SUMMARY OF PRODUCT CHARACTERISTICS

CARVALS H 80 + 12.5/160 + 25 mg
(Valsartan and Hydrochlorothiazide Tablets)

1. NAME OF THE MEDICINAL PRODUCT

CARVALS H

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

CARVALS H 80/12.5 mg
Each film coated tablet contains:
Valsartan USP...…… 80 mg
Hydrochlorothiazide Ph. Eur.…….12.5 mg

CARVALS H 160/25 mg
Each film coated tablet contains:
Valsartan USP...……..160 mg
Hydrochlorothiazide Ph. EUR…….. 25 mg

For excipients, see **section 6.1**

3. PHARMACEUTICAL FORM

Film coated tablet

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of essential hypertension in adults.

CARVALS H (valsartan and hydrochlorothiazide tablets) are indicated in patients whose blood pressure is not adequately controlled on valsartan or hydrochlorothiazide monotherapy.

4.2 Posology and method of administration

CARVALS H (valsartan and hydrochlorothiazide tablets) 80 + 12.5/160 + 25 mg may not be suitable for all dosages and therefore, other suitable available strengths of valsartan + hydrochlorothiazide tablet should be used in such cases.

Posology
The recommended dose of **CARVALS H** 80/12.5 (valsartan and hydrochlorothiazide tablet) is one tablet once daily. Dose titration with the individual components is recommended. In each case, up-titration of individual components to the next dose should be followed in order to reduce the risk of hypotension and other adverse events.

When clinically appropriate direct change from monotherapy to the fixed combination may be considered in patients whose blood pressure is not adequately controlled on valsartan or hydrochlorothiazide monotherapy, provided the recommended dose titration sequence for the individual components is followed.

The clinical response to **CARVALS H** should be evaluated after initiating therapy and if blood pressure remains uncontrolled, the dose may be increased to a maximum dose of valsartan and hydrochlorothiazide 320 + 25 mg.

The antihypertensive effect is substantially present within 2 weeks.

In most patients, maximal effects are reported within 4 weeks. However, in some patients, 4-8 weeks treatment may be required. This should be taken into account during dose-titration.

Method of administration
CARVALS H (valsartan and hydrochlorothiazide tablets) can be taken with or without food and should be administered with water.

Special populations

Patients with renal impairment
No dose adjustment is required for patients with mild to moderate renal impairment [Glomerular Filtration Rate (GFR) ≥ 30 ml/min]. Due to the hydrochlorothiazide component, **CARVALS H** (valsartan and hydrochlorothiazide tablets) are contraindicated in patients with severe renal impairment (GFR < 30 mL/min) and anuria (see **sections 4.3, 4.4 and 5.2**).

Patients with hepatic impairment
In patients with mild to moderate hepatic impairment without cholestasis the dose of valsartan should not exceed 80 mg (see **section 4.4**). No adjustment of the hydrochlorothiazide dose is required for patients with mild to moderate hepatic

impairment. Due to the valsartan component, **CARVALS H** is contraindicated in patients with severe hepatic impairment or with biliary cirrhosis and cholestasis (see **sections 4.3, 4.4 and 5.2**).

Older people
No dose adjustment is required in elderly patients.

Paediatric patients
CARVALS H Tablets (valsartan and hydrochlorothiazide tablet) is not recommended for use in children below the age of 18 years due to a lack of data on safety and efficacy.

4.3 Contraindications

- Hypersensitivity to active substances, other sulfonamide-derived medicinal products or to any of the excipients listed in section 6.1.
- Second and third trimester of pregnancy (see **section 4.4 and 4.6**).
- Severe hepatic impairment, biliary cirrhosis and cholestasis.
- Severe renal impairment (creatinine clearance <30 ml/min), anuria.
- Refractory hypokalaemia, hyponatraemia, hypercalcaemia, and symptomatic hyperuricaemia.
- Concomitant use of valsartan and hydrochlorothiazide combination with aliskiren containing products in patients with diabetes mellitus or renal impairment (GFR < 60 mL/min/1.73m^2) (see **sections 4.5 and 5.1**).

4.4 Special warnings and precautions for use

Serum electrolyte changes

Valsartan
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.

Hydrochlorothiazide
Hypokalaemia has been reported under treatment with thiazide diuretics, including hydrochlorothiazide. Frequent monitoring of serum potassium is recommended.

Treatment with thiazide diuretics, including hydrochlorothiazide, has been associated with hyponatraemia and hypochloraemic alkalosis. Thiazides, including hydrochlorothiazide, increase the urinary excretion of magnesium, which may result in hypomagnesaemia. Calcium excretion is decreased by thiazide diuretics. This may result in hypercalcaemia.

As for any patient receiving diuretic therapy, periodic determination of serum electrolytes should be performed at appropriate intervals.

Sodium and/or volume-depleted patients
Patients receiving thiazide diuretics, including hydrochlorothiazide, should be observed for clinical signs of fluid or electrolyte imbalance.

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 and hydrochlorothiazide combination. Sodium and/or volume depletion should be corrected before starting treatment with valsartan and hydrochlorothiazide combination.

Patients with severe chronic heart failure or other conditions with stimulation of the renin-angiotensin-aldosterone-system
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 angiotensin converting enzyme inhibitors has been associated with oliguria and/or progressive azotaemia, and in rare cases with acute renal failure and/or death. Evaluation of patients with heart failure or post-myocardial infarction should always include assessment of renal function. The use of valsartan and hydrochlorothiazide combination in patients with severe chronic heart failure has not been reported.

Hence it cannot be excluded that because of the inhibition of the renin-angiotensin-aldosterone system, the application of valsartan and hydrochlorothiazide combination as well may be associated with impairment of the renal function. Valsartan and hydrochlorothiazide combination should not be used in these patients.

Renal artery stenosis
Valsartan and hydrochlorothiazide combination should not be used to treat hypertension in patients with unilateral or bilateral renal artery stenosis or stenosis

of the artery to a solitary kidney, since blood urea and serum creatinine may increase in such patients.

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

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

Renal impairment
No dosage adjustment is required for patients with renal impairment with a creatinine clearance ≥30 ml/min (see **section 4.2**). Periodic monitoring of serum potassium, creatinine and uric acid levels is recommended when combination of valsartan and hydrochlorothiazide is used in patients with renal impairment.

Kidney transplantation
There is currently no experience reported on the safe use of combination valsartan and hydrochlorothiazide in patients who have recently undergone kidney transplantation.

Hepatic impairment
In patients with mild to moderate hepatic impairment without cholestasis, combination of valsartan and hydrochlorothiazide should be used with caution (see **sections 4.2 and 5.2**). Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

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 and hydrochlorothiazide combination should be immediately discontinued in patients who develop angioedema, and valsartan and hydrochlorothiazide combination should not be re-administered (see **section 4.8**).

Systemic lupus erythematosus
Thiazide diuretics, including hydrochlorothiazide, have been reported to exacerbate or activate systemic lupus erythematosus.

Other metabolic disturbances
Thiazide diuretics, including hydrochlorothiazide, may alter glucose tolerance and raise serum levels of cholesterol, triglycerides and uric acid. In diabetic patients dosage adjustments of insulin or oral hypoglycaemic agents may be required.

Thiazides may reduce urinary calcium excretion and cause an intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcaemia may be evidence of underlying hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Photosensitivity
Cases of photosensitivity reactions have been reported with thiazide diuretics (see **section 4.8**). If photosensitivity reaction occurs during treatment, it is recommended to stop the treatment. If a re-administration of the diuretic is deemed necessary, it is recommended to protect exposed areas to the sun or to artificial UVA.

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 **section 4.3 and 4.6**).

General
Caution should be exercised in patients who have reported prior hypersensitivity to other angiotensin II receptor antagonists. Hypersensitivity reactions to hydrochlorothiazide are more likely in patients with allergy and asthma.

Acute Angle-Closure Glaucoma
Hydrochlorothiazide, a sulfonamide, has been associated with an idiosyncratic reaction resulting in acute transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and

typically occur within hours to week of a drug initiation. Untreated acute-angle closure glaucoma can lead to permanent vision loss.

The primary treatment is to discontinue hydrochlorothiazide as rapidly as possible. Prompt medical or surgical treatment may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle closure glaucoma may include a history of sulfonamide or penicillin allergy.

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

Non-melanoma skin cancer
An increased risk of non-melanoma skin cancer (NMSC) [basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)] with increasing cumulative dose of hydrochlorothiazide exposure has been reported in two epidemiological studies based on the Danish National Cancer Registry. Photosensitising actions of hydrochlorothiazide could act as a possible mechanism for NMSC.

Patients taking hydrochlorothiazide should be informed of the risk of NMSC and advised to regularly check their skin for any new lesions and promptly report any suspicious skin lesions. Possible preventive measures such as limited exposure to sunlight and UV rays and, in case of exposure, adequate protection should be advised to the patients in order to minimize the risk of skin cancer. Suspicious skin lesions should be promptly examined potentially including histological examinations of biopsies. The use of hydrochlorothiazide may also need to be reconsidered in patients who have experienced previous NMSC (see also section 4.8).

4.5 Interaction with other medicinal products and other forms of interaction

Interactions related to both valsartan and hydrochlorothiazide

Concomitant use not recommended

Lithium:
Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors, angiontensin II receptor antagonist or thiazides, including hydrochlorothiazide. Since renal clearance of lithium is reduced by thiazides, the risk of lithium toxicity may presumably be increased further with valsartan and hydrochlorothiazide combination. If the combination proves necessary, a careful monitoring of serum lithium levels is recommended.

Concomitant use requiring caution

Other antihypertensive agents:
Valsartan and hydrochlorothiazide combination may increase the effects of other agents with antihypertensive properties (e.g. guanethidine, methyldopa, vasodilators, ACEI, ARBs, beta-blockers, calcium channel blockers and DRIs).

Pressor amines (e.g. noradrenaline, adrenaline:
Possible decreased response to pressor amines. The clinical significance of this effect is uncertain and not sufficient to preclude their use.

Non-steroidal anti-inflammatory medicines (NSAIDs), including selective COX-2 inhibitors, acetylsalicylic acid >3 g/day), and non-selective NSAIDs:
NSAIDS can attenuate the antihypertensive effect of both angiotensin II antagonists and hydrochlorothiazide when administered simultaneously. Furthermore, concomitant use of valsartan and hydrochlorothiazide combination and NSAIDs may lead to 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.

Interactions related to valsartan

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

Clinical trial data reported 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 s single RAAS-acting agent (see **section 4.3 and 4.4**).

Concomitant use not 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.

Transporters:
In vitro data reported 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.

No interaction:
In drug interaction studies with valsartan, no interactions of clinical significance have been reported with valsartan or any of the following substances: cimetidine, warfarin, furosemide, digoxin, atenolol, indomethacin, hydrochlorothiazide, amlodipine, glibenclamide. Digoxin and indomethacin could interact with the hydrochlorothiazide component of valsartan and hydrochlorothiazide combination (see interactions related to hydrochlorothiazide).

Interactions related to hydrochlorothiazide

Concomitant use requiring caution

Medicinal products affecting serum potassium level:
The hypokalaemic effect of hydrochlorothiazide may be increased by concomitant administration of kaliuretic diuretics, corticosteroids, laxatives, ACTH, amphotericin, carbenoxolone, penicillin G, salicylic acid and derivatives.

If these medicinal products are to be prescribed with the hydrochlorothiazide-valsartan combination, monitoring of potassium plasma levels is advised (see **section 4.4**).

Medicinal products that could induce torsades de pointes:
Due to the risk of hypokalaemia, hydrochlorothiazide should be administered with caution when associated with medicinal products that could induce torsades de pointes, in particular Class Ia and Class III antiarrhythmics and some antipsychotics.

Medicinal products affecting serum sodium level:
The hyponatraemic effect of diuretics may be intensified by concomitant administration of drugs such as antidepressants, antipsychotics, antiepileptics, etc. Caution is advised in long-term administration of these drugs.

Digitalis glycosides:
Thiazide-induced hypokalaemia or hypomagnesaemia may occur as undesirable effects favouring the onset of digitalis-induced cardiac arrhythmias (see **section 4.4**).

Calcium salts and vitamin D:
Administration of thiazide diuretics, including hydrochlorothiazide, with vitamin D or with calcium salts may potentiate the rise in serum calcium. Concomitant use of thiazide type diuretics with calcium salts may cause hypercalcaemia in patients pre-disposed for hypercalcaemia (e.g. hyperparathyroidism, malignancy or vitamin-D-mediated conditions) by increasing tubular calcium reabsorption.

Antidiabetic agents (oral agents and insulin):
Thiazides may alter glucose tolerance. Dose adjustment of the antidiabetic medicinal product may be necessary.

Metformin should be used with caution because of the risk of lactic acidosis induced by possible functional renal failure linked to hydrochlorothiazide.

Beta blockers and diazoxide:
Concomitant use of thiazide diuretics, including hydrochlorothiazide, with beta blockers may increase the risk of hyperglycaemia. Thiazide diuretics, including hydrochlorothiazide, may enhance the hyperglycaemic effect of diazoxide.

Medicinal products used in the treatment of gout (probenecid, sulfinpyrazone and allopurinol):
Dose adjustment of uricosuric medications may be necessary as hydrochlorothiazide may raise the level of serum uric acid. Increase of dosage of probenecid or sulfinpyrazone may be necessary. Co-administration of thiazide diuretics, including hydrochlorothiazide, may increase the incidence of hypersensitivity reactions to allopurinol.

Anticholinergic agents and other medicinal products affecting gastric motility:
The bioavailability of thiazide-type diuretics may be increased by anticholinergic agents (e.g. atropine, biperiden), apparently due to a decrease in gastrointestinal motility and the stomach emptying rate. Conversely, it is anticipated that prokinetic drugs such as cisapride may decrease the bioavailability of thiazide-type diuretics.

Amantadine:
Thiazides, including hydrochlorothiazide, may increase the risk of adverse effects caused by amantadine.

Ion exchange resins:
Absorption of thiazide diuretics, including hydrochlorothiazide, is decreased by cholestyramine or colestipol. This could result in sub-therapeutic effects of thiazide diuretics. However, staggering the dosage of hydrochlorothiazide and resin such that hydrochlorothiazide is administered at least 4 h before or 4-6 h after the administration of resins would potentially minimise the interaction.

Cytotoxic agents:
Thiazides, including hydrochlorothiazide, may reduce renal excretion of cytotoxic agents (e.g. cyclophosamide, methotrexate) and potentiate their myelosuppressive effects.

Non-depolarising skeletal muscle relaxants (e.g. tubocurarine):
Thiazides, including hydrochlorothiazide, potentiate the action of skeletal muscle relaxants such as curare derivatives.

Ciclosporin:
Concomitant treatment with ciclosporin may increase the risk of hyperuricaemia and gout-type complications.

Alcohol, barbiturates or narcotics:
Concomitant administration of thiazide diuretics with substances that also have a blood pressure lowering effect (e.g. by reducing sympathetic central nervous system activity or direct vasodilatation activity) may potentiate orthostatic hypotension.

Methyldopa:
There have been isolated reports of haemolytic anaemia in patients receiving concomitant treatment with methyldopa and hydrochlorothiazide.

Iodine contrast media:
In case of diuretic-induced dehydration, there is an increased risk of acute renal failure, especially with high doses of the iodine product. Patients should be rehydrated before the administration.

4.6 Fertility, pregnancy and lactation

Pregnancy

Valsartan

The use of Angiotensin II Receptor Antagonists (AIIRAs) is not recommended during 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 reported 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 reported on the risk with Angiotensin II Receptor Inhibitors (AIIRAs), similar risks may exist for this class of drugs. 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.

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).

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

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

Hydrochlorothiazide
There is limited experience reported with hydrochlorothiazide during pregnancy, especially during the first trimester. Reported animal studies are insufficient. Hydrochlorothiazide crosses the placenta. Based on the pharmacological mechanism of action of hydrochlorothiazide its use during the second and third trimester may compromise foeto-placental perfusion and may cause foetal and neonatal effects like icterus, disturbance of electrolyte balance and thrombocytopenia.

Lactation

No information is reported regarding the use of valsartan during breastfeeding. Hydrochlorothiazide is excreted in human milk. Therefore the use of combination valsartan and hydrochlorothiazide during breast feeding is not recommended. Alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

4.7 Effects on ability to drive and use machines

No studies on the effect of valsartan and hydrochlorothiazide combination, on the ability to drive and use machines 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

Adverse drug reactions reported in clinical trials and laboratory findings occurring more frequently with valsartan plus hydrochlorothiazide versus placebo and individual post-marketing reports are presented below according to system organ class. Adverse reactions known to occur with each component given individually but which have not been reported in clinical trials may occur during treatment with valsartan/hydrochlorothiazide.

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 (cannot be reported from the available data).

Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.

Table: Frequency of adverse reactions with valsartan/hydrochlorothiazide	
Metabolism and nutrition disorders	
Uncommon	Dehydration
Nervous system disorders	
Very rare	Dizziness
Uncommon	Paraesthesia
Not known	Syncope
Eye disorders	
Uncommon	Vision blurred
Ear and labyrinth disorders	
Uncommon	Tinnitus
Vascular disorders	
Uncommon	Hypotension
Respiratory, thoracic and mediastinal disorders	
Uncommon	Cough
Not known	Non cardiogenic pulmonary oedema
Gastrointestinal disorders	
Very rare	Diarrhoea
Musculoskeletal and connective tissue disorders	
Uncommon	Myalgia
Very rare	Arthralgia

Renal and urinary disorders	
Not known	Impaired renal function
General disorders and administration site conditions	
Uncommon	Fatigue
Investigations	
Not known	Serum uric acid increased, Serum bilirubin and Serum creatinine increased, Hypokalaemia, Hyponatraemia, Elevation of Blood Urea Nitrogen, Neutropenia

Additional information on the individual components

Adverse reactions previously reported with one of the individual components may be potential undesirable effects with valsartan plus hydrochlorothiazide as well, even if not reported in clinical trials or during post-marketing period.

Valsartan

Table: Frequency of adverse reactions with valsartan

Blood and lymphatic system disorders	
Not known	Decrease in haemoglobin, decrease in haematocrit, thrombocytopenia
Immune system disorders	
Not known	Other hypersensitivity/allergic reactions 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
Gastrointestinal disorders	
Uncommon	Abdominal pain
Hepatobiliary disorders	

Not known	Elevation of liver function values
Skin and subcutaneous tissue disorders	
Not known	Angioedema, dermatitis bullous, rash, pruritus
Renal and urinary disorders	
Not known	Renal failure

Hydrochlorothiazide

Hydrochlorothiazide has been extensively prescribed for many years, frequently in higher doses than those administered with valsartan and hydrochlorothiazide combination. The following adverse reactions have been reported in patients treated with monotherapy of thiazide diuretics, including hydrochlorothiazide:

Table: Frequency of adverse reactions with hydrochlorothiazide

Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	
Not known	Non-melanoma skin cancer (Basal cell carcinoma and Squamous cell carcinoma)
Blood and lymphatic system disorders	
Rare	Thrombocytopenia sometimes with purpura
Very rare	Agranulocytosis, leucopenia, haemolytic anaemia, bone marrow failure
Not known	Aplastic anemia
Immune system disorders	
Very rare	Hypersenstivity reactions
Metabolism and nutrition disorders	
Very common	Hypokalaemia, blood lipids increased (mainly at higher doses)
Common	Hyponatraemia, hypomagnesaemia, hyperuricaemia
Rare	Hypercalcaemia, hyperglycaemia, glycosuria and worsening of diabetic metabolic state
Very rare	Hypochloraemic alkalosis
Psychiatric disorders	
Rare	Depression, sleep disturbances
Nervous system disorders	
Rare	Headache, dizziness, paraesthesia
Eye disorders	

Rare	Visual impairment
Not known	Acute angle-closure glaucoma
Cardiac disorders	
Rare	Cardiac arrhythmias
Vascular disorders	
Common	Postural hypotension
Respiratory, thoracic and mediastinal disorders	
Very rare	Respiratory distress including pneumonitis and pulmonary oedema
Gastrointestinal disorders	
Common	Loss of appetite, mild nausea and vomiting
Rare	Constipation, gastrointestinal discomfort, diarrhea
Very rare	Pancreatitis
Hepatobiliary disorders	
Rare	Intrahepatic cholestasis or jaundice
Renal and urinary disorders	
Not known	Renal dysfunction, acute renal failure
Skin and subcutaneous tissue disorders	
Common	Urticaria and other forms of rash
Rare	Photosensitisation
Very rare	Necrotising vasculitis and toxic epidermal necrolysis, cutaneous lupus erythematosus-like reactions, reactivation of cutaneous lupus erythematosus
Not known	Erythema multiforme
General disorders and administration site conditions	
Not known	Pyrexia, asthenia
Musculoskeletal and connective tissue disorders	
Not known	Muscle spasm
Reproductive system and breast disorders	
Common	Impotence

Description of selected adverse reactions

Non-melanoma skin cancer: based on available data from reported epidemiological studies, cumulative dose dependent association between hydrochlorothiazide and NMSC has been reported (see also **sections 4.4**).

To report any side effects:

- ***Saudi Arabia:***

National Pharmacovigilance and Drug Safety Centre Center (NPC) Fax : +966-1-210-7398 Call NPC at +966-11-2038222, Exts: 2317-2356-2353-2354-2334-2340. Toll free phone: 8002490000 Email : npc.drug@sfda.gov.sa Website: www.sfda.gov.sa/npc

- ***Other GCC States:***

Please contact the relevant competent Authority.

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. In addition, the following signs and symptoms may occur due to an overdose of the hydrochlorothiazide component: nausea, somnolence, hypovolaemia, and electrolyte disturbances associated with cardiac arrhythmias and muscle spasms.

Treatment

The therapeutic measures depend on the time of ingestion and the type and severity of the symptoms, stabilisation of the circulatory condition being of prime importance.

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

Valsartan cannot be eliminated by means of haemodialysis because of its strong plasma binding behaviour whereas clearance of hydrochlorothiazide will be achieved by dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Angiotensin II antagonists and diuretics, valsartan and diuretics; ATC code: C09D A03

Valsartan

Valsartan is an orally active 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 ($P < 0.05$) lower in patients treated with valsartan than in those treated with an ACE inhibitor. 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 reported to result in reduction of blood pressure without affecting pulse rate. In most patients, after administration of a single oral dose, onset of antihypertensive activity occurs within 2 hours, and the peak reduction of blood pressure is achieved within 4-6 hours. The antihypertensive effect persists over 24 hours after dosing. During repeated dosing, the maximum reduction in blood pressure with any dose is generally attained within 2-4 weeks and is sustained during long-term therapy. Combined with hydrochlorothiazide, a significant additional reduction in blood pressure is achieved.

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

In hypertensive patients with type 2 diabetes and microalbuminuria, valsartan has been reported to reduce the urinary excretion of albumin.

Other: Dual blockade of the renin-angiotensin-aldosterone system (RAAS)
Two large randomised, reported controlled trials (involving telmisartan alone and in combination with ramipril) have examined the use of the combination of an ACE-inhibitor with an angiotensin II receptor blocker. One reported study was conducted in patients with a history of cardiovascular or cerebrovascular disease, or type 2 diabetes mellitus accompanied by evidence of end-organ damage. The other reported study was conducted in patients with type 2 diabetes mellitus and diabetic nephropathy. These studies have reported 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 reported. Given their similar pharmacodynamic properties, these results are also deemed 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.

Hydrochlorothiazide
The site of action of thiazide diuretics is primarily in the renal distal convoluted tubule. It has been reported that there is a high-affinity receptor in the renal cortex as the primary binding site for the thiazide diuretic action and inhibition of NaCl transport in the distal convoluted tubule. The mode of action of thiazides is through inhibition of the Na+Cl- symporter perhaps by competing for the Cl- site, thereby affecting electrolyte reabsorption mechanisms: directly increasing sodium and chloride excretion to an approximately equal extent, and indirectly by this diuretic action reducing plasma volume, with consequent increases in plasma renin activity, aldosterone secretion and urinary potassium loss, and a decrease in serum potassium. The renin-aldosterone link is mediated by angiotensin II, so with co-administration of valsartan the reduction in serum potassium is less pronounced as observed under monotherapy with hydrochlorothiazide.

5.2 Pharmacokinetic properties

Valsartan/hydrochlorthiazide

The systemic availability of hydrochlorothiazide is reduced by about 30% when co-administered with valsartan. The kinetics of valsartan are not markedly

affected by the co-administration of hydrochlorothiazide. This reported interaction has no impact on the combined use of valsartan and hydrochlorothiazide, since controlled clinical trials have reported a clear anti-hypertensive effect, greater than that obtained with either active substance given alone, or placebo.

Valsartan

Absorption
Following oral administration of valsartan alone, peak plasma concentrations of valsartan are reached in 2–4 hours. Mean absolute bioavailability is 23%. 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 ($t_{½\alpha}$ <1 h and $t_{½\beta}$ about 9 h). Valsartan is primarily eliminated in faeces (about 83% of dose) and urine (about 13% of dose), mainly as unchanged drug. Following intravenous administration, plasma clearance of valsartan is about 2 l/h and its renal clearance is 0.62 l/h (about 30% of total clearance). The half-life of valsartan is 6 hours.

Hydrochlorothiazide

Absorption

The absorption of hydrochlorothiazide, after an oral dose, is rapid (t_{max} about 2 h). The increase in mean AUC is linear and dose proportional in the therapeutic range.

The effect of food on hydrochlorothiazide absorption, if any, has little clinical significance. Absolute bioavailability of hydrochlorothiazide is 70% after oral administration.

Distribution
The apparent volume of distribution is 4-8 l/kg.

Circulating hydrochlorothiazide is bound to serum proteins (40-70%), mainly serum albumin. Hydrochlorothiazide also accumulates in erythrocytes at approximately 3 times the level in plasma.

Elimination
Hydrochlorothiazide is eliminated predominantly as unchanged drug. Hydrochlorothiazide is eliminated from plasma with a half-life averaging 6 to 15 hours in the terminal elimination phase. There is no change in the kinetics of hydrochlorothiazide on repeated dosing, and accumulation is minimal when dosed once daily. There is more than 95% of the absorbed dose being excreted as unchanged compound in the urine. The renal clearance is composed of passive filtration and active secretion into the renal tubule.

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.

Limited data is reported on whether the systemic clearance of hydrochlorothiazide is reduced in both healthy and hypertensive elderly subjects compared to young healthy volunteers.

Renal impairment
At the recommended dose of valsartan and hydrochlorothiazide combination, no dose adjustment is required for patients with a Glomerular Filtration Rate (GFR) of 30–70 ml/min.

In patients with severe renal impairment (GFR <30 ml/min) and patients undergoing dialysis no data has been reported for combination of valsartan and hydrochlorothiazide. Valsartan is highly bound to plasma protein and is not to be removed by dialysis, whereas clearance of hydrochlorothiazide will be achieved by dialysis.

In the presence of renal impairment, mean peak plasma levels and AUC values of hydrochlorothiazide are increased and the urinary excretion rate is reduced. In patients with mild to moderate renal impairment, a 3-fold increase in hydrochlorothiazide AUC has been reported. In patients with severe renal impairment an 8-fold increase in AUC has been reported. Hydrochlorothiazide is contraindicated in patients with severe renal impairment (see **section 4.3**).

Hepatic impairment
In a reported pharmacokinetics study in patients with mild (n=6) to moderate (n=5) hepatic dysfunction, exposure to valsartan was increased approximately 2-fold compared with healthy volunteers (see **sections 4.2 and 4.4**).

There is no data reported on the use of valsartan in patients with severe hepatic dysfunction (see **section 4.3**). Hepatic disease does not significantly affect the pharmacokinetics of hydrochlorothiazide.

5.3 Preclinical safety data

The potential toxicity of the valsartan plus hydrochlorothiazide combination after oral administration has been reported in rats and marmosets in studies lasting up to six months. No findings reported that would exclude the use of therapeutic doses in man.

The changes produced by the combination in the reported chronic toxicity studies are most likely to have been caused by the valsartan component. The toxicological target organ was the kidney, the reaction being more marked in the marmoset than the rat. The combination led to kidney damage (nephropathy with tubular basophilia, rises in plasma urea, plasma creatinine and serum potassium, increases in urine volume and urinary electrolytes from 30 mg/kg/day valsartan + 9 mg/kg/day hydrochlorothiazide in rats and 10 + 3 mg/kg/d in marmosets), probably by way of altered renal haemodynamics. These doses in rat, respectively, represent 0.9 and 3.5–times the maximum recommended human dose (MRHD) of valsartan and hydrochlorothiazide combination on a mg/m^2 basis. These doses in marmoset, respectively, represent 0.3 and 1.2–times the

maximum recommended human dose (MRHD) of valsartan and hydrochlorothiazide combination on a mg/m^2 basis. (Calculations assume an oral dose of 320 mg/day valsartan in combination with 25 mg/day hydrochlorothiazide and a 60-kg patient.)

High doses of the valsartan-hydrochlorothiazide combination caused falls in red blood cell indices (red cell count, haemoglobin, haematocrit, from 100 + 31 mg/kg/d in rats and 30 + 9 mg/kg/d in marmosets). These doses in rat, respectively, represent 3.0 and 12 times the maximum recommended human dose (MRHD) of valsartan and hydrochlorothiazide combination on a mg/m^2 basis. These doses in marmoset, respectively, represent 0.9 and 3.5 times the maximum recommended human dose (MRHD) of valsartan and hydrochlorothiazide combination on a mg/m^2 basis. (Calculations assume an oral dose of 320 mg/day valsartan in combination with 25 mg/day hydrochlorothiazide and a 60-kg patient).

In marmosets, damage was reported in the gastric mucosa (from 30 + 9 mg/kg/d). The combination also led in the kidney to hyperplasia of the afferent aterioles (at 600 + 188 mg/kg/d in rats and from 30 + 9 mg/kg/d in marmosets). These doses in marmoset, respectively, represent 0.9 and 3.5 times the maximum recommended human dose (MRHD) of valsartan and hydrochlorothiazide combination on a mg/m^2 basis. These doses in rat, respectively, represent 18 and 73 times the maximum recommended human dose (MRHD) of valsartan and hydrochlorothiazide combination on a mg/m^2 basis. (Calculations assume an oral dose of 320 mg/day valsartan in combination with 25 mg/day hydrochlorothiazide and a 60-kg patient).

The above mentioned effects appear to be due to the pharmacological effects of high valsartan doses (blockade of angiotensin II-induced inhibition of renin release, with stimulation of the renin-producing cells) and also occur with ACE inhibitors. These findings appear to have no relevance to the use of therapeutic doses of valsartan in humans.

The valsartan and hydrochlorothiazide combination was not tested for mutagenicity, chromosomal breakage or carcinogenicity, since there is no evidence of interaction reported between the two substances. However, these tests have been reported separately with valsartan and hydrochlorothiazide, and produced no evidence of mutagenicity, chromosomal breakage or carcinogenicity.

In rats, maternally toxic doses of valsartan (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. 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). Similar findings have been reported with valsartan plus hydrochlorothiazide in rats and rabbits. In reported embryo-fetal development (Segment II) studies with valsartan and hydrochlorothiazide in rat and rabbit, there was no evidence of teratogenicity; however, fetotoxicity associated with maternal toxicity have been reported.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients: Microcrystalline Cellulose, Crospovidone, Silica Colloidal Anhydrous, Talc, Magnesium Stearate, Starch Pregelatinised, Ferric Oxide Red, Opadry 20A 58878 (white), Hydroxypropyl Cellulose, HPMC 2910/Hypromellose ScP, Titanium Dioxide, Purified Water .

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Store below 30°C, protected from light.

6.5 Nature and contents of container

Available in Blisters of 10 tablets. Such 3 blisters are further packed in a Show Box along with pack insert.

7. MARKETING AUTHORISATION HOLDER

SPIL

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

January 2019

REFERENCES

1. Summary of Product Characteristics, Co-Diovan 80/12.5 mg, 160/25 mg Tablets, Novartis Pharmaceuticals UK Limited, January 2019.