SUMMARY OF PRODUCT CHARACTERISTICS

Carvals 80 /160

(Valsartan Tablets 80/160 mg)

1. Name of the medicinal product

Carvals 80/160

2. Qualitative and quantitative composition

Each film-coated tablet contains:
Valsartan USP 80/160 mg

For the full list of excipients, see **section 6.1**.

3. Pharmaceutical form

Film-coated tablet.

4. Clinical particulars [1, 2]

4.1 Therapeutic indications

Hypertension

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

Recent myocardial infarction

Treatment of clinically stable adult patients with symptomatic heart failure or asymptomatic left ventricular systolic dysfunction after a recent (12 hours-10 days) myocardial infarction (see **section 4.4**).

Heart failure

Treatment of adult patients with symptomatic heart failure when Angiotensin Converting Enzyme (ACE) inhibitors are not tolerated or in beta-blocker intolerant patients as add-on

therapy to ACE inhibitors when mineralocorticoid receptor antagonists cannot be used (see **sections 4.2, 4.4 and 4.5**).

4.2 Posology and method of administration

Posology

Hypertension

The recommended starting dose of **Carvals** 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.

Carvals may also be administered with other antihypertensive agents (see **sections 4.3, 4.4 and 4.5**). The addition of a diuretic such as hydrochlorothiazide will decrease blood pressure even further in these patients.

Recent myocardial infarction

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 occurs, 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 **section 4.4**).

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

Heart failure

The recommended starting dose of valsartan tablet is 40 mg twice daily. Up-titration 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 has been reported to be 320 mg in divided doses.

Valsartan may be administered with other heart failure therapies. However, the triple combination of an ACE inhibitor, valsartan and a beta blocker or a potassium-sparing diuretic is not recommended (see **section 4.4**).

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

Additional information on special populations

Older people

No dose adjustment is required in elderly patients.

Patients with Renal impairment

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

Patients with Hepatic impairment

Carvals 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 reported clinical trials please refer to the table below.

Doses higher than those listed have not been reported and are therefore not recommended.

Weight	Maximum dose studied in reported 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 and 5.2**. However safety and efficacy of valsartan in children aged 1 to 6 years have not been reported.

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 reported, 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, **Carvals** 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 reported 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

Carvals 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

Carvals 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**).
- Concomitant use of valsartan with aliskiren-containing products in patients with diabetes mellitus or renal impairment (GFR < 60 mL/min/1.73m^2) (see **section 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 reported 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.

It has been reported that short-term administration of valsartan to 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 reported experience on the safe use of valsartan in patients who have recently undergone kidney transplantation.

Primary hyperaldosteronism

Patients with primary hyperaldosteronism should not be treated with valsartan as their renin-angiotensin system is not activated.

Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy

As with all other vasodilators, special caution is indicated in patients suffering from aortic or mitral stenosis, or hypertrophic obstructive cardiomyopathy (HOCM).

Pregnancy

Angiotensin II Receptor Antagonists (AIIRAs) should not be initiated during pregnancy. Unless continued AIIRAs therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with AIIRAs should be stopped immediately, and, if appropriate, alternative therapy should be started (see **sections 4.3 and 4.6**).

Recent myocardial infarction

The combination of captopril and valsartan has reported no additional clinical benefit, instead the risk for adverse events increased compared to treatment with the respective therapies (see **section 4.2**). 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

The risk of adverse reactions, especially hypotension, hyperkalaemia and decreased renal function (including acute renal failure), may increase when valsartan is used in combination with an ACE inhibitor. In patients with heart failure, the triple combination of an ACE inhibitor, a beta blocker and valsartan has not reported any clinical benefit. This combination apparently increases the risk for adverse events and is therefore not recommended. Triple combination of an ACE inhibitor, a mineralocorticoid receptor antagonist and valsartan is also not recommended. Use of these combinations should be under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure.

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-aldosterone system (e.g. patients with severe congestive heart failure), treatment with ACE 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 receptor blocker, it cannot be excluded that the use of valsartan may be associated with impairment of the renal function.

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

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 (see **section 4.8**).

Dual Blockade of the Renin-Angiotensin-Aldosterone System (RAAS)

There is reported 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 the RAAS through the combined use of ACE inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended (see **section 4.5**).

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.

Paediatric population

Impaired renal function

Use in paediatric patients with a creatinine clearance <30 ml/min and paediatric patients undergoing dialysis has not been reported, 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 reported 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-Aldosterone System (RAS) with ARBs, ACEIs, or aliskiren

Reported 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 and 4.4**).

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

Reported *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 (e.g. rifampin, ciclosporin) or efflux transporter (e.g. ritonavir) may increase the systemic exposure to valsartan. Exercise appropriate care when initiating or ending concomitant treatment with such drugs.

Others

In reported 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**).

Reported 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 reported 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**).

Breast-feeding

Because no information is reported 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

No studies on the effects on the ability to drive have been reported. When driving vehicles or operating machines it should be taken into account that occasionally dizziness or weariness may occur.

4.8 Undesirable effects

In reported 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 reported incidence of ADRs did not appear to be related to dose or treatment duration and also no association with gender, age or race was reported.

The ADRs reported from clinical studies, post-marketing experience and laboratory findings are listed below according to system organ class.

Adverse Drug Reactions

Adverse drug 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 drug 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 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, 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 reported in two randomised, double-blind clinical studies in paediatric patients from 6 to 18 years of age with and without chronic kidney disease (CKD). 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 reported 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 reported no overall clinically relevant adverse impact after treatment with valsartan for up to one year.

In a reported double-blind randomized study in 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 reported. These cases were reported in a population who had significant comorbidities. A causal relationship to valsartan has not been reported. In a second reported study in which children aged 1 to 6 years were randomised, no significant liver transaminase elevations or death occurred with valsartan treatment.

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

A pooled analysis of paediatric hypertensive patients (aged 6-17 years) receiving either valsartan monotherapy or combination antihypertensive therapy including valsartan was reported to be conducted. Of the total patients, 15.2% were reported to had CKD (baseline GFR <90 mL/min/1.73m^2). Overall, 8.0% patients were reported to discontinue study due to adverse events. Overall 19.8% patients were reported to experience an adverse drug reaction (ADR), with headache (5.4%), dizziness (2.3%), and hyperkalaemia (2.3%) being the most frequent. In patients with CKD, the most frequently reported ADRs were hyperkalaemia (12.9%), headache (7.1%), blood creatinine increased (5.9%), and hypotension (4.7%). In patients without CKD, the most frequently reported ADRs were headache (5.1%) and dizziness (2.7%). ADRs were reported more frequently in patients receiving valsartan in combination with other antihypertensive medications than valsartan alone.

The safety profile reported in controlled-clinical studies in adult patients with post-myocardial infarction and/or heart failure varies from the overall safety profile reported in hypertensive

patients. This may relate to the patients underlying disease. ADRs that have been reported in adult patients with post-myocardial infarction and/or heart failure patients are listed below.

- ***Post-myocardial infarction and/or heart failure (reported 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
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
Hepato-biliary disorders	
Not known	Elevation of liver function values
Skin and subcutaneous tissue disorders	
Uncommon	Angioedema
Not known	Dermatitis bullous, Rash, Pruritis

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

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[1, 2]

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Angiotensin II Antagonists

Valsartan is an orally active, potent, and specific angiotensin II (Ang II) receptor antagonist. It acts selectively on the AT_1 receptor subtype, which is responsible for the known actions of angiotensin II. The increased plasma levels of Ang II following AT_1 receptor blockade with valsartan may stimulate the unblocked AT_2 receptor, which appears to counterbalance the effect of the AT_1 receptor. Valsartan does not exhibit any partial agonist activity at the AT_1 receptor and has much (about 20,000 fold) greater affinity for the AT_1 receptor than for the AT_2 receptor.

Valsartan is not known to bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

Valsartan does not inhibit ACE (also known as kininase II) which converts Ang I to Ang II and degrades bradykinin. Since there is no effect on ACE and no potentiation of bradykinin or substance P, angiotensin II antagonists are unlikely to be associated with coughing. In reported 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 reported 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 ($p<0.05$).

Administration of valsartan to patients with hypertension results in reduction of blood pressure without affecting pulse rate. 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 reported to reduce the urinary excretion of albumin.

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. 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 reported in plasma at low concentrations (less than 10% of the valsartan AUC). This metabolite is pharmacologically inactive.

Excretion

Valsartan shows multiexponential decay kinetics ($t_{½\alpha}$ <1 h and $t_{½\beta}$ 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.

In heart failure patients:

The average time to peak concentration and elimination half-life of valsartan in heart failure patients are similar to that reported in healthy volunteers. AUC and C_{max} values of 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. The apparent clearance of valsartan following oral administration is approximately 4.5 l/h. Age does not affect the apparent clearance in heart failure patients.

Special populations

Older people

A somewhat higher systemic exposure to valsartan was reported in some elderly subjects than in young subjects; however, this has not been reported 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 reported 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 reported 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 reported in patients with mild to moderate hepatic impairment compared to healthy subjects. However, no correlation was reported between plasma valsartan concentrations versus degree of hepatic dysfunction. There are no reported studies of valsartan in patients with severe hepatic dysfunction (see **sections 4.2, 4.3 and 4.4**).

Paediatric population

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

Impaired renal function

Use in paediatric patients with a creatinine clearance <30 ml/min and paediatric patients undergoing dialysis has not been reported, 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

Reported non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential.

In rats, it was reported that 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 reported 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 reported 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 reported 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

It was reported that 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 reported 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 reported 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 reported preclinical data do not indicate a safety concern for children older than 1 year.

6. Pharmaceutical particulars

6.1 List of excipient(s)

Carvals 80: Microcrystalline cellulose, Crospovidone, Colloidal anhydrous silica, Magnesium stearate, Pregelatinised starch, Purified talc and Opadry 03G52389 (Yellow)

Carvals 160: Microcrystalline cellulose, Crospovidone, Colloidal anhydrous silica, Magnesium stearate, Pregelatinised starch, Purified talc and Opadry 03G54386 (Pink).

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Store below 30ºC, protect from heat and moisture.

6.5 Nature and contents of container

Carvals tablets are packed in cold form blister pack and each blister containing 10 tablets. Carvals tablets supplied in 3x10's pack size.

6.6 Special precautions for disposal and other handling

No special requirement.

7. MARKETING AUTHORISATION HOLDER

Sun Pharmaceutical Industries Limited
Sun House, 201 B/1
Western Express Highway
Goregaon (East)
Mumbai -400 063
India

8. MARKETING AUTHORISATION NUMBER(S)

Not Applicable

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

02/09/2010

10. DATE OF REVISION OF THE TEXT

September 2021

References

1. Summary of Product Characteristics of Diovan 80 mg film-coated tablets, Novartis Ireland Limited, July 2018.
2. Summary of Product Characteristics of Diovan 160 mg film-coated tablets, Novartis Ireland Limited, July 2018.