

## SUMMARY OF PRODUCT CHARACTERISTICS

### 1. NAME OF THE MEDICINAL PRODUCT

Valsotens 40 mg film-coated tablets.  
Valsotens 80 mg film-coated tablets.  
Valsotens 160 mg film-coated tablets.

### 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipients: Each Valsotens 40 mg film-coated tablet contains 21.11 mg lactose monohydrate and 0.126 mg lecithin (contains soya oil)

Each Valsotens 80 mg film-coated tablet contains 42.22 mg lactose monohydrate and 0.252 mg lecithin (contains soya oil)

Each Valsotens 160 mg film-coated tablet contains 84.44 mg lactose monohydrate and 0.504 mg lecithin (contains soya oil)

For a full list of excipients, see section 6.1.

### 3. PHARMACEUTICAL FORM

Film-coated tablet

Valsotens 40 mg tablets: Yellow, oval, biconvex, film-coated tablets, 9 x 4.5 mm, with a scoreline on one side and marked with a "V" on the other.

Valsotens 80 mg tablets: Pink, round, biconvex, film-coated tablets, 8 mm in diameter, with a scoreline on both sides and marked with a "V" on one side.

Valsotens 160 mg tablets: Yellow, oval, biconvex, film-coated tablets, 15 x 6.5 mm, with a scoreline on one side and marked with a "V" on the other.

The tablet can be divided into equal halves.

### 4. CLINICAL PARTICULARS

#### 4.1 Therapeutic indications

##### *Hypertension*

Treatment of essential hypertension

##### *Recent-myocardial infarction*

Valsotens is indicated to improve survival following recent (12 hours – 10 days) myocardial infarction in clinically stable patients with signs, symptoms or radiological evidence of left ventricular failure and/or with left ventricular systolic dysfunction (see Section 4.4 and 5.1).

#### 4.2 Posology and method of administration

*Method of administration:*

The tablets should be swallowed with a sufficient amount of fluid (e. g. one glass of water). The tablet can be taken with or without food.

*Hypertension*

The recommended dose of Valsotens is 80 mg once daily for most patients. The antihypertensive effect is substantially present within 2 weeks and maximal effects are seen after 4 weeks. In some patients whose blood pressure is not adequately controlled, the dose can be increased to 160 mg. Further blood pressure reduction may be achieved by adding in a thiazide diuretic.

Valsotens may also be administered with other antihypertensive agents.

Use in patients over 75 years:

A lower starting dose of 40 mg once daily is recommended.

Use in renal impairment:

No initial dose adjustment is required in patients with mild renal impairment (i.e. creatinine clearance 20-50 ml/min). For patients with severe renal impairment valsartan is contraindicated (see section 4.3.)

Use in patients with intravascular volume depletion:

For those patients who have intravascular volume depletion (e.g. those treated with high dose diuretics who are unable to have their dose of diuretic reduced) a starting dose of 40 mg is recommended.

Use in patients with mild to moderate hepatic impairment:

Treatment should commence at a dose of 40 mg once daily. A daily dose of 80 mg should not be exceeded. Patients with severe hepatic impairment, cirrhosis or biliary obstruction should not use Valsotens (see Section 4.3).

Use in children and adolescents:

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

*Recent-myocardial infarction*

Therapy may be initiated as early as 12 hours after a myocardial infarction in clinically stable patients. After an initial dose of 20 mg twice daily, valsartan therapy should be titrated to 40 mg, 80 mg, and 160 mg 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 a day. It is generally recommended that patients have reached an 80 mg dose twice a day, two weeks after the treatment was initiated and that a maximum dose, 160 mg twice a day has been reached after three months, based on the patient's tolerability. If symptomatic hypotension or renal dysfunction occur, 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, statins and diuretics. Concurrent use of ACE-inhibitors is not recommended (see sections 4.4, 4.8 and 5.1).

Evaluation of patients with a history of myocardial infarction should always include evaluation of renal function.

Use in renal impairment:

In the indication of post myocardial infarction no dosage adjustment is required for patients with mild to moderate renal impairment. There are currently no data available in post myocardial patients with severe renal impairment (creatinine clearance <10 ml/min). Valsotens should therefore not be used in patients with severe renal impairment (see Section 4.3).

Use in patients with mild to moderate hepatic impairment:

Doses higher than 80mg twice daily should only be considered if the clinical benefit is likely to outweigh the possible risk associated with increased exposure of valsartan. Patients with severe hepatic impairment, cirrhosis or biliary obstruction should not use Valsotens (see Section 4.3).

Use in children and adolescents:

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

### **4.3 Contraindications**

Hypersensitivity to valsartan, soya oil, peanut oil or to any of the excipients (see section 6.1).  
Severe hepatic impairment, biliary cirrhosis and cholestasis.  
Severe renal impairment (creatinine clearance <10 ml/min) and patients undergoing dialysis.  
2nd and 3rd trimester of pregnancy (see section 4.4 and 4.6)  
Lactation (see section 4.6).

### **4.4 Special warnings and precautions for use**

*Hyperkalemia*

Caution should be exercised during concurrent use of potassium supplements, potassium sparing diuretics, salt substitutes containing potassium or other medicinal products that may increase potassium levels (heparin, etc.) and frequent monitoring of potassium levels should be performed.

*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 shall be corrected prior to initiation of treatment with valsartan, e.g. by diuretic dose reduction.

*Renal artery stenosis*

Safety of valsartan use in patients with bilateral renal artery stenosis or stenosis to a solitary kidney has not been demonstrated.

Short-term use of valsartan in twelve patients with renovascular 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 may increase blood urea and serum creatinine in patients with unilateral renal artery stenosis, monitoring is recommended as a safety measure.

#### *Kidney transplantation*

No experience with respect to the safe use of valsartan in patients after recent kidney transplantation is yet available.

#### *Primary hyperaldosteronism*

Valsartan should not be used in patients with primary hyperaldosteronism since the disease affects the renin-angiotensin-aldosterone system.

#### *Aortic and mitral stenosis, obstructive hypertrophic cardiomyopathy*

As with other vasodilators, special caution should be exercised in patients with aortic and mitral stenosis, or obstructive hypertrophic cardiomyopathy.

#### *Renal impairment*

No dose adjustment is necessary in patients with impaired renal function with creatinine clearance >10 ml/min.

#### *Hepatic impairment*

Caution should be exercised when valsartan is used in patients with mild to moderate non-cholestatic hepatic impairment. The dose of valsartan should not exceed 80 mg.

#### *Recent myocardial infarction*

Increased clinical benefits of concurrent use of captopril and valsartan have not been confirmed, and instead the risk of adverse effects was increased compared to treatment with the products separately (see section 5.1 and 4.8). Concomitant use of these products is therefore not recommended.

Caution should be exercised when initiating treatment in post-myocardial infarction patients. Evaluation of post-myocardial infarction patients should always include evaluation of renal function (see section 4.2).

Use of valsartan in post-myocardial infarction patients is commonly accompanied by some blood pressure reduction but usually treatment does not need to be discontinued due to continued symptomatic hypotension, provided that dose recommendations are being followed.

#### *Heart failure*

Clinical benefits of a triple combination with ACE-inhibitor, beta-blocker and valsartan have not been confirmed for patients with heart failure (see section 5.1). This combination seems to increase the risk of adverse events and is therefore not recommended.

The use of valsartan in patients with heart failure commonly causes some blood pressure reduction, but usually treatment does not need to be discontinued due to continued symptomatic hypotension, provided that dose recommendations are being followed. Caution should be observed when initiating therapy in patients with heart failure.

In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (e.g. patients with severe congestive heart failure) treatment with ACE-inhibitors has been associated with oliguria and/or progressive azotemia and in rare cases acute renal failure. Since valsartan is an angiotensin II receptor antagonist, it has an inhibitory effect on the renin-angiotensin-aldosterone system and therefore it cannot be excluded that the use of valsartan may be associated with impairment of the renal function.

### *Pregnancy*

Angiotensin II Receptor Inhibitors (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 detected, treatment with AIIRAs should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

### *Galactose intolerance, Lapp lactase deficiency, glucose-galactose malabsorption*

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

### *Lecithin*

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

## **4.5 Interaction with other medicinal products and other forms of interaction**

Caution should be exercised during concurrent use of potassium supplements, potassium sparing diuretics, salt substitutes containing potassium, or other drugs that may increase the level of potassium (heparin, etc.) and frequent measurements of potassium levels should be performed.

Other antihypertensive agents can increase the antihypertensive effects of valsartan.

Combination with NSAIDs: When Angiotensin II antagonists are administered simultaneously with non-steroidal anti-inflammatory drugs (i.e. selective COX-2 inhibitors, acetylsalicylic acid (>3g/day) and non-selective NSAIDs), attenuation of the antihypertensive effect may occur.

As with ACE inhibitors, concomitant use of Angiotensin II antagonists and NSAIDs may lead to an increased risk of worsening of renal function, including possible acute renal failure, and an increase in serum potassium, especially in patients with poor pre-existing renal function. The combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy, and periodically thereafter.

Reversible increases in lithium serum concentration and toxic effects have been reported during concomitant use of ACE-inhibitors. There is only limited experience with the concurrent use of valsartan and lithium. In case of concurrent use, monitoring serum levels of lithium is recommended.

No interactions of clinical relevance have been seen in association with the use of the following products commonly used for the treatment of patients with hypertension: cimetidine, warfarin, furosemide, digoxin, atenolol, indomethacin, hydrochlorothiazide, amlodipine, and glibenclamide.

Interaction studies have only been performed in adults.

## **4.6 Pregnancy and lactation**

The use of Angiotensin II Receptor Inhibitors is not recommended during the first trimester of pregnancy (see section 4.4). The use of Angiotensin II Receptor Inhibitors is contraindicated during the 2nd and 3rd trimester of pregnancy (see section 4.3 and 4.4)

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Whilst there is no controlled epidemiological data on the risk with Angiotensin II Receptor Inhibitors (AIIRAs), similar risks may exist for this class of drugs. Unless continued ARB 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 detected, treatment with AIIRAs should be stopped immediately and, if appropriate, alternative therapy should be started.

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

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

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

It is not known whether valsartan is excreted into human milk. Valsartan was excreted into the milk of rats. Lactating mothers should not breast-feed while taking valsartan.

#### **4.7 Effects on ability to drive and use machines**

No studies on the effects on the ability to drive and use machines have been performed. When driving and using machines it should be considered that orthostatic hypotension, dizziness or weariness may occur.

#### **4.8 Undesirable effects**

In controlled clinical trials in patients with hypertension the overall frequency of adverse events was comparable with that of placebo. The rate of adverse events did not seem to be related to dose or duration of treatment and was not related to sex, age or race.

Adverse events reported in clinical trials in hypertensive patients, irrespective of causality with valsartan, and which occurred more frequently with valsartan than with placebo, and adverse reactions from individual reports, are listed below according to organ class.

Safety of valsartan in post-myocardial infarction patients was consistent with the pharmacology of the medicinal product and generally related to the underlying disease. Serious, non fatal, adverse events, seen in the VALIANT study in a frequency of  $\geq 0.1\%$  and considered related to the study medicinal product, are included in the list below.

Adverse reactions reported in clinical trials in patients with heart failure, in a frequency of more than 1% and which occurred more often in relation to valsartan than placebo, are also included in the following list.

Frequencies are defined as:

Very common ( $\geq 1/10$ )

Common ( $\geq 1/100$  to  $< 1/10$ )

Uncommon ( $\geq 1/1,000$  to  $< 1/100$ )

Rare ( $\geq 1/10,000$  to  $< 1/1,000$ )

Very rare (<1/10,000)

Not known (cannot be estimated from the available data)

#### Cardiac disorders

Uncommon: Cardiac failure\*.

#### Blood and lymphatic system disorders

Very rare: Thrombocytopenia.

#### Nervous system disorders

Common: Postural dizziness<sup>#</sup>

Uncommon: Syncope\*.

Rare: Dizziness<sup>##</sup>, neuralgia.

Very rare: Headache<sup>##</sup>, mild and transient taste disturbance.

#### Eye disorders

Uncommon: Conjunctivitis.

#### Ear and labyrinth disorders

Uncommon: Vertigo.

#### Respiratory, thoracic and mediastinal disorders

Uncommon: Cough, epistaxis.

#### Gastrointestinal disorders

Uncommon: Diarrhoea, abdominal pain.

Very rare: Nausea<sup>##</sup>.

#### Renal and urinary disorders

Very rare: Renal impairment<sup>\*\*##</sup>, acute renal failure<sup>\*\*</sup>, renal insufficiency<sup>\*\*</sup>.

#### Skin and subcutaneous tissue disorders

Rare: Angioneurotic oedema<sup>\*\*</sup>, rash, pruritus.

#### Musculoskeletal and connective tissue disorders

Uncommon: Back pain, muscle cramps, myalgia, arthritis.

Very rare: Arthralgia.

#### Metabolism and nutrition disorders

Uncommon: Hyperkalaemia<sup>\*#</sup>.

#### Infections and infestations

Common: Viral infections.

Uncommon: Upper respiratory tract infections, pharyngitis, sinusitis.

Very rare: Gastroenteritis, rhinitis.

#### Vascular disorders

Common: Orthostatic hypotension<sup>#</sup>.

Uncommon: Hypotension<sup>\*##</sup>.

Rare: Vasculitis.

Very rare: Haemorrhage.

### General disorders and administration site conditions

Uncommon: Fatigue, asthenia, oedema.

### Immune system disorders

Rare: Hypersensitivity, including serum sickness.

### Hepatobiliary Disorders

Very rare: Liver function abnormalities

### Psychiatric disorders

Uncommon: Depression, insomnia, libido decrease.

\* Reported in post-myocardial infarction indication.

# Reported in heart failure indication.

\*\* Reported as uncommon in post-myocardial infarction indication.

## Reported more frequently in heart failure indication (common: dizziness, renal impairment, hypotension, uncommon: headache, nausea).

In the VALIANT study there were primarily four adverse events registered, i.e. hypotension, renal dysfunction, cough and angioneurotic edema. The pre-specified adverse event which most commonly resulted in permanent discontinuation of study medicinal product was hypotension: 1.8% of patients treated with valsartan + captopril reported this event, compared to 1.4% of patients treated with valsartan and 0.8% of patients treated with captopril. Impaired renal function was least common in patients treated with captopril and cough was least common in patients treated with valsartan. No difference was found between the medicinal products with respect to angioneurotic edema.

The ratio of patients who permanently discontinued using the medicinal product due to adverse events was 5.8% in the group receiving valsartan, 7.7% in the group receiving captopril and 9.0% in patients treated with valsartan and captopril.

### *Laboratory findings*

Uncommonly, valsartan may be associated with a decrease in haemoglobin and haematocrit. In controlled clinical trials 0.8% and 0.4% of patients receiving valsartan showed significant decrease (>20%) in haematocrit and haemoglobin, respectively. In comparison, decrease in haematocrit and haemoglobin was seen in 0.1% of patients receiving placebo.

Neutropenia was observed in 1.9% of patients receiving valsartan, in comparison to 1.6% of patients receiving ACE-inhibitors e.g. enalapril 20 mg or lisinopril 10 mg or 20 mg, compared to 0.8% who received placebo.

In controlled clinical trials a significant increase in serum levels of creatinine, potassium and total bilirubin was seen in 0.8%, 4.4% and 6% of patients receiving valsartan, compared to 1.6%, 6.4% and 12.9% in patients receiving ACE-inhibitors, respectively.

In post-myocardial infarction patients, more than double serum levels of creatinine were seen in 4.2% of patients receiving valsartan, 4.8% of patients receiving valsartan + captopril and 3.4% of patients receiving captopril.

In patients with heart failure, more than a 50% increase in serum levels of creatinine was seen in 3.9% of patients being treated with valsartan, compared to 0.9% of patients receiving placebo. In these patients increases of more than 20% in serum potassium were observed in 10% of the patients treated with valsartan compared to 5.1% of patients receiving placebo.

In heart failure studies, an increase of more than 50% was seen in BUN (blood urea nitrogen) in 16.6% of patients being treated with valsartan compared to 6.3% of patients receiving placebo.

Occasional elevation of liver function values were reported in hypertensive patients treated with valsartan.

## **4.9 Overdose**

### *Symptoms*

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

### *Treatment*

Treatment is based on the time of ingestion and the type and severity of symptoms, stabilisation of the circulatory condition being of prime importance.

The patient should always be given a sufficient amount of activated charcoal.

If hypotension occurs, the patient should be positioned in a supine position and salt and volume supplementation should be given rapidly.

Valsartan cannot be removed by dialysis due to strong plasma protein binding.

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

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

The active hormone of the RAAS (renin-angiotensin-aldosterone system) 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 reduces the excretion of sodium and stimulates secretion of aldosterone.

Valsartan is an orally active specific angiotensin II (Ang II) receptor antagonist. It acts selectively on the AT<sub>1</sub> receptor subtype, which is responsible for the known actions of angiotensin II. It is possible that increased plasma levels of angiotensin II following AT<sub>1</sub> receptor blockade by valsartan induces the unblocked AT<sub>2</sub> receptor, which seems to balance the effects of the AT<sub>1</sub> receptor. Valsartan does not exhibit any partial agonist activity at the AT<sub>1</sub> receptor and has much (about 20,000 fold) greater affinity for the AT<sub>1</sub> receptor than for the AT<sub>2</sub> receptor.

Valsartan does not inhibit ACE, also known as kininase II, which converts Ang I to Ang II and degrades bradykinin. No potentiation of bradykinin related side effects should be expected. In

clinical studies where valsartan was compared with an ACE-inhibitor the incidence of dry cough was significantly lower ( $P < 0.05$ ) in patients treated with valsartan than in patients treated with an ACE-inhibitor (2.6% versus 7.9%, respectively). In a clinical study of patients with a history of dry cough during ACE-inhibitor treatment, 19.5% of those receiving valsartan and 19% of those receiving a thiazide diuretic experienced cough compared to 68.5% of those treated with an ACE-inhibitor ( $P < 0.05$ ). Valsartan neither binds to nor blocks 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 antihypertensive activity is detectable within 2 hours and maximum reduction of blood pressure is reached within 4-6 hours following a single dose. The antihypertensive effects persist for 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 treatment. 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.

### *Recent myocardial infarction*

The VALIANT study (VALsartan In Acute myocardial iNfarcTion trial) was a randomized, controlled, multinational, double blind study in 14,703 patients with acute myocardial infarction and signs, symptoms or radiological evidence of congestive and/or evidence of left ventricular systolic dysfunction (manifested as ejection fraction  $\leq 40\%$  according to radionuclide ventriculography or  $\leq 35\%$  according to echocardiography or ventricular contrast angiography). Within 12 hours to 10 days from the onset of symptoms of myocardial infarction the patients were randomized into groups receiving valsartan, captopril or both. Duration of treatment was on average two years.

Valsartan was equally 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. Concurrent use of captopril and valsartan did not provide additional benefits compared to use of captopril alone. There was no difference between valsartan and captopril with respect to all-cause mortality, based on gender, age, race, treatments received upon onset of myocardial infarction or underlying disease. Valsartan also delayed and reduced cardiovascular mortality, hospitalization due to heart failure, recurrent myocardial infarction, resuscitation due to cardiac arrest and a non-fatal stroke.

There was no difference in all-cause mortality, cardiovascular mortality or morbidity during concurrent administration of beta-blockers and valsartan + captopril, valsartan alone or captopril alone. Irrespective of the study drug treatment, the mortality was lower in the group of patients receiving beta-blockers, which indicated that known benefits of beta-blockers in this population have remained through the study.

### *Heart failure*

Val-HeFT was a randomised, controlled, multi national clinical study where valsartan was compared to placebo on mortality and morbidity in patients with heart failure of NYHA class II

(62%), III (36%), and IV (2%) receiving usual treatment and with left ventricular ejection fraction (LVEF) <40% and left ventricular internal diastolic diameter (LVIDD) >2.9 cm/m<sup>2</sup>. Baseline therapy included ACE-inhibitors (93%), diuretics (86%), digoxin (67%) and beta-blockers (36%). Follow up lasted on the average for two years. The mean daily dose of valsartan in Val-HeFT was 254 mg. The study had two primary endpoints: all-cause mortality (time to death) and heart failure morbidity (time to first morbid event), defined as death, cardiac arrest with resuscitation, hospitalization due to heart failure or intravenous administration of inotropic or vasodilatory drug 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 (28.8% vs. 32.1%). The primary benefit was a 27.5% reduction in risk for time to first heart failure hospitalisation (13.9% vs. 18.5%). Results appearing to favour placebo were observed for those patients receiving the triple combination of an ACE inhibitor, a beta-blocker and valsartan.

The benefits were greatest in patients not receiving either an ACE inhibitor or a beta blocker. In patients not receiving an ACE inhibitor, morbidity was significantly reduced by 44% (24.9% vs. 42.5%), and the risk for time to first heart failure hospitalisation was significantly reduced by 53% (13.0% vs. 26.5%) with valsartan compared to placebo.

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

## **5.2 Pharmacokinetic properties**

Absorption of valsartan after oral administration is rapid, although the amount absorbed varies widely. Mean absolute bioavailability for valsartan is 23%. Valsartan shows multi-exponential decay kinetics ( $t_{1/2\alpha}$ <1 hour and  $t_{1/2\beta}$  about 9 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.

Valsartan is highly bound to serum protein (94-97%), mainly serum albumin. Steady state volume of distribution is about 17 liters. Plasma clearance is relatively slow (about 2 l/hour) compared with hepatic blood flow (about 30 l/hour). Elimination of valsartan is mainly in bile and urine, as unchanged compound. At normal glomerular filtration rate (120 ml/min) the renal clearance is about 30% of total plasma clearance. A hydroxy metabolite has been identified in plasma at low levels (less than 10% of valsartan AUC). This metabolite is pharmacologically inactive. After oral administration 83% is excreted in the faeces and 13% in the urine, mainly as unchanged compound.

When valsartan is given with food, AUC of valsartan is reduced by 48%, although from about 8 hours post dosing plasma level of valsartan are similar for the fed and fasted group. This

reduction of AUC is however not associated with a clinically significant reduction in therapeutic effect.

Mean values for time to peak concentration and elimination half life of valsartan in patients with heart failure are similar to that observed in healthy volunteers. AUC and  $C_{\max}$  values for valsartan are almost proportional with increasing dose over the clinical dosing range (40 to 160 mg twice a day). The average accumulation factor is about 1.7. Apparent clearance of valsartan following oral administration is about 4.5 l/hour. Age does not affect the apparent clearance in patients with heart failure.

#### Special populations:

##### *Elderly*

A somewhat higher systemic exposure to valsartan was observed in some elderly subjects compared with young subjects; and a lower starting dose (40 mg) is recommended for the elderly

##### *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 mild renal impairment (creatinine clearance 20-50 ml/min). Limited data are available in patients with moderate-severe impairment of renal function and a starting dose of 40 mg is recommended for these patients. No studies have been performed in patients undergoing dialysis. However valsartan is highly bound to protein and is unlikely to be removed by dialysis.

##### *Impaired hepatic function*

In a pharmacokinetics trial in patients with mild (n=6) to moderate (n=5) hepatic dysfunction, exposure to valsartan was increased approximately 2-fold compared with healthy volunteers. No information is available regarding patients with severe hepatic dysfunction.

### **5.3 Preclinical safety data**

Non-clinical data reveal no special hazard for human based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.

In non-clinical safety studies, high doses of valsartan (200 to 600 mg/kg body weight) in rats caused reduction in red blood cell parameters (erythrocytes, haemoglobin, haematocrit) and evidence of changes in renal haemodynamics (minor increase of urea in plasma, and renal tubular hyperplasia and basophilia in males). In marmosets similar doses resulted in similar alterations, though more severe, especially in the kidneys, where alterations evolved into nephropathy, which led to elevation of urea and creatinine.

Hypertrophy of renal juxtaglomerular cells was also seen in both species. All alterations were considered resulting from pharmacological action of valsartan which produces prolonged hypotension, especially in marmosets. Hypertrophy of renal juxtaglomerular cells does not seem to be of relevance in humans receiving recommended doses of valsartan.

There were no indications of mutagenesis, clastogenicity or carcinogenicity.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

#### *Tablet core*

Lactose monohydrate  
Cellulose, microcrystalline  
Croscarmellose sodium  
Povidone K29-K32  
Talc  
Magnesium Stearate  
Colloidal anhydrous silica

#### *Film-coat*

Polyvinyl alcohol  
Macrogol 3350  
Talc  
Lecithin (contains soya oil) (E322)  
Titanium dioxide (E171)

Valsotens 40 mg, 80 mg and 160 mg contain yellow iron oxide (E172)

Valsotens 80 mg and 160 mg also contain red iron oxide (E172)

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

2 years for tablets packed in PVC/PE/PVDC-Al blisters

30 months for tablets packed in polyethylene tablet containers

### **6.4 Special precautions for storage**

PVC/PE/PVDC-Al blisters: Do not store above 30°C. Store in the original package in order to protect from light and moisture.

Polyethylene tablet containers: Store in the original package in order to protect from light and moisture.

### **6.5 Nature and contents of container**

PVC/PE/PVDC-Al blister.

Pack sizes: 7, 14, 28, 56, 98 and 280 film-coated tablets

Polyethylene tablet container (securitainer, PE).

Pack sizes: 7, 14, 28, 56, 98 and 280 film-coated tablets

Not all pack sizes may be marketed.

## **6.6 Special precautions for disposal**

No special requirements.

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

## **7. MARKETING AUTHORISATION HOLDER**

Actavis Group PTC ehf  
Reykjavikurvegur 76-78  
220 Hafnarfjordur  
Iceland

## **8. MARKETING AUTHORISATION NUMBER(S)**

40 mg:	MA 628/02401
80 mg:	MA 628/02402
160 mg:	MA 628/02403

## **9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

19<sup>th</sup> November 2008

## **10. DATE OF REVISION OF THE TEXT**