatinine. If co-medication is considered necessary, monitoring of serum potassium is advisable.

Non-Steroidal Anti-Inflammatory Agents (NSAIDs) including Selective Cyclooxygenase-2 Inhibitors (COX-2 Inhibitors)
When angiotensin II antagonists are administered simultaneously with NSAIDs, attenuation of the antihypertensive effect may occur. Furthermore, in patients who are elderly, volume-depleted (including those on diuretic therapy), or have compromised renal function, concomitant use of angiotensin II antagonists and NSAIDs may lead to an increased risk of worsening of renal function. Therefore, monitoring of renal function is recommended when initiating or modifying the treatment in patients on valsartan who are taking NSAIDs concomitantly.

Lithium
Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors or angiotensin II receptor antagonists, including Valsartan. Therefore, careful monitoring of serum lithium levels is recommended during concomitant use. If a diuretic is also used, the risk of lithium toxicity may presumably be increased further with Valsartan.

Transporters
The results from an *in vitro* study with human liver tissue indicate that valsartan is a substrate of the hepatic uptake transporter OATP1B1 and the hepatic efflux transporter MRP2. Co-administration of inhibitors of the uptake transporter (e.g., rifampin, ciclosporin) or efflux transporter (e.g., ritonavir) may increase the systemic exposure to valsartan.

No drug interactions of clinical significance have been found. Compounds which have been studied in clinical trials include cimetidine, warfarin, furosemide, digoxin, atenolol, indomethacin, hydrochlorothiazide, amlodipine and glibenclamide.

As valsartan is not metabolized to a significant extent; clinically relevant drug-drug interactions in the form of metabolic induction or inhibition of the cytochrome P450 system are not expected with valsartan. Although valsartan is highly bound to plasma proteins, *in vitro* studies have not shown any interaction at this level with a range of molecules which are also highly protein bound, such as diclofenac, furosemide, and warfarin.

Pediatric 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 in these patients.

4.6 Fertility, pregnancy and lactation

Pregnancy
As for any drug that acts directly on the RAAS, Valsartan must not be used during pregnancy (see section 4.3).

Due to the mechanism of action of angiotensin II antagonists, a risk for the fetus cannot be excluded. In utero exposure to ACE inhibitors (a specific class of drugs acting on the RAAS) during the second and third trimesters has been reported to cause injury and death to the developing fetus. In addition, in retrospective data, first trimester use of ACE inhibitors has been associated with a potential risk of birth defects. There have been reports of spontaneous abortion, oligohydramnios and new-born renal dysfunction, when pregnant women have inadvertently taken valsartan.

If pregnancy is detected during therapy, Valsartan should be discontinued as soon as possible (see section Animal data).

Clinical considerations
Disease-associated maternal and/or embryo/fetal risk
Hypertension in pregnancy increases the maternal risk for pre-eclampsia, gestational diabetes, premature delivery, and delivery complications (e.g., need for cesarean section, and post-partum hemorrhage). Hypertension increases the fetal risk for intrauterine growth restriction and intrauterine death.

Fetal/Neonatal Risk
Oligohydramnios in pregnant women who use drugs affecting the renin-angiotensin system in the second and third trimesters of pregnancy can result in the following: reduced fetal renal function leading to anuria and renal failure, fetal lung hypoplasia, skeletal deformations, including skull hypoplasia, hypotension and death.

In case of accidental exposure to ARB therapy, appropriate fetal monitoring should be considered.

Infants whose mothers have taken ARB therapy should be closely observed for hypotension.

Animal data
In embryofetal development studies in mice, rats and rabbits, fetotoxicity was observed in association with maternal toxicity in rats at valsartan doses of 600 mg/kg/day
approximately 18 times the maximum recommended human dose on a mg/m2 basis (calculations assume an oral dose of 320 mg/day and a 60-kg patient) and in rabbits at doses of 10 mg/kg/day approximately 0.6 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). There was no evidence of maternal toxicity or fetotoxicity in mice up to a dose level of 600 mg/kg/day approximately 9 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).

Lactation
It is not known whether valsartan is transferred into human milk. Since valsartan was transferred into the milk of lactating rats, it is not advisable to use Valsartan in breast-feeding mothers.

Fertility
As for any drug that acts directly on the RAAS, Valsartan should not be used in women planning to become pregnant. Healthcare professionals prescribing any agents acting on the RAAS should counsel women of childbearing potential about the potential risk of these agents during pregnancy.

There is no information on the effects of Valsartan on human fertility. Studies in rats did not show any effects of valsartan on fertility (see section 5.3).

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 dizziness or weariness may occur.

4.8 Undesirable effects

In controlled clinical studies in adult 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.

Table Error! No text of specified style in document.**-1 Adverse drug reactions in Hypertension**

Blood and lymphatic system disorders	
Not known	Hemoglobin decreased, hematocrit decreased, neutropenia, thrombocytopenia
Immune system disorders	
Not known	Hypersensitivity including serum sickness
Metabolism and nutrition disorders	
Not known	Blood potassium increased
Ear and labyrinth system disorders	
Uncommon	Vertigo
Vascular disorders	
Not known	Vasculitis
Respiratory, thoracic and mediastinal disorders	
Uncommon	Cough
Gastrointestinal disorders	
Uncommon	Abdominal pain
Hepato-biliary disorders	
Not known	Liver function test abnormal including blood bilirubin increase
Skin and subcutaneous tissue disorders	
Not known	Angioedema, dermatitis bullous, rash, pruritus
Musculoskeletal and connective tissue disorders	
Not known	Myalgia
Renal and urinary disorders	
Not known	Renal failure and impairment, blood creatinine increased
General disorders and administration site conditions	
Uncommon	Fatigue

The following events have also been observed during clinical trials in hypertensive patients irrespective of their causal association with the study drug: Arthralgia, asthenia, back pain, diarrhoea, dizziness, headache, insomnia, libido decrease, nausea, edema, pharyngitis, rhinitis, sinusitis, upper respiratory tract infection, viral infections.

Pediatric population (Hypertension)
The antihypertensive effect of valsartan has been evaluated in two randomized, double-blind clinical studies in 561 pediatric patients from 6 to less than 18 years of age. No relevant differences in terms of type, frequency and severity of adverse reactions were identified between the safety profile for pediatric patients aged 6 to less than 18 years and that previously reported for adult patients. Neurocognitive and developmental assessment of pediatric 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 less than 6 years, which was followed by a one-year open-label extension, two deaths and isolated cases of marked liver transaminases

elevations were observed. In a second study in which 75 children aged 1 to less than 6 years were randomized, no deaths and one case of marked liver transaminase elevations occurred during a one year open-label extension. These cases occurred in a population who had significant comorbidities. A causal relationship to Valsartan has not been established.

Hyperkalaemia has been observed in children and adolescents aged 6 to less than 18 years with underlying chronic kidney disease.

Heart failure and/or post-myocardial infarction

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

Table Error! No text of specified style in document.**-2 Adverse drug reactions in heart failure and/or post-myocardial infarction**

Blood and lymphatic system disorders	
Not known	Thrombocytopenia
Immune system disorders	
Not known	Hypersensitivity including serum sickness
Metabolism and nutrition disorders	
Uncommon	Hyperkalaemia[#]
Nervous system disorders	
Common	Dizziness, postural dizziness
Uncommon	Syncope, headache
Ear and labyrinth system disorders	
Uncommon	Vertigo
Cardiac disorders	
Uncommon	Cardiac failure
Vascular disorders	
Common	Hypotension, orthostatic hypotension
Not known	Vasculitis
Respiratory, thoracic and mediastinal disorders	
Uncommon	Cough
Gastrointestinal disorders	
Uncommon	Nausea, diarrhoea
Hepato-biliary disorders	
Not known	Liver function test abnormal
Skin and subcutaneous tissue disorders	
Uncommon	Angioedema
Not known	Dermatitis bullous,rash, pruritus
Musculoskeletal and connective tissue disorders	
Not known	Myalgia
Renal and urinary disorders	
Common	Renal failure and impairment
Uncommon	Acute renal failure, blood creatinine increased
Not known	Blood urea increased
General disorders and administration site conditions	
Uncommon	Asthenia, fatigue

Blood potassium increased (frequency unknown)- reported in post market reporting.

The following events have also been observed during clinical trials in patients with heart failure and/or post-myocardial infarction irrespective of their causal association with the study drug: Arthralgia , abdominal pain, back pain, insomnia, libido decrease, neutropenia, edema, pharyngitis, rhinitis, sinusitis, upper respiratory tract infection, viral infections.

Hypertensive adult patients with Impaired Glucose Tolerance at cardiovascular risk
In the NAVIGATOR study, adverse events with VALSARTAN were similar to those reported previously for patients with hypertension.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions.

4.9 Overdose

Overdosage with Valsartan may result in marked hypotension, which could lead to depressed level of consciousness, circulatory collapse and/or shock. If the ingestion is recent, vomiting should be induced. Otherwise, the usual treatment would be i.v. infusion of normal saline solution.

Valsartan is unlikely to be removed by hemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action
The active hormone of the RAAS is angiotensin II, which is formed from angiotensin I through ACE. Angiotensin II binds to specific receptors located in the cell membranes of various tissues. It has a wide variety of physiological effects, including in particular both direct and indirect involvement in the regulation of blood pressure. As a potent vasoconstrictor, angiotensin II exerts a direct pressor response. In addition, it promotes sodium retention and stimulation of aldosterone secretion.

Valsartan (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 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 cough.

Clinical studies and efficacy
In clinical trials where valsartan was compared with an ACE inhibitor, the incidence of dry cough was significantly ($P < 0.05$) lower in patients treated with valsartan than in those treated with an ACE inhibitor (2.6% versus 7.9% respectively). In a clinical trial of patients with a history of dry cough during ACE inhibitor therapy, 19.5% of trial subjects receiving valsartan and 19.0% of those receiving a thiazide diuretic experienced cough compared to 68.5% of those treated with an ACE inhibitor ($P < 0.05$). Valsartan does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

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 maximum reduction in blood pressure with any dose is generally attained within 2-4 weeks and is sustained during long-term therapy. Combined with hydrochlorothiazide, a significant additional reduction in blood pressure is achieved.

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

In multiple dose studies in hypertensive patients valsartan had no notable effects on total cholesterol, fasting triglycerides, fasting serum glucose, or uric acid.

Heart failure
Hemodynamics and neurohormones. Hemodynamics and plasma neurohormones were measured in NYHA class II-IV heart failure patients with pulmonary capillary wedge pressure >15 mmHg in 2 short-term, chronic therapy studies. In one study, which included patients chronically treated with ACE inhibitors, single and multiple doses of valsartan given in combination with an ACE inhibitor improved hemodynamics including pulmonary capillary wedge pressure (PCWP), pulmonary artery diastolic pressure (PAD) and systolic blood pressure (SBP). Reductions were observed in plasma aldosterone (PA) and plasma noradrenalin (PNE) levels after 28 days of treatment. In the second study, which included only patients untreated with ACE inhibitors for at least 6 months prior to enrolment, valsartan significantly improved PCWP, systemic vascular resistance (SVR), cardiac output (CO) and SBP after 28 days of treatment. In the long-term Val-HeFT study, plasma noradrenalin and brain natriuretic peptide (BNP) were significantly reduced from baseline in the valsartan group compared to placebo.

Morbidity and mortality
Val-HeFT was a randomized, controlled, multinational clinical trial of valsartan compared with placebo on morbidity and mortality in 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 . The study enrolled 5010 patients in 16 countries who were randomized to receive either valsartan or placebo in addition to all other appropriate therapy including ACE inhibitors (93%), diuretics (86%), digoxin (67%) and beta-blockers (36%). The mean duration of follow-up was nearly two years. The mean daily dose of Valsartan in Val-HeFT was 254 mg. The study had 2 primary endpoints: all-cause mortality (time to death) and heart failure morbidity (time to first morbid event) defined as death, sudden death with resuscitation, hospitalization for heart failure, or administration of intravenous inotropic or vasodilator drugs for four hours or more without hospitalization. All-cause mortality was similar in the valsartan and placebo groups. Morbidity was significantly reduced by 13.2% with valsartan compared with placebo. The primary benefit was a 27.5% reduction in risk for time to first heart failure hospitalization. The benefits were greatest in patients not receiving either an ACE inhibitor or a beta-blocker. However, risk reductions favoring placebo were observed for those patients treated with the triple combination of a beta-blocker, an ACE inhibitor and valsartan. Further studies such as VALIANT (see section on Post-myocardial infarction), where mortality was not increased in these patients, have reduced the concerns regarding the triple combination.

Exercise tolerance and capacity
The effects of valsartan in addition to usual heart failure therapy on exercise tolerance using the Modified Naughton Protocol were measured in NYHA class II-IV heart failure patients with left ventricular dysfunction (LVEF ≤40%). Increased exercise time from baseline was observed for all treatment groups. Greater mean increases from baseline in exercise time were observed for the

valsartan groups compared to the placebo group, although statistical significance was not achieved. The greatest improvements were observed in the subgroup of patients not receiving ACE inhibitor therapy where mean changes in exercise time were two times greater for the valsartan groups compared to the placebo group. The effects of valsartan compared to enalapril on exercise capacity using the six minute walk test were determined in NYHA class II and III heart failure patients with left ventricular ejection fraction ≤45% who had been receiving ACE inhibitor therapy for at least 3 months prior to study entry. Valsartan 80 mg to 160 mg once daily was at least as effective as enalapril 5 mg to 10 mg twice daily, with respect to exercise capacity, as measured by the six minute walk test in patients previously stabilized on ACE inhibitors and directly switched to valsartan or enalapril.

NYHA class, Signs and symptoms, Quality of life, Ejection fraction
In Val-HeFT, valsartan treated patients showed significant improvement in NYHA class, and heart failure signs and symptoms, including dyspnoea, fatigue, edema and rales compared to placebo. Patients on 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.

Post-myocardial infarction
The VALsartan In Acute myocardial iNfarcTion trial (VALIANT) was a randomized, controlled, multinational, double-blind study in 14,703 patients with acute myocardial infarction and signs, symptoms or radiological evidence of congestive heart failure and/or evidence of left ventricular systolic dysfunction (manifested as an ejection fraction ≤ 40% by radionuclide ventriculography or ≤ 35% by echocardiography or ventricular contrast angiography). Patients were randomized within 12 hours to 10 days after the onset of myocardial infarction symptoms to one of three treatment groups: valsartan (titrated from 20 mg twice daily to highest tolerated dose up to a maximum of 160 mg twice daily), the ACE inhibitor captopril (titrated from 6.25 mg three times daily to highest tolerated dose up to a maximum of 50 mg three times daily), or the combination of valsartan plus captopril. In the combination group, the dose of valsartan was titrated from 20 mg twice daily to highest tolerated dose up to a maximum of 80 mg twice daily; the dose of captopril was the same as for monotherapy. The mean treatment duration was two years. The mean daily dose of Valsartan in the monotherapy group was 217 mg. Baseline therapy included acetylsalicylic acid (91%), beta-blockers (70%), ACE inhibitors (40%), thrombolytics (35%), and statins (34%). The population studied was 69% male, 94% Caucasian, and 53% were 65 years of age or older. The primary endpoint was time to all-cause mortality.

Valsartan was at least 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. Valsartan was also effective in prolonging the time to and reducing cardiovascular mortality, hospitalization for heart failure, recurrent myocardial infarction, resuscitated cardiac arrest, and non-fatal stroke (secondary composite endpoint).

Since this was a trial with an active control (captopril), an additional analysis of all-cause mortality was performed to estimate how valsartan would have performed versus placebo. Using the results of the previous reference myocardial infarction trials – SAVE, AIRE, and TRACE – the estimated effect of valsartan preserved 99.6% of the effect of captopril (97.5% CI = 60–139%). Combining valsartan with captopril did not add further benefit over captopril alone. There was no difference in all-cause mortality based on age, gender, race, baseline therapies or underlying disease.

There was no difference in all-cause mortality or cardiovascular mortality or morbidity when beta-blockers were administered together with the combination of valsartan + captopril, valsartan alone, or captopril alone. Irrespective of study drug treatment, mortality was higher in the group of patients not treated with a beta-blocker, suggesting that the known beta blocker benefit in this population was maintained in this trial. In addition, the treatment benefits of the combination of valsartan + captopril, valsartan monotherapy, and captopril monotherapy were maintained in patients treated with beta-blockers.

Hypertensive adult patients with Impaired Glucose Tolerance at cardiovascular risk

The Nateglinide And Valsartan Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) trial was a multinational, double-blind, placebo-controlled, forced-titration 2x2 factorial design study in which 9,306 patients with impaired glucose tolerance at cardiovascular risk were randomized to placebo, valsartan (titrated from 80 mg once daily to 160 mg once daily, as tolerated), nateglinide (a D-phenylalanine derivative with insulinotropic activity) or nateglinide + valsartan, in addition to lifestyle modification. Patients were followed for a median of about 5 years for the development of diabetes. The population studied was 49% male, 43% 65 years or older and 83% Caucasian. The most commonly reported cardiovascular risk factors at baseline included hypertension (78%) and dyslipidemia (45%) with the majority of these patients receiving antihypertensive and lipid lowering therapy, respectively. Established cardiovascular disease was present in 24% of patients with the most common diagnoses being previous myocardial infarction (12%) and angina with documented multivessel coronary artery disease (9%). During the study, lipid lowering agents were used by 56% of patients and anti-thrombotic agents by 55% of patients.

There were three co-primary endpoints: 1) development of diabetes, 2) extended composite cardiovascular endpoint (death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, hospitalization for heart failure, arterial revascularization or hospitalization for unstable angina), 3) core composite cardiovascular endpoint that excluded unstable angina and arterial revascularization.

There was a statistically significant 14% reduction in the risk of progression to diabetes in valsartan-treated patients also receiving lifestyle intervention measures. However, there was a neutral effect on the core and extended cardiovascular endpoints. These effects were consistent in the large subgroup of patients with hypertension and also across subgroups defined by age, gender, and race. The number of black patients was small and results in this subgroup should be viewed with caution.

There also was a significant reduction in risk of the development of microalbuminuria in valsartan-treated patients compared to non-valsartan treated patients [5.8% vs. 8.4%; HR 0.68; 95% CI (0.573, 0.800); $p<0.0001$].

Pediatric population (Hypertension)

The antihypertensive effect of valsartan have been evaluated in four randomized, double-blind clinical studies in 561 pediatric patients from 6 to less than 18 years of age and 291 pediatric patients 1 to less than 6 years of age. Renal and urinary disorders, and obesity were the most common underlying medical conditions potentially contributing to hypertension in the children and adolescents enrolled in these studies.

Clinical experience in children and adolescents at or above 6 years of age

In a clinical study (CVAL489A2302) involving 261 hypertensive pediatric 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 (CVAL489K2302) involving 300 hypertensive pediatric 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 1 to less than 6 years of age
Three clinical studies were conducted in 291 patients aged 1 to less than 6 years. No children below the age of 1 year were enrolled in these studies.

In the first study (CVAL489A2307) of 90 patients, the efficacy of valsartan was confirmed compared to placebo but a dose-response could not be demonstrated.

In the second study (CVAL489K2303) of 75 patients, 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.

The third study (CVAL489K2306) was a 6 week, randomized double-blind study to evaluate the dose response of valsartan in 126 children 1 to less than 6 years of age with hypertension, with or without chronic kidney disease (CKD) randomized to either 0.25 mg/kg or 4 mg/kg body weight. At endpoint, the reduction in Mean systolic blood pressure (MSBP)/ Mean diastolic blood pressure (MDBP) with valsartan 4.0 mg/kg compared to valsartan 0.25 mg/kg was 8.5/6.8 mmHg vs. 4.1/0.3 mmHg, respectively; (p=0.0157/p<0.0001). Similarly the CKD subgroup also showed reductions in MSBP/MDBP with valsartan 4.0 mg/kg compared to 0.25 mg/kg (9.2/6.5 mmHg vs 1.2/ +1.3 mmHg).

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%. When valsartan is given with food, the area under the plasma concentration curve (AUC) of valsartan is reduced by 48%, although from about 8 hours post dosing plasma valsartan concentrations are similar for the fed and fasted group. 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
Steady-state volume of distribution of valsartan after intravenous administration is about 17 liters, indicating that valsartan is not distributed into tissues extensively. Valsartan is highly bound to serum proteins (94–97%), mainly serum albumin.

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

Elimination
Valsartan shows multiexponential decay kinetics ($t_{½\alpha}$ <1 h and $t_{½\beta}$ about 9 h). Valsartan is primarily eliminated in feces (about 83% of dose) and urine (about 13% of dose), mainly as unchanged drug. Following intravenous administration, plasma clearance of valsartan is about 2 L/h and its renal clearance is 0.62 L/h (about 30% of total clearance). The half-life of valsartan is 6 hours.

The pharmacokinetics of valsartan are linear in the dose range tested. There is no change in the kinetics of valsartan on repeated administration, and little accumulation when dosed once daily. Plasma concentrations were observed to be similar in males and females.

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 increase linearly and are almost proportional with increasing dose over the clinical dosing range (40 to 160 mg twice a day). The average accumulation factor is about 1.7. The apparent clearance of valsartan following oral

administration is approximately 4.5 L/h. Age does not affect the apparent clearance in heart failure patients.

Special populations
Elderly patients (aged 65 years or above)
A somewhat higher systemic exposure to valsartan was observed in some elderly subjects compared to 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. No studies have been performed in patients undergoing dialysis. However, valsartan is highly bound to plasma protein and is unlikely to be removed by dialysis.

Hepatic impairment
About 70% of the absorbed dose is excreted in the bile mainly as unchanged compound. Valsartan does not undergo extensive biotransformation, and, as expected, systemic exposure to valsartan is not correlated with the degree of liver dysfunction. No dose adjustment for valsartan is therefore necessary in patients with hepatic impairment of non-biliary origin and without cholestasis. The AUC with valsartan has been observed to approximately double in patients with biliary cirrhosis or biliary obstruction (see section 4.4).

Pediatric population
In a study of 26 pediatric 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 (liters/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 (see section 6 Warnings and precautions in pediatric patients. Valsartan pharmacokinetics have not been investigated in pediatric patients less than 1 year of age.

5.3 Preclinical safety data

Preclinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity, carcinogenic potential and effects on fertility.

Safety pharmacology and long term toxicity
In a variety of preclinical safety studies conducted in several animal species, there were no findings that would exclude the use of therapeutic doses of valsartan in humans.

In preclinical safety studies, high doses of valsartan (200 to 600 mg/kg/day body weight) caused in rats a reduction of red blood cell parameters (erythrocytes, hemoglobin, hematocrit) and evidence of changes in renal hemodynamics (slightly raised blood urea nitrogen, and renal tubular hyperplasia and basophilia in males). These doses in rats (200 and 600 mg/kg/day) are approximately 6 and 18 times the maximum recommended human dose on a mg/m2 basis (calculations assume an oral dose of 320 mg/day and a 60-kg patient). In marmosets at comparable doses, the changes were similar though more severe, particularly in the kidney where the changes developed to a nephropathy including raised blood urea nitrogen 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.

Reproductive toxicity
Valsartan had no adverse effects on the reproductive performance of male or female rats at oral doses up to 200 mg/kg/day, approximately 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).

Mutagenicity

Valsartan was devoid of mutagenic potential at either the gene or chromosome level when investigated in various standard in vitro and in vivo genotoxicity studies.

Carcinogenicity
There was no evidence of carcinogenicity when valsartan was administered in the diet to mice and rats for 2 years at doses up to 160 and 200 mg/kg/day, respectively.

Pediatric 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 pediatric dose of approximately 4 mg/kg/day on systemic exposure basis) produced persistent, irreversible kidney damage. These effects mentioned above 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 less than1 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
Crospovidone
Colloidal anhydrous silica
Magnesium stearate
Hypromellose
Titanium dioxide (E171)
Macrogol 8000
Red iron oxide (E172)
Yellow iron oxide (E172)
Black iron oxide (E172) (160 mg tablets only)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 30°C. Store in the original package in order to protect from moisture.

Keep out of the reach and sight of children.

6.5 Nature and contents of container

PVC/PVDC/Alu blisters
Pack sizes: 14, 28, 30, 56, 90, 98 film-coated tablets

PVC/PVDC/Alu calendar blisters
Pack sizes: 14, 28, 56, 98 film-coated tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Novartis Pharma AG
Lichtstrasse 35
4056 Basel
Switzerland

Manufacturer
Siegfried Barbera, S.L.
Ronda de Santa Maria, 158
08210 Barberà del Vallès
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8. MARKETING AUTHORISATION NUMBER(S)

Prescription only medication.

Kenya: H2017/CTD4096/058

9. DATE OF FIRST AUTHORISATION

Valsartan 80 mg film-coated tablet
Kenya: 15 October 2015

Valsartan 160 mg film-coated tablet
Kenya: 15 October 2015

10. DATE OF REVISION OF THE TEXT

February 2021 (CDS)