Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Valsartan Krka 320 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 320 mg valsartan.

Excipient with known effect: lactose 114mg/tablet

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

Appearance of 320 mg film-coated tablets: light brown, capsule shaped, biconvex film-coated tablets scored on one side, tablet dimensions 16 mm x 8.5 mm.
The tablet can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology

Hypertension
The recommended starting dose of Valsartan Krka 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 Krka may also be administered with other antihypertensive agents (see sections 4.3, 4.4, 4.5 and 5.1). The addition of a diuretic such as hydrochlorothiazide will decrease blood pressure even further in these patients.

Additional information on special populations

Elderly
No dose adjustment is required in elderly patients.

Renal impairment
No dose adjustment is required for adult patients with a creatinine clearance >10 ml/min (see sections 4.4 and 5.2).

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 less than 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 and tolerability. 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. The safety and efficacy of valsartan in children below 1 year of age have not been established.

Use in paediatric patients aged 6 to less than 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 less than 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 listed in section 6.1.
- Severe hepatic impairment, biliary cirrhosis and cholestasis.
- Second and third trimester of pregnancy (see sections 4.4 and 4.6).
- The concomitant use of Valsartan Krka with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2) (see sections 4.5 and 5.1).

4.4 Special warnings and precautions for use

Hyperkalaemia
Concomitant use with potassium supplements, potassium-sparing diuretics, salt substitutes containing potassium, or other agents that may increase potassium levels (heparin, etc.) is not recommended. Monitoring of potassium should be undertaken as appropriate.

Impaired renal function
There is currently no experience on the safe use in patients with a creatinine clearance <10 ml/min and patients undergoing dialysis, therefore valsartan should be used with caution in these patients. No dose adjustment is required for adult patients with creatinine clearance >10 ml/min (see sections 4.2 and 5.2).

Hepatic impairment
In patients with mild to moderate hepatic impairment without cholestasis, valsartan should be used with caution (see sections 4.2 and 5.2).

Sodium- and/or volume-depleted patients
In severely sodium-depleted and/or volume-depleted patients, such as those receiving high doses of diuretics, symptomatic hypotension may occur in rare cases after initiation of therapy with valsartan. Sodium and/or volume depletion should be corrected before starting treatment with valsartan, for example by reducing the diuretic dose.

Renal artery stenosis
In patients with bilateral renal artery stenosis or stenosis to a solitary kidney, the safe use of valsartan has not been established.

Short-term administration of 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.

Intestinal angioedema
Intestinal angioedema has been reported in patients treated with angiotensin II receptor antagonists, including valsartan (see section 4.8). These patients presented with abdominal pain, nausea, vomiting and diarrhoea. Symptoms resolved after discontinuation of angiotensin II receptor antagonists. If intestinal angioedema is diagnosed, valsartan should be discontinued and appropriate monitoring should be initiated until complete resolution of symptoms has occurred.

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).

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 Krka should be immediately discontinued in patients who develop angioedema, and Valsartan Krka should not be re-administered.

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)
There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended (see sections 4.5 and 5.1).

If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure.

ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

Other conditions with stimulation of the renin-angiotensin system
In patients whose renal function may depend on the activity of the renin-angiotensin system (e.g patients with severe congestive heart failure), treatment with angiotensin converting enzyme inhibitors has been associated with oliguria and/or progressive azotaemia and in rare cases with acute renal failure and/or death.
As valsartan is an angiotensin II antagonist, it cannot be excluded that the use of valsartan may be associated with impairment of the renal function.

Paediatric population

Impaired renal function

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

Impaired hepatic function

As in adults, valsartan 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.

Valsartan Krka contains lactose. Patients with rare hereditary problems of galactose intolerance, the total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Valsartan Krka contains sodium. This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

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:
Clinical trial data has shown that dual blockade of the renin-angiotensin-aldosterone-system (RAAS) through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent (see sections 4.3, 4.4 and 5.1).

Concomitant use not recommended

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

Potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium and other substances that may increase potassium levels
If a medicinal product that affects potassium levels is considered necessary in combination with valsartan, monitoring of potassium plasma levels is advised.

Caution required with concomitant use

Non-steroidal anti-inflammatory medicines (NSAIDs), including selective COX-2 inhibitors, acetylsalicylic acid >3 g/day), and non-selective NSAIDs
When angiotensin II antagonists are administered simultaneously with NSAIDs, attenuation of the antihypertensive effect may occur. Furthermore, concomitant use of angiotensin II antagonists and NSAIDs may lead to an increased risk of worsening of renal function and an increase in serum potassium. Therefore, monitoring of renal function at the beginning of the treatment is recommended, as well as adequate hydration of the patient.

Transporters
In vitro data indicates that valsartan is a substrate of the hepatic uptake transporter OATP1B1/OATP1B3 and the hepatic efflux transporter MRP2. The clinical relevance of this finding is unknown. Co-administration of inhibitors of the uptake transporter (eg. rifampin, ciclosporin) or efflux transporter (eg. ritonavir) may increase the systemic exposure to valsartan. Exercise appropriate care when initiating or ending concomitant treatment with such drugs.

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

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

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however, a small increase in risk cannot be excluded. Whilst there is no controlled epidemiological data on the risk with AIIRAs, similar risks may exist for this class of drugs. Unless continued AIIRA therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with AIIRAs should be stopped immediately, and, if appropriate, alternative therapy should be started.
AIIRAs therapy exposure during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalemia); see also section 5.3 “Preclinical safety data”.
Should exposure to AIIRAs have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.
Infants whose mothers have taken AIIRAs should be closely observed for hypotension (see also sections 4.3 and 4.4).

Breast-feeding
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^2 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

Nostudies on the effects on the ability to drive have been performed. Whendriving vehicles or operating machines it should be taken into account that dizzinessor 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), not known (frequency cannot be estimated from the available data). 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, hyponatremia
Ear and labyrinth disorders	
Uncommon	Vertigo
Vascular disorders	
Not known	Vasculitis
Respiratory, thoracic and mediastinal disorders	
Uncommon	Cough
Gastrointestinal disorders	
Uncommon	Abdominal pain
Very rare	Intestinal angioedema
Hepato-biliary disorders	
Not known	Elevation of liver function values including increase of serum bilirubin
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, 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 (each followed by an extension period or study) and one open-label study. These studies included 711 paediatric patients from 6 to less than 18 years of age with and without chronic kidney disease (CKD), of which 560 patients received valsartan. With the exception of isolated gastrointestinal disorders (such as 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 less than 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.

A pooled analysis of 560 paediatric hypertensive patients (aged 6-17 years) receiving either valsartan monotherapy [n=483] or combination antihypertensive therapy including valsartan [n=77] was conducted. Of the 560 patients, 85 (15.2%) had CKD (baseline GFR <90 mL/min/1.73m2). Overall, 45 (8.0%) patients discontinued a study due to adverse events. Overall 111 (19.8%) patients experienced an adverse drug reaction (ADR), with headache (5.4%), dizziness (2.3%), and hyperkalemia (2.3%) being the most frequent. In patients with CKD, the most frequent ADRs were hyperkalaemia (12.9%), headache (7.1%), blood creatinine increased (5.9%), and hypotension (4.7%). In patients without CKD, the most frequent ADRs were headache (5.1%) and dizziness (2.7%). ADRs were observed more frequently in patients receiving valsartan in combination with other antihypertensive medications than valsartan alone.

The antihypertensive effect of valsartan in children 1 to less than 6 years of age has been evaluated in three randomised, double-blind clinical studies (each followed by an extension period). In the first study in 90 children aged 1 to less than 6 years, 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 the two subsequent studies in which 202 children aged 1 to less than 6 years were randomised, no significant liver transaminase elevations or death occurred with valsartan treatment.

In a pooled analysis of the two subsequent studies in 202 hypertensive children (aged 1 to less than 6 years), all patients received valsartan monotherapy in the double blind periods (excluding the placebo withdrawal period). Of these, 186 patients continued in either extension study or open label period. Of the 202 patients, 33 (16.3%) had CKD (baseline eGFR <90 ml/min). In the double blind period, two patients (1%) discontinued due to an adverse event and in the open label or extension period four patients (2.1%) discontinued due to an adverse event. In the double blind period,

13 (7.0%) patients experienced at least one ADR. The most frequent ADRs were vomiting n=3 (1.6%) and diarrhoea n=2 (1.1%). There was one ADR (diarrhoea) in the CKD group. In the open label period, 5.4% patients (10/186) had at least one ADR. The most frequent ADR was decreased appetite which was reported by two patients (1.1%). In both the double blind period and the open label periods, hyperkalaemia was reported for one patient in each period. There were no cases of hypotension or dizziness in either double blind or open label periods.

Hyperkalaemia was more frequently observed in children and adolescents aged 1 to less than 18 years with underlying chronic kidney disease (CKD). The risk of hyperkalaemia may be higher in children aged 1 to 5 years compared to children aged 6 to less than 18 years.

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, hyponatremia
Nervous system disorders	
Common	Dizziness, Postural dizziness
Uncommon	Syncope, Headache
Ear and labyrinth 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
Very rare	Intestinal angioedema
Hepato-biliary disorders	
Not known	Elevation of liver function values
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, Elevation of serum creatinine
Not known	Increase in Blood Urea Nitrogen
General disorders and administration site conditions	
Uncommon	Asthenia, Fatigue

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 via:
HPRA Pharmacovigilance
Website: www.hpra.ie.

4.9 Overdose

Symptoms

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

Treatment

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Agents acting on the renin-angiotensin system; Angiotensin II antagonists, plain. ATC code: C09CA03.

Valsartan is an orally active, potent, and specific angiotensin II (Ang II) receptor antagonist. It acts selectively on the AT_1receptor subtype, which is responsible for the known actions of angiotensin II. The increased plasma levels of Ang II following AT_1receptor blockade with valsartan may stimulate the unblocked AT_2receptor, which appears to counterbalance the effect of the AT_1receptor. Valsartan does not exhibit any partial agonist activity at the AT_1receptor and has much (about 20,000 fold) greater affinity for the AT_1receptor than for the AT_2receptor. Valsartan is not known to bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

Valsartan does not inhibit ACE (also known as kininase II) which converts Ang I to Ang II and degrades bradykinin. Since there is no effect on ACE and no potentiation of bradykinin or substance P, angiotensin II antagonists are unlikely to be associated with coughing. In clinical trials where valsartan was compared with an ACE inhibitor, the incidence of dry cough was significantly ($P<0.05$) less in patients treated with valsartan than in those treated with an ACE inhibitor (2.6% versus 7.9% respectively). In a clinical trial of patients with a history of dry cough during ACE inhibitor therapy, 19.5% of trial subjects receiving valsartan and 19.0% of those receiving a thiazide diuretic experienced cough compared to 68.5% of those treated with an ACE inhibitor ($P<0.05$).

Hypertension

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

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

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

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

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

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)
Two large randomised, controlled trials (ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) and VA NEPHRON-D (The Veterans Affairs Nephropathy in Diabetes)) have examined the use of the combination of an ACE-inhibitor with an angiotensin II receptor blocker.

ONTARGET was a study conducted in patients with a history of cardiovascular or cerebrovascular disease, or type 2 diabetes mellitus accompanied by evidence of end-organ damage. VA NEPHRON-D was a study in patients with type 2 diabetes mellitus and diabetic nephropathy.

These studies have shown no significant beneficial effect on renal and/or cardiovascular outcomes and mortality, while an increased risk of hyperkalaemia, acute kidney injury and/or hypotension as compared to monotherapy was observed. Given their similar pharmacodynamic properties, these results are also relevant for other ACE-inhibitors and angiotensin II receptor blockers.

ACE-inhibitors and angiotensin II receptor blockers should therefore not be used concomitantly in patients with diabetic nephropathy.

ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints) was a study designed to test the benefit of adding aliskiren to a standard therapy of an ACE-inhibitor or an angiotensin II receptor blocker in patients with type 2 diabetes mellitus and chronic kidney disease, cardiovascular disease, or both. The study was terminated early because of an increased risk of adverse outcomes. Cardiovascular death and stroke were both numerically more frequent in the aliskiren group than in the placebo group and adverse events and serious adverse events of interest (hyperkalaemia, hypotension and renal dysfunction) were more frequently reported in the aliskiren group than in the placebo group.

Paediatric population

Hypertension

The antihypertensive effect of valsartan have been evaluated in four randomized, double-blind clinical studies in 561 paediatric patients from 6 to less than 18 years of age and 165 paediatric patients 1 to 6 years of age.

Renal and urinary disorders, and obesity were the most common underlying medical conditions potentially contributing to hypertension in the children enrolled in these studies.

Clinical experience in children at or above 6 years of age
In a clinical study involving 261 hypertensive paediatric patients 6 to 16 years of age, patients who weighed <35 kg received 10, 40 or 80 mg of valsartan tablets daily (low, medium and high doses), and patients who weighed ≥35 kg received 20, 80, and 160 mg of valsartan tablets daily (low, medium and high doses). At the end of 2 weeks, valsartan reduced both systolic and diastolic blood pressure in a dose-dependent manner.

Overall, the three dose levels of valsartan (low, medium and high) significantly reduced systolic blood pressure by 8, 10, 12 mm Hg from the baseline, respectively. Patients were re-randomized to either continue receiving the same dose of valsartan or were switched to placebo. In patients who continued to receive the medium and high doses of valsartan, systolic blood pressure at trough was -4 and -7 mmHg 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 dosedependent antihypertensive effect of valsartan was consistent across all the demographic subgroups.

In a second clinical study involving 300 hypertensive paediatric patients 6 to less than 18 years of age, eligible patients were randomized to receive valsartan or enalapril tablets for 12 weeks. Children weighing between ≥18 kg and <35 kg received

valsartan 80 mg or enalapril 10 mg; those between ≥35 kg and <80 kg received valsartan 160 mg or enalapril 20 mg; those ≥80 kg received valsartan 320 mg or enalapril 40 mg. Reductions in systolic blood pressure were comparable in patients receiving valsartan (15 mmHg) and enalapril (14 mmHg) (non-inferiority p-value <0.0001). Consistent results were observed for diastolic blood pressure with reductions of 9.1 mmHg and 8.5 mmHg with valsartan and enalapril, respectively.

In a third, open label clinical study, involving 150 paediatric hypertensive patients 6 to 17 years of age, eligible patients (systolic BP ≥95th percentile for age, gender and height) received valsartan for 18 months to evaluate safety and tolerability. Out of the 150 patients participating in this study, 41 patients also received concomitant antihypertensive medication. Patients were dosed based on their weight categories for starting and maintenance doses. Patients weighing >18 to < 35 kg, ≥35 to < 80 kg and ≥ 80 to < 160 kg received 40 mg, 80 mg and 160 mg and the doses were titrated to 80 mg, 160 mg and 320 mg respectively after one week. One half of the patients enrolled (50.0%, n=75) had CKD with 29.3% (44) of patients having CKD Stage 2 (GFR 60 – 89 mL/min/1.73m2) or Stage 3 (GFR 30-59 mL/min/1.73m2). Mean reductions in systolic blood pressure were 14.9 mmHg in all patients (baseline 133.5 mmHg), 18.4 mmHg in patients with CKD (baseline 131.9 mmHg) and 11.5 mmHg in patients without CKD (baseline 135.1 mmHg). The percentage of patients who achieved overall BP control (both systolic and diastolic BP <95th percentile) was slightly higher in the CKD group (79.5%) compared to the non-CKD group (72.2%).

Clinical experience in children less than 6 years of age
Three clinical studies were conducted in 291 patients aged 1 to 5 years. No children below the age of 1 year were enrolled in these studies.

In the first study of 90 patients, dose-response could not be demonstrated, but in the second study of 75 patients, higher doses of valsartan were associated with greater BP reductions.

The third study was a 6 week, randomised double-blind study to evaluate the dose response of valsartan in 126 children aged 1 to 5 years with hypertension, with or without CKD randomised 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 and 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).

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

5.2 Pharmacokinetic properties

Absorption:
Following oral administration of valsartan alone, peak plasma concentrations of valsartan are reached in 2–4 hours with tablets and 1–2 hours with solution formulation. Mean absolute bioavailability is 23% and 39% with tablets and solution formulation, respectively. The systemic exposure and peak plasma concentration of valsartan is about 1.7-fold and 2.2-fold higher with the solution compared to the tablets.
Food decreases exposure (as measured by AUC) to valsartan by about 40% and peak plasma concentration (C_{max}) by about 50%, although from about 8 h post dosing plasma valsartan concentrations are similar for the fed and fasted groups. This reduction in AUC is not, however, accompanied by a clinically significant reduction in the therapeutic effect, and valsartan can therefore be given either with or without food.

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

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

Elimination:
Valsartan shows multiexponential decay kinetics ($t_{1/2a}$<1 h and $t_{1/2\beta}$ about 9 h). Valsartan is primarily eliminated by biliary excretion in faeces (about 83% of dose) and renally in urine (about 13% of dose), mainly as unchanged drug. Following

intravenous administration, plasma clearance of valsartan is about 2 l/h and its renal clearance is 0.62 l/h (about 30% of total clearance). The half-life of valsartan is 6 hours.

Special populations

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

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

Hepatic impairment
Approximately 70% of the dose absorbed is eliminated in the bile, essentially in the unchanged form. Valsartan does not undergo any noteworthy biotransformation. A doubling of exposure (AUC) was observed in patients with mild to moderate hepatic impairment compared to healthy subjects. However, no correlation was observed between plasma valsartan concentration versus degree of hepatic dysfunction. Valsartan has not been studied in patients with severe hepatic dysfunction (see sections 4.2, 4.3 and 4.4).

Paediatric population
In a study of 26 paediatric hypertensive patients (aged 1 to 16 years) given a single dose of a suspension of valsartan (mean: 0.9 to 2 mg/kg, with a maximum dose of 80 mg), the clearance (litres/h/kg) of valsartan was comparable across the age range of 1 to 16 years and similar to that of adults receiving the same formulation (see Absorption information under section 5.2).

Impaired renal function
Use in paediatric patients with a creatinine clearance <30 ml/min and paediatric patients undergoing dialysis has not been studied, therefore valsartan is not recommended in these patients. No dose adjustment is required for paediatric patients with a creatinine clearance >30 ml/min. Renal function and serum potassium should be closely monitored (see sections 4.2 and 4.4).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential.
In rats, maternally toxic doses (600 mg/kg/day) during the last days of gestation and lactation led to lower survival, lower weight gain and delayed development (pinna detachment and ear-canal opening) in the offspring (see section 4.6). These doses in rats (600 mg/kg/day) are approximately 18 times the maximum recommended human dose on a mg/m^2 basis (calculations assume an oral dose of 320 mg/day and a 60-kg patient).
In non-clinical safety studies, high doses of valsartan (200 to 600 mg/kg body weight) caused in rats a reduction of red blood cell parameters (erythrocytes, haemoglobin, haematocrit) and evidence of changes in renal haemodynamics (slightly raised plasma urea, and renal tubular hyperplasia and basophilia in males). These doses in rats (200 and 600 mg/kg/day) are approximately 6 and 18 times the maximum recommended human dose on a mg/m^2 basis (calculations assume an oral dose of 320 mg/day and a 60-kg patient).
In marmosets at similar doses, the changes were similar though more severe, particularly in the kidney where the changes developed to a nephropathy which included raised urea and creatinine.
Hypertrophy of the renal juxtaglomerular cells was also seen in both species. All changes were considered to be caused by the pharmacological action of valsartan which produces prolonged hypotension, particularly in marmosets. For therapeutic doses of valsartan in humans, the hypertrophy of the renal juxtaglomerular cells does not seem to have any relevance.

Paediatric population
Daily oral dosing of neonatal/juvenile rats (from a postnatal day 7 to postnatal day 70) with valsartan at doses as low as 1 mg/kg/day (about 10-35% of the maximum recommended paediatric dose of 4 mg/kg/day on systemic exposure basis) produced persistent, irreversible kidney damage. These effects above mentioned represent an expected exaggerated pharmacological effect of angiotensin converting enzyme inhibitors and angiotensin II type 1 blockers; such effects are observed if rats are treated during the first 13 days of life.

This period coincides with 36 weeks of gestation in humans, which could occasionally extend up to 44 weeks after conception in humans. The rats in the juvenile valsartan study were dosed up to day 70, and effects on renal maturation (postnatal 4-6 weeks) cannot be excluded. Functional renal maturation is an ongoing process within the first year of life in humans. Consequently, a clinical relevance in children <1 year of age cannot be excluded, while preclinical data do not indicate a safety concern for children older than 1 year.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Lactose monohydrate
Cellulose, microcrystalline
Povidone
Croscarmellose sodium
Silica, colloidal anhydrous
Magnesium stearate

Film coating:
Hypromellose
Titanium dioxide (E171)
Macrogol 4000
Iron oxide, yellow (E172)
Iron oxide, red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Blister (PVC/PE/PVDC//Alu): 7, 10, 14, 20, 28, 30, 56, 60, 84, 90, 98 film-coated tablets, in a box.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

KRKA, d.d., Novo mesto
Šmarješka cesta 6
8501 Novo mesto
Slovenia

8 MARKETING AUTHORISATION NUMBER

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