NOVARTIS

TRADE NAME

CO-DIOVAN® Film-coated tablets 80/12.5 mg, 160/12.5 mg, 160/25 mg

DESCRIPTION AND COMPOSITION

Pharmaceutical form

Film-coated tablets (FCT) 80/12.5 mg, 160/12.5 mg, 160/25 mg

Co-Diovan 80/12.5 mg: Ovaloid slightly convex, non-divisible, film-coated tablets measuring approximately 10.2 mm in length and approximately 5.4 mm in width, and weighing approximately 156 mg. The tablets are coloured light orange and debossed "HGH" on one side and "CG" on the other side.

Co-Diovan 160/12.5 mg: Ovaloid slight convex, non-divisible, film-coated tablets measuring approximately 15.2 mm in length and approximately 6.2 mm in width, and weighing approximately 312 mg. The tablets are coloured dark red and debossed "HHH" on one side and "CG" on the other side.

Co-Diovan 160/25 mg: Ovaloid slightly convex, non-divisible, film-coated tablets measuring approximately 14.2 mm in length and approximately 5.7 mm in width, and weighing approximately 310 mg. The tablets are coloured brown-orange and debossed "HXH" on one side and "NVR" on the other side.

Co-Diovan FCT cannot be divided into equal doses.

Appearance of tablets may vary between countries. Certain dosage strengths may not be available in all countries.

Active substances

One tablet contains 80 mg valsartan and 12.5 mg hydrochlorothiazide, or 160 mg valsartan and 12.5 mg hydrochlorothiazide, or 160 mg valsartan and 25 mg hydrochlorothiazide

Excipients

Co-Diovan 80/12.5 mg: Colloidal silicon dioxide; crospovidone; hydroxypropyl methylcellulose; magnesium stearate; microcrystalline cellulose; polyethylene glycol; talc; titanium dioxide (E171); red iron oxide (E172); yellow iron oxide (E172).

Co-Diovan 160/12.5 mg: Colloidal silicon dioxide; crospovidone; hydroxypropyl-methylcellulose; magnesium stearate; microcrystalline cellulose; polyethylene glycol; talc; titanium dioxide (E171); red iron oxide (E172).

Co-Diovan 160/25 mg: Colloidal silicon dioxide; crospovidone; hydroxypropyl methylcellulose; magnesium stearate; microcrystalline cellulose; polyethylene glycol; talc; titanium dioxide (E171), red iron oxide (E172), yellow iron oxide (E172), black iron oxide (E172).

Pharmaceutical formulations may vary between countries.

INDICATIONS

Treatment of hypertension in adults, 18 years of age and older.

Co-Diovan may be used for the treatment of hypertension in patients whose blood pressure is not adequately controlled by monotherapy.

DOSAGE REGIMEN AND ADMINISTRATION

Dosage regimen

The recommended dose of Co-Diovan is 1 coated tablet per day. When clinically appropriate either 80 mg valsartan and 12.5 mg hydrochlorothiazide or 160 mg valsartan and 12.5 mg hydrochlorothiazide or 320 mg valsartan and 12.5 mg hydrochlorothiazide may be used. When necessary 160 mg valsartan and 25 mg hydrochlorothiazide or 320 mg valsartan and 25 mg hydrochlorothiazide may be used. The maximum daily dose is 320 mg/25 mg.

The maximum antihypertensive effect is seen within 2 to 4 weeks.

Renal impairment

No dosage adjustment is required for patients with mild to moderate renal impairment (creatinine clearance>30 mL/min). Due to the hydrochlorothiazide component, Co-Diovan is contraindicated in patients with anuria and severe renal impairment (creatinine clearance <30mL/min) (see section WARNINGS AND PRECAUTIONS, CONTRAINDICATIONS and CLINICAL PHARMACOLOGY subsection PHARMACOKINETICS).

Hepatic impairment

No dosage adjustment is required in patients with mild to moderate hepatic impairment. Due to the hydrochlorothiazide component, Co-Diovan is contraindicated in patients with severe hepatic impairment. Due to the valsartan component, Co-Diovan should be used with particular caution in patients with biliary obstructive disorders (see sections CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS).

Pediatric patients (below 18 years)

The safety and efficacy of Co-Diovan have not been established in children below the age of 18 years.

CONTRAINDICATIONS

Known hypersensitivity to valsartan, hydrochlorothiazide, other sulphonamide derived medicinal products or to any of the excipients of Co-Diovan.

Pregnancy (see section PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL).

Biliary cirrhosis and cholestasis.

Because of hydrochlorothiazide, Co-Diovan is contraindicated in patients with anuria.

Severe hepatic impairment, severe renal impairment (creatinine clearance <30mL/min), refractory hypokalemia, hyponatremia, hypercalcemia, and symptomatic hyperuricemia.

The concomitant use of Co-Diovan with aliskiren-containing products is contraindicated in

patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73m^2) (see section INTERACTIONS).

WARNINGS AND PRECAUTIONS

Sensitivity reactions may occur in patients receiving thiazides with or without any previous history of allergy of bronchial asthma.

Serum electrolyte changes

Concomitant use with potassium supplements, potassium-sparing diuretics, salt substitutes containing potassium, or other drugs that may increase potassium levels (heparin, etc.) should be used with caution.

Thiazide diuretics can precipitate new onset hypokalemia or exacerbate pre-existing hypokalemia. Thiazide diuretics should be administered with caution in patients with conditions involving enhanced potassium loss, for example salt-losing nephropathies and prerenal (cardiogenic) impairment of kidney function. If hypokalemia is accompanied by clinical signs (e.g. muscular weakness, paresis, or ECG alterations), Co-Diovan should be discontinued. Correction of hypokalemia and any coexisting hypomagnesemia is recommended prior to the initiation of thiazides. Potassium and magnesium serum concentrations should be checked periodically. All patients receiving thiazide diuretics should be monitored for imbalances in electrolytes, particularly potassium.

Thiazide diuretics can precipitate new onset hyponatremia and hypochloremic alkalosis or exacerbate pre-existing hyponatremia. Hyponatremia, accompanied by neurological symptoms (nausea, progressive disorientation, apathy) has been observed in isolated cases. Regular monitoring of serum sodium concentrations is recommended.

Thiazides, including hydrochlorothiazide, increase the urinary excretion of magnesium, which may result in hypomagnesemia. Calcium excretion is decreased by thiazide diuretics. This may result in hypercalcemia. Thiazides should be discontinued before carrying out tests for parathyroid function.

Patients with sodium- and/or volume-depletion

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 Co-Diovan. Co-Diovan should be used only after correction of any pre-existing sodium and/or volume depletion otherwise the treatment should start under close medical supervision.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, given an i.v. infusion of normal saline. Treatment can be continued once the blood pressure has stabilized.

Patients with renal artery stenosis

Co-Diovan should be used with caution to treat hypertension in patients with unilateral or bilateral renal artery stenosis or stenosis to a solitary kidney, since blood urea and serum creatinine may increase in such patients.

Patients with renal impairment

No dosage adjustment is required for patients with mild to moderate renal impairment (creatinine clearance>30 mL/min). Due to the hydrochlorothiazide component use of Co-Diovan is contraindicated in patients with severe renal impairment (creatinine clearance <30 mL/min). Thiazide diuretics may precipitate azotemia in patients with chronic kidney disease. (see sections DOSAGE REGIMEN AND ADMINISTRATION and CLINICAL PHARMACOLOGY subsection PHARMACOKINETICS).

The use of ARBs - including valsartan- or of ACEIs with aliskiren should be avoided in patients with severe renal impairment (GFR < 30 mL/min) (see section INTERACTIONS, subsection dual blockade of the RAS).

Patients with hepatic impairment

In patients with mild to moderate hepatic impairment without cholestasis, no dosage adjustment is required. Co-Diovan should be used with particular caution in patients with biliary obstructive disorders and is contraindicated in patients with severe hepatic impairment (see sections DOSAGE REGIMEN AND ADMINISTRATION and CLINICAL PHARMACOLOGY subsection PHARMACOKINETICS)

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

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 and triglycerides.

Like other diuretics, hydrochlorothiazide may raise the serum uric acid level due to reduced clearance of uric acid and may cause or exacerbate hyperuricemia and precipitate gout in susceptible patients.

Thiazides decrease urinary calcium excretion and may cause mild elevation of serum calcium in the absence of known disorders of calcium metabolism. Since hydrochlorothiazide can increase serum calcium concentrations, it is contraindicated in patients with hypercalcemia. Marked hypercalcemia unresponsive to thiazide withdrawal or ≥12 mg/dL may be evidence of an underlying thiazide independent hypercalcemic process.

Pathological changes in the parathyroid gland of patients with hypercalcemia and hypophosphatemia have been observed in a few patients on prolonged thiazide therapy. If hypercalcemia occurs, further diagnostic clarification is necessary.

Thiazides may decrease serum protein bound iodine levels without signs of thyroid

disturbance.

General

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.

Patients with heart failure/post-myocardial infarction

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 or angiotensin receptor antagonists has been associated with oliguria and/or progressive azotemia, 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.

Dual Blockade of the Renin-Angiotensin System (RAS)

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 RAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended (see INTERACTIONS).

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 observed in two epidemiological studies based on Danish National cancer registry. The risk for NMSC appears to increase with long-term use (see section CLINICAL

PHARMACOLOGY). Photosensitizing 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 adequate protection when exposed to sunlight 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 examination of biopsies. The use of hydrochlorothiazide may also need to be reconsidered in patients who have previously experienced NMSC (see section ADVERSE DRUG REACTIONS).

ADVERSE DRUG REACTIONS

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 seen 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 estimated from the available data). Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.

Table 1 Frequency of adverse drug reactions with valsartan/hydrochlorothiazide

Blood and lymphatic system disorders	
Not known	Neutropenia
Metabolism and nutrition disorders	
Uncommon	Dehydration
Not known	Hypokalaemia, hyponatraemia
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	Renal impairment
General disorders and administration site conditions	
Uncommon	Fatigue
Investigations	
Not known	Blood uric acid increased, blood bilirubin and blood creatinine increased, blood urea increased

The following events have also been observed during clinical trials in hypertensive patients irrespective of their causal association with the study drug: Abdominal pain, abdominal pain upper, anxiety, arthritis, asthenia, back pain, bronchitis, bronchitis acute, chest pain, dizziness postural, dyspepsia, dyspnea, dry mouth, epistaxis, erectile dysfunction, gastroenteritis, headache, hyperhydrosis, hypoesthesia, influenza, insomnia, ligament sprain, muscle spasms, muscle strain, nasal congestion, nasopharyngitis, nausea, neck pain, oedema, oedema peripheral, otitis media, pain in extremity, palpitations, pharyngolaryngeal pain, pollakiuria, pyrexia, sinusitis, sinus congestion, somnolence, tachycardia, upper respiratory tract infections, urinary tract infections, vertigo, viral infections, vision disturbance.

Additional information on the individual components

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

Valsartan

Table 2 Frequency of adverse drug reactions with valsartan

Blood and lymphatic system disorders	
Not known	Haemoglobin decreased, haematocrit decreased, neutropenia thrombocytopenia
Immune system disorders	
Not known	Hypersensitivity including serum sickness
Metabolism and nutrition disorders	
Not known	Blood potassium increased
Ear and labyrinth system disorders	
Uncommon	Vertigo
Vascular disorders	
Not known	Vasculitis
Respiratory, thoracic and mediastinal disorders	
Uncommon	Cough
Gastrointestinal disorders	
Uncommon	Abdominal pain
Hepato-biliary disorders	
Not known	Liver function test abnormal
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

The following events have also been observed during clinical trials in hypertensive patients irrespective of their causal association with the study drug: Arthralgia, asthenia, back pain,
diarrhoea, dizziness, headache, insomnia, libido decrease, nausea, oedema, pharyngitis, rhinitis, sinusitis, upper respiratory tract infection, viral infections.

The following serious adverse events, irrespective of causality and with unknown frequency, have been reported from clinical studies or post-marketing experiences: Toxic epidermal necrolysis (TEN), Stevens-Johnsons syndrome (SJS), erythema multiforme (EM), toxic skin eruption, skin necrosis, exfoliative rash, pemphigus and pemphigoid.

Hydrochlorothiazide

Table 3 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) (see sections WARNINGS AND PRECAUTIONS and CLINICAL PHARMACOLOGY)
Blood and lymphatic system disorders	
Rare:	Thrombocytopenia sometimes with purpura.
Very rare:	Leucopenia, agranulocytosis, bone marrow failure and hemolytic anemia
Not known:	Aplastic anemia
Immune system disorders	
Very rare:	Vasculitis necrotizing, hypersensitivity reactions - respiratory distress including pneumonitis and pulmonary oedema
Metabolism and nutrition disorders	
Very common:	Mainly at higher doses, blood lipids increased, hypokalemia
Common:	Hypomagnesaemia, hyponatramia and hyperuricaemia, decreased appetite
Rare:	Hypercalcaemia, hyperglycaemia, glycosuria and worsening of diabetic metabolic state.
Very rare:	Alkalosis hypochloremic
Psychiatric disorder	
Rare:	Sleep disorders
Nervous system disorders	
Rare:	Headache, dizziness, depression and paresthesia
Eye disorders	
Rare:	Visual impairment particularly in the first few weeks of treatment
Not known:	Angle-closure glaucoma

Cardiac disorders	
Rare:	Arrhythmias
Vascular disorders	
Common:	Orthostatic hypotension, which may be aggravated by alcohol, anesthetics or sedatives
Gastrointestinal disorders	
Common:	Mild nausea and vomiting
Rare:	Abdominal discomfort, constipation and diarrhoea.
Very rare:	Pancreatitis
Hepatobiliary disorders	
Rare:	Cholestasis or jaundice
Skin and subcutaneous tissue disorders	
Common:	Urticaria and other forms of rash
Rare:	Photosensitivity reaction
Very rare:	Toxic epidermal necrolysis, cutaneous lupus erythematosus-like reactions, reactivation of cutaneous lupus erythematosus
Not known	Erythema multiforme
Musculoskeletal and connective tissue disorders	
Not known	Muscle spasms
Renal and urinary disorders	
Not known:	Acute renal failure, renal disorder
Reproductive system and breast disorders	
Common:	Erectile dysfunction
General disorders and administration site conditions	
Not known	Pyrexia, asthenia

INTERACTIONS

Valsartan-hydrochlorothiazide

The following drug interactions may occur due to both components (valsartan and/or hydrochlorothiazide) of Co-Diovan:

Lithium: Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors, angiotensin II receptor antagonists or thiazides. Since renal clearance of lithium is reduced by thiazides, the risk of lithium toxicity may presumably be increased further with Co-Diovan. Therefore, careful monitoring of serum lithium concentrations is recommended during concomitant use.

Valsartan

The following potential drug interactions may occur due to the valsartan component of Co-Diovan:

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 system (RAS) 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 RAS-acting agent (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS).

It is recommended to monitor blood pressure, renal function and electrolytes in patients on Co-Diovan and other agents that affect the RAS (see section WARNINGS AND

PRECAUTIONS).

The concomitant use of ARBs - including valsartan - or of ACEIs with aliskiren, should be avoided in patients with severe renal impairment (GFR < 30 mL/min) (see section WARNINGS AND PRECAUTIONS).The concomitant use of ARBs - including valsartan- or of ACEIs with aliskiren is contraindicated in patients with Type 2 diabetes (see section CONTRAINDICATIONS).

Potassium: Concomitant use with potassium supplements, potassium-sparing diuretics, salt substitutes containing potassium, or other drugs that may alter potassium levels (heparin, etc.) should be used with caution and with frequent monitoring of potassium.

Non-Steroidal Anti-Inflammatory Agents (NSAIDs) including Selective Cyclooxygenase- 2 Inhibitors (COX-2 Inhibitors): When angiotensin II antagonists are administered simultaneously with NSAIDs, attenuation of the antihypertensive effect may occur. Furthermore, in patients who are elderly, volume-depleted (including those on diuretic therapy), or have compromised renal function, concomitant use of angiotensin II antagonists and NSAIDs may lead to an increased risk of worsening of renal function, including possible acute renal failure. Therefore, monitoring of renal function is recommended when initiating or modifying the treatment in patients on valsartan who are taking NSAIDs concomitantly.

Transporters*:* The results from an *in vitro* study with human liver tissue indicate that valsartan is a substrate of the hepatic uptake transporter OATP1B1 and the hepatic efflux transporter MRP2. 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.
In monotherapy with valsartan, no drug interactions of clinical significance have been found with the following drugs: cimetidine, warfarin, furosemide, digoxin, atenolol, indomethacin, hydrochlorothiazide, amlodipine, glibenclamide.

Hydrochlorothiazide

The following potential drug interactions may occur due to the thiazide component of Co-Diovan:
Other anti-hypertensive drugs: Thiazides potentiate the antihypertensive action of other antihypertensive drugs (e.g. guanethidine, methyldopa, beta-blockers, vasodilators, calcium channel blockers, ACE inhibitors, Angiotensin Receptor Blockers (ARBs) and Direct Renin Inhibitors (DRIs))

Skeletal muscle relaxants: Thiazides, including hydrochlorothiazide, potentiate the action of skeletal muscle relaxants such as curare derivatives.

Medicinal products affecting serum potassium levels: The hypokalemic effect of diuretics may be increased by concomitant administration of kaliuretic diuretics, corticosteroids, ACTH, amphotericin, carbenoxolone, penicillin G, salicylic acid derivatives or antiarrhythmics (see section WARNINGS AND PRECAUTIONS).

Medicinal products affecting serum sodium levels: 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 (see section WARNINGS AND PRECAUTIONS)

Antidiabetic agents: Thiazides may alter glucose tolerance. It may be necessary to adjust the

dosage of insulin and of oral antidiabetic agents.

Digitalis glycosides: Thiazide-induced hypokalemia or hypomagnesemia may occur as unwanted effects, favoring the onset of digitalis-induced cardiac arrhythmias. (see section WARNINGS AND PRECAUTIONS).

NSAIDs and Cox-2 selective inhibitors: Concomitant administration of NSAIDs (e.g. salicylic acid derivative, indomethacin) may weaken the diuretic and antihypertensive activity of the thiazide component of Co-Diovan. Concurrent hypovolemia may induce acute renal failure.

Allopurinol: Co-administration of thiazide diuretics (including hydrochlorothiazide) may increase the incidence of hypersensitivity reactions to allopurinol.

Amantadine: Co-administration of thiazide diuretics (including hydrochlorothiazide) may increase the risk of adverse effects caused by amantadine.

Antineoplastic agents (e.g. cyclophosphamide, methotrexate): Concomitant use of thiazide diuretics may reduce renal excretion of cytotoxic agents and enhance their myelosuppressive effects.

Anticholinergic agents: 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 prokinetic drugs such as cisapride may decrease the bioavailability of thiazide-type diuretics.

Ion exchange resins: Absorption of thiazide diuretics, including hydrochlorothiazide, is decreased by cholestyramine or colestipol. 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 minimize the interaction

Vitamin D: Administration of thiazide diuretics, including hydrochlorothiazide, with vitamin D or with calcium salts may potentiate the rise in serum calcium.

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

Calcium salts: Concomitant use of thiazide type diuretics may lead to hypercalcemia by increasing tubular calcium reabsorption.

Diazoxide: Thiazide diuretics may enhance the hyperglycaemic effect of diazoxide.

Methyldopa: There have been reports in the literature of haemolytic anaemia occurring with concomitant use of hydrochlorothiazide and methyldopa.

Alcohol, barbiturates or narcotics: Concomitant administration of thiazide diuretics with alcohol, barbiturates, or narcotics may potentiate orthostatic hypotension.

Pressor amines: Hydrochlorothiazide may reduce the response to pressor amines such as noradrenaline. The clinical significance of this effect is uncertain and not sufficient to preclude their use.

PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Pregnancy

Risk Summary

As for any drug that acts directly on the RAS, Co-Diovan must not be used during pregnancy (see section CONTRAINDICATIONS).

Due to the mechanism of action of angiotensin II antagonists, a risk for the fetus cannot be excluded. In utero exposure to angiotensin converting enzyme (ACE) inhibitors (a specific class of drugs acting on the renin- angiotensin system – RAS) given to pregnant women during the second and third trimesters has been reported to cause injury and death to the developing fetus. In addition, in retrospective data, first trimester use of ACE inhibitors has been associated with a potential risk of birth defects. There have been reports of spontaneous abortion, oligohydramnios and newborn renal dysfunction, when pregnant women have inadvertently taken valsartan.

Intrauterine exposure to thiazide diuretics, including hydrochlorothiazide, is associated with fetal or neonatal jaundice or thrombocytopenia, and may be associated with other adverse reactions that have occurred in adults.

If pregnancy is detected during therapy, Co-Diovan should be discontinued as soon as possible (see section NON-CLINICAL SAFETY DATA).

Clinical considerations

Disease-associated maternal and/or embryo/fetal risk

Hypertension in pregnancy increases the maternal risk for pre-eclampsia, gestational diabetes, premature delivery, and delivery complications (e.g., need for cesarean section, and post-partum hemorrhage). Hypertension increases the fetal risk for intrauterine growth restriction and intrauterine death.

Fetal/Neonatal Risk

Oligohydramnios in pregnant women who use drugs affecting the renin-angiotensin system in the second and third trimesters of pregnancy can result in the following: reduced fetal renal function leading to anuria and renal failure, fetal lung hypoplasia, skeletal deformations, including skull hypoplasia, hypotension and death.

In case of accidental exposure to ARB therapy, appropriate fetal monitoring should be considered.

Infants whose mothers have taken ARB therapy should be closely observed for hypotension.

Animal data

Valsartan: In embryofetal development studies in mice, rats and rabbits, fetotoxicity was observed in association with maternal toxicity in rats at valsartan doses of 600 mg/kg/day 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) and in rabbits at doses of 10 mg/kg/day approximately 0.6 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). There was no evidence of maternal toxicity or fetotoxicity in mice up to a dose level of 600 mg/kg/day approximately 9 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).

Hydrochlorothiazide: Hydrochlorothiazide was not teratogenic and had no effects on fertility and conception. No teratogenic potential was revealed in 3 animal species tested. There was no dose-related fetotoxicity at oral dose levels of 0, 100, 300 and 1000 mg/kg in rats. A decrease in weight gain in suckling rat pups was attributed to the high dose and diuretic effects of hydrochlorothiazide, with subsequent effects on milk production.

Lactation

Risk summary

It is not known whether valsartan is transferred into human milk. Valsartan was transferred into the milk of lactating rats. Hydrochlorothiazide crosses the placenta and is transferred into human milk. Thus, it is not advisable to use Co-Diovan in breast-feeding mothers.

Females and males of reproductive potential

As for any drug that acts directly on the RAS, Co-Diovan should not be used in women planning to become pregnant. Healthcare professionals prescribing any agents acting on the RAS should counsel women of childbearing potential about the potential risk of these agents during pregnancy.

Infertility

There is no information on the effects of valsartan or hydrochlorothiazide on human fertility. Studies in rats did not show any effects of valsartan or hydrochlorothiazide on fertility (see section NON-CLINICAL SAFETY DATA).

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

As with other antihypertensive agents, it is advisable to exercise caution when driving or operating machinery.

OVERDOSAGE

Overdose with valsartan may result in marked hypotension, which could lead to depressed level of consciousness, circulatory collapse and/or shock. If the ingestion is recent, vomiting should be induced. Otherwise, the usual treatment would be i.v. infusion of normal saline solution.

Valsartan cannot be eliminated by means of hemodialysis because of its strong plasma binding behavior, whereas clearance of hydrochlorothiazide will be achieved by dialysis.

CLINICAL PHARMACOLOGY

Pharmacotherapeutic group, ATC

Angiotensin II antagonists combinations (valsartan) with diuretics (hydrochlorothiazide); ATC code: C09D A03.

PHARMACODYNAMICS (PD)

The active hormone of the RAS is angiotensin II, which is formed from angiotensin I through ACE. Angiotensin II binds to specific receptors located in the cell membranes of various tissues. It has a wide variety of physiological effects, including in particular both direct and indirect involvement in the regulation of blood pressure. As a potent vasoconstrictor, angiotensin II exerts a direct pressor response. In addition, it promotes sodium retention and stimulation of aldosterone secretion.

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 does not inhibit ACE, also known as kininase II, which converts Ang I to Ang II and degrades bradykinin. No potentiation of bradykinin-related side effects should be expected. In clinical 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 ($P <0.05$). Valsartan does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

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 to 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 to 4 weeks and is sustained during long-term therapy. Combined with hydrochlorothiazide, a significant additional reduction in blood pressure is achieved.

The site of action of thiazide diuretics is primarily in the renal distal convoluted tubule. It has been shown that there is a high affinity receptor in the renal cortex with 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 affecting mechanisms of electrolyte reabsorption: – directly increasing excretion of sodium and chloride in approximately equivalent amounts, – indirectly, diuretic action reducing plasma volume, with consequent increases in plasma renin activity, increases in aldosterone secretion, increases in urinary potassium loss, and decreases in serum potassium. The renin-aldosterone link is mediated by angiotensin II, so co-administration of an angiotensin II receptor antagonist tends to reverse the potassium loss associated with these diuretics.

Non-melanoma skin cancer

Based on available data from epidemiological studies, cumulative dose-dependent association between HCTZ and NMSC has been observed. One study included a population comprised of 71,533 cases of BCC and of 8,629 cases of SCC matched to 1,430,833 and 172,462 population controls, respectively. High HCTZ use (≥50,000 mg cumulative) was associated with an adjusted OR of 1.29 (95% CI: 1.23-1.35) for BCC and 3.98 (95% CI: 3.68-4.31) for SCC. A clear cumulative dose response relationship was observed for both BCC and SCC. Another study showed a possible association between lip cancer (SCC) and exposure to HCTZ: 633 cases of lip-cancer were matched with 63,067 population controls, using a risk-set sampling strategy. A clear cumulative dose-response relationship was demonstrated with an adjusted OR 2.1 (95% CI: 1.7-2.6) increasing to OR 3.9 (3.0-4.9) for high use (~25,000 mg) and OR 7.7 (5.7-10.5) for the highest cumulative dose (~100,000 mg). For example: A 100,000 mg cumulative dose corresponds to more than 10 years' daily use with a defined daily dose of 25 mg (see section WARNINGS AND PRECAUTIONS and ADVERSE DRUG REACTIONS).

PHARMACOKINETICS (PK)

Valsartan

Absorption

Following oral administration of valsartan alone, peak plasma concentrations of valsartan are reached in 2-4 hours. Mean absolute bioavailability is 23%. When valsartan is given with food, the area under the plasma concentration curve (AUC) of valsartan is reduced by 48%, although from about 8 hours post dosing plasma valsartan concentrations are similar for the fed and fasted group. 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 liters, indicating that valsartan is not distributed into tissues extensively. Valsartan is highly bound to serum protein (94 to 97%), mainly serum albumin.

Biotransformation/Metabolism

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 hour and $t_{½}$ beta about 9 hours).

Valsartan is primarily eliminated in feces (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.

The pharmacokinetics of valsartan is linear in the dose range tested. There is no change in the kinetics of valsartan on repeated administration, and little accumulation when dosed once

daily. Plasma concentrations were observed to be similar in males and females.

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. Concomitant administration with food has been reported to both increase and decrease the systemic availability of hydrochlorothiazide compared with the fasted state. The magnitude of these effects is small and has little clinical importance. Absolute bioavailability of hydrochlorothiazide is 70 % after oral administration.

Distribution

The distribution and elimination kinetics have generally been described as a bi-exponential decay function. 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.

Biotransformation

Hydrochlorothiazide is eliminated predominantly as unchanged drug.

Elimination

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. More than 95 % of the absorbed dose is excreted as unchanged compound in the urine.

Valsartan/hydrochlorothiazide

The systemic availability of hydrochlorothiazide is reduced by about 30% when co-administered with valsartan. The kinetics of valsartan is not markedly affected by the co-administration of hydrochlorothiazide. This observed interaction has no impact on the combined use of valsartan and hydrochlorothiazide, since controlled clinical trials have shown a clear antihypertensive effect, greater than that obtained with drug given alone, or placebo.

Special Populations

Geriatric patients (aged 65 years or above)

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.

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

Renal Impairment

No dose adjustment is required for patients with a creatinine clearance of 30 to 70 mL/min.

In patients with severe renal impairment (creatinine clearance <30 mL/min) and patients undergoing dialysis, no data are available for Co-Diovan. 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, the mean elimination half-life is almost doubled. The renal clearance of hydrochlorothiazide is also reduced to a great extent compared with the renal clearance of around 300 mL/min in patients with normal renal function. Therefore, Co-Diovan is contraindicated in patients with severe renal impairment (creatinine clearance< 30 mL/min) (see section WARNINGS AND PRECAUTIONS).

Renal clearance of hydrochlorothiazide is composed of passive filtration and active secretion into the renal tubule. As expected for a compound which is cleared almost exclusively via the kidneys, renal function has a marked effect on the kinetics of hydrochlorothiazide (see section WARNINGS AND PRECAUTIONS).

Hepatic impairment

In a pharmacokinetics trial in patients with mild (n=6) to moderate (n=5) hepatic dysfunction, exposure to valsartan was increased approximately twofold compared with healthy volunteers. There is no data available on the use of valsartan in patients with severe hepatic dysfunction.

Hepatic disease does not significantly affect the pharmacokinetics of hydrochlorothiazide, and no dose reduction is considered necessary.

However, Co-Diovan should be used with particular caution in patients with biliary obstructive disorders and is contraindicated in patients with severe hepatic impairment (see section WARNINGS AND PRECAUTIONS).

CLINICAL STUDIES

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 to 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 to 4 weeks and is sustained during long-term therapy. Combined with hydrochlorothiazide, a significant additional reduction in blood pressure is achieved.

Initial therapy with valsartan/HCTZ combination starting with a dose of 160/12.5 mg produced significantly greater reductions in blood pressure compared to valsartan monotherapy starting with a dose of 160 mg after 4 weeks in patients with severe hypertension (sitting diastolic blood pressure 110 mmHg and systolic blood pressure 140 mmHg). In other studies, the probability of achieving systolic or diastolic blood pressure control was greater with initial combination therapy than valsartan and HCTZ monotherapy at all levels of baseline blood pressure.

NON-CLINICAL SAFETY DATA

Valsartan: hydrochlorothiazide

In a variety of preclinical safety studies conducted in several animal species, there were no findings that would exclude the use of therapeutic doses of valsartan:hydrochlorothiazide in humans. High doses of valsartan:hydrochlorothiazide (100:31.25 to 600:187.5 mg/kg body weight) caused, in rats, a reduction of red blood cell parameters (erythrocytes, hemoglobin, hematocrit) and evidence of changes in renal hemodynamics (moderate to severe raised plasma urea, increases in plasma potassium and magnesium and mild increases in urinary volume and electrolytes, minimal to slight tubular basophilia, and afferent arteriolar hypertrophy at the highest dose level). In marmosets (30:9.375 to 400:125 mg/kg), the changes were fairly similar though more severe, particularly at the higher dose levels and in the kidney, where the changes developed to a nephropathy, which included raised urea and creatinine. Marmosets also had gastrointestinal mucosal changes at 30: 9.373 to 400: 125 mg/kg.

Hypertrophy of the renal juxtaglomerular cells was also seen in rats and marmosets. All changes were considered to be caused by the pharmacological action of valsartan:hydrochlorothiazide which is synergistic (potentiation is about tenfold compared to valsartan alone) rather than additive, producing prolonged hypotension particularly in marmosets. For therapeutic doses of valsartan:hydrochlorothiazide in humans, the hypertrophy of the renal juxtaglomerular cells does not seem to have any relevance. The main preclinical safety findings are attributed to the pharmacological action of the compounds which appear to act synergistically with no evidence of any interaction between the two compounds. In the clinic, the actions of the two compounds are additive, and the preclinical findings have not been demonstrated to have any clinical significance.

The combination valsartan:hydrochlorothiazide was not tested for mutagenicity, clastogenicity, or carcinogenicity as there was no evidence for any interaction between the two compounds.

Valsartan

Preclinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity, carcinogenic potential and effects on fertility.

Safety pharmacology and Long term toxicity: In a variety of preclinical safety studies conducted in several animal species, there were no findings that would exclude the use of therapeutic doses of valsartan in humans.

In preclinical safety studies, high doses of valsartan (200 to 600 mg/kg/day body weight) caused in rats a reduction of red blood cell parameters (erythrocytes, hemoglobin, hematocrit) and evidence of changes in renal hemodynamics (slightly raised blood urea nitrogen, 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/m2 basis (calculations assume an oral dose of 320 mg/day and a 60-kg patient). In marmosets at comparable doses, the changes were similar though more severe, particularly in the kidney where the changes developed to a nephropathy including raised blood urea nitrogen 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.

Reproductive toxicity: Valsartan had no adverse effects on the reproductive performance of male or female rats at oral doses up to 200 mg/kg/day, approximately 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).

Mutagenicity: Valsartan was devoid of mutagenic potential at either the gene or chromosome level when investigated in various standard in vitro and in vivo genotoxicity studies.

Carcinogenicity: There was no evidence of carcinogenicity when valsartan was administered in the diet to mice and rats for 2 years at doses up to 160 and 200 mg/kg/day, respectively

Hydrochlorothiazide

Hydrochlorothiazide has been tested for mutagenicity, clastogenicity, reproductive performance and carcinogenicity with negative results.

According to the experimental data available, hydrochlorothiazide did not reveal evidence of carcinogenic activity in rats and mice (hepatocellular tumors in mice were only seen in the high-dosed males; the incidence did not exceed those levels historically found in controls).

The mutagenic potential was assessed in a series of in vitro and in vivo test systems. While some positive results were obtained in vitro, all in vivo studies provided negative results. Hydrochlorothiazide enhanced the UVA-induced formation of pyrimidine dimers in vitro and in the skin of mice following oral treatment. It is therefore concluded that there is no relevant mutagenic potential in vivo, although hydrochlorothiazide could enhance the genotoxic effects of UVA light.

PHARMACEUTICAL INFORMATION

Incompatibilities

Not applicable.

Storage

See folding box.

Co-Diovan should not be used after the date marked “EXP” on the pack.

Co-Diovan must be kept out of the reach and sight of children.

Instructions for use and handling

No special requirements.

Manufacturer:

See folding box.

International Package Leaflet

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Novartis Pharma AG, Basel, Switzerland