

### **Valsartan**

40 mg, 80 mg, 160 mg, 320 mg film-coated tablets  
80 mg, 160 mg hard gelatin capsules

### **Core Safety Profile**

## **4 CLINICAL PARTICULARS**

### **4.2 Posology and method of administration**

#### Posology

##### Hypertension (only 80 mg, 160 mg and 320 mg)

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

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

##### Recent myocardial infarction (only 40 mg, 80 mg and 160 mg)

In clinically stable patients, therapy may be initiated as early as 12 hours after a myocardial infarction. After an initial dose of 20 mg twice daily, valsartan 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 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, 160 mg twice daily, be achieved by three months, based on the patient's tolerability. If symptomatic hypotension or renal dysfunction occur, consideration should be given to a dose reduction.

Valsartan may be used in patients treated with other post-myocardial infarction therapies, e.g. thrombolytics, acetylsalicylic acid, beta blockers, statins, and diuretics. The combination with ACE inhibitors is not recommended (see sections 4.4 and 5.1).

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

##### Heart failure (only 40 mg, 80 mg and 160 mg)

The recommended starting dose of valsartan is 40 mg twice daily. Uptitration to 80 mg and 160 mg twice daily should be done at intervals of at least two weeks to the highest dose, as tolerated by the patient. Consideration should be given to reducing the dose of concomitant diuretics. The maximum daily dose administered in clinical trials is 320 mg in divided doses.

Valsartan may be administered with other heart failure therapies. However, the triple combination of an ACE inhibitor, a beta blocker and valsartan is not recommended (see sections 4.4 and 5.1).

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

## Additional information on special populations

### Elderly

No dose adjustment is required in elderly patients.

### Renal impairment

No dose adjustment is required for adult patients with a creatinine clearance >10 ml/min (see sections 4.4 and 5.2). Concomitant use of valsartan with aliskiren is contraindicated in patients with renal impairment (GFR < 60 mL/min/1.73 m<sup>2</sup>) (see section 4.3).

### Diabetes Mellitus

Concomitant use of valsartan with aliskiren is contraindicated in patients with diabetes mellitus (see section 4.3).

### Hepatic impairment

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

### Paediatric population

#### 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 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**

- 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).
- Concomitant use of angiotensin receptor antagonists (ARBs) - including valsartan - or of angiotensin-converting-enzyme inhibitors (ACEIs) with aliskiren in patients with diabetes mellitus or renal impairment ( $\text{GFR} < 60 \text{ mL/min/1.73m}^2$ ) (see sections 4.4 and 4.5).

### **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  $< 10 \text{ mL/min}$  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  $> 10 \text{ mL/min}$  (see sections 4.2 and 5.2).

The concomitant use of ARBs - including valsartan - or of ACEIs with aliskiren is contraindicated in patients with renal impairment ( $\text{GFR} < 60 \text{ mL/min/1.73m}^2$ ) (see sections 4.3 and 4.5).

#### 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 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 (only 40 mg, 80 mg and 160 mg)

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

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

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

#### Heart Failure (only 40 mg, 80 mg and 160 mg)

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.

#### History of 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-Aldosterone System (RAAS)

Hypotension, syncope, stroke, hyperkalaemia, and changes in renal function (including acute renal failure) have been reported in susceptible individuals, especially if combining medicinal products that affect this system.

Caution is required while co-administering ARBs, including valsartan, with other agents blocking the RAS such as ACEIs or aliskiren (see sections 4.3 and 4.5).

Concomitant use of angiotensin receptor antagonists (ARBs) - including valsartan - or of angiotensin-converting-enzyme inhibitors (ACEIs) with aliskiren in patients with diabetes mellitus or renal impairment (GFR < 60 mL/min/1.73m<sup>2</sup>) is contraindicated (see sections 4.3 and 4.5).

#### Other conditions with stimulation of the renin-angiotensin system (only 320 mg)

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. The concomitant use of ARBs - including valsartan - or of ACEIs with aliskiren is contraindicated in patients with renal impairment ( $\text{GFR} < 60 \text{ mL/min/1.73m}^2$ ) (see sections 4.3 and 4.5).

#### 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**

*Dual blockade of the Renin-Angiotensin- System (RAS) with ARBs, ACEIs, or aliskiren:*

Concomitant use of angiotensin receptor antagonists (ARBs) - including valsartan - or of angiotensin-converting-enzyme inhibitors (ACEIs) with aliskiren in patients with diabetes mellitus or renal impairment ( $\text{GFR} < 60 \text{ mL/min/1.73m}^2$ ) is contraindicated (see sections 4.3 and 4.4).

#### 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  $>3 \text{ g/day}$ , and non-selective NSAIDs*

When angiotensin II antagonists are administered simultaneously with NSAIDs, attenuation of the antihypertensive effect may occur. Furthermore, concomitant use of angiotensin II antagonists and NSAIDs may lead to an increased risk of worsening of renal function and an increase in serum potassium. Therefore, monitoring of renal function at the beginning of the treatment is recommended, as well as adequate hydration of the patient.

## *Others*

In drug interaction studies with valsartan, no interactions of clinical significance have been found with valsartan or any of the following substances: cimetidine, warfarin, furosemide, digoxin, atenolol, indometacin, hydrochlorothiazide, amlodipine, glibenclamide.

## Paediatric population

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

## **4.6 Fertility, pregnancy and lactation**

### Pregnancy

The use of Angiotensin II Receptor Antagonists (AIIRAs) is not recommended during the first trimester of pregnancy (see section 4.4). The use of AIIRAs is contra-indicated during the second and third trimester of pregnancy (see sections 4.3 and 4.4).

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however, a small increase in risk cannot be excluded. Whilst there is no controlled epidemiological data on the risk with AIIRAs, similar risks may exist for this class of drugs. Unless continued AIIRA therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with AIIRAs should be stopped immediately, and, if appropriate, alternative therapy should be started.

AIIRAs therapy exposure during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia); 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/m<sup>2</sup> 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 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 ( $\geq 1/10$ ); 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 ( $< 1/10,000$ ), including isolated reports. Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.

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

#### **- Hypertension**

---

##### **Blood and lymphatic system disorders**

Not known	Decrease in haemoglobin, Decrease in haematocrit, Neutropenia, Thrombocytopenia
-----------	---

##### **Immune system disorders**

Not known	Hypersensitivity including serum sickness
-----------	---

##### **Metabolism and nutrition disorders**

Not known	Increase of serum potassium, hyponatraemia
-----------	--

##### **Ear and labyrinth system disorders**

Uncommon	Vertigo
----------	---------

##### **Vascular disorders**

Not known	Vasculitis
-----------	------------

##### **Respiratory, thoracic and mediastinal disorders**

Uncommon	Cough
----------	-------

##### **Gastrointestinal disorders**

Uncommon	Abdominal pain
----------	----------------

##### **Hepato-biliary disorders**

Not known	Elevation of liver function values including increase of serum bilirubin
-----------	--

---

## Skin and subcutaneous tissue disorders

Not known

## Angioedema, Rash, Pruritus

## Musculoskeletal and connective tissue disorders

Not known

## Myalgia

## Renal and urinary disorders

Not known

Renal failure and impairment, Elevation of serum creatinine

## General disorders and administration site conditions

Uncommon

## Fatigue

### Paediatric population

## Hypertension

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

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

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

Hyperkalaemia was more frequently observed in children and adolescents aged 6 to 18 years with underlying chronic kidney disease.

The safety profile seen in controlled-clinical studies in adult 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 adult patients with post-myocardial infarction and/or heart failure patients are listed below.

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

## Blood and lymphatic system disorders

Not known

## Thrombocytopenia

## Immune system disorders

Not known

Hypersensitivity including serum sickness

## Metabolism and nutrition disorders

Uncommon	Hyperkalaemia
Not known	Increase of serum potassium, hyponatraemia
<b>Nervous system disorders</b>	
Common	Dizziness, Postural dizziness
Uncommon	Syncope, Headache
<b>Ear and labyrinth system disorders</b>	
Uncommon	Vertigo
<b>Cardiac disorders</b>	
Uncommon	Cardiac failure
<b>Vascular disorders</b>	
Common	Hypotension, Orthostatic hypotension
Not known	Vasculitis
<b>Respiratory, thoracic and mediastinal disorders</b>	
Uncommon	Cough
<b>Gastrointestinal disorders</b>	
Uncommon	Nausea, Diarrhoea
<b>Hepato-biliary disorders</b>	
Not known	Elevation of liver function values
<b>Skin and subcutaneous tissue disorders</b>	
Uncommon	Angioedema
Not known	Rash, Pruritis
<b>Musculoskeletal and connective tissue disorders</b>	
Not known	Myalgia
<b>Renal and urinary disorders</b>	
Common	Renal failure and impairment
Uncommon	Acute renal failure, Elevation of serum creatinine
Not known	Increase in Blood Urea Nitrogen
<b>General disorders and administration site conditions</b>	
Uncommon	Asthenia, Fatigue

## 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.