NOVARTIS

Regulatory Affairs

Co-Diovan®

(valsartan/hydrochlorothiazide)

80/12,5mg; 160/12,5mg; 160/25mg; 320/12,5mg y 320/25mg, comprimidos con cubierta pelicular

International Package Leaflet

Effective date:	03-Aug-2022
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Version:	Final

1. NAME OF THE MEDICINAL PRODUCT

Co-Diovan 80 mg/12.5 mg film-coated tablets
Co-Diovan 160 mg/12.5 mg film-coated tablets
Co-Diovan Forte 160 mg/25 mg film-coated tablets
Co-Diovan 320 mg/12.5 mg film-coated tablets
Co-Diovan Forte 320 mg/25 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 80 mg valsartan and 12.5 mg hydrochlorothiazide.
Each film-coated tablet contains 160 mg valsartan and 12.5 mg hydrochlorothiazide.
Each film-coated tablet contains 160 mg valsartan and 25 mg hydrochlorothiazide.
Each film-coated tablet contains 320 mg valsartan and 12.5 mg hydrochlorothiazide.
Each film-coated tablet contains 320 mg valsartan and 25 mg hydrochlorothiazide.

For the full list of excipients see section 6.1.

3. DOSAGE FORM

Film-coated tablets.

80 mg/12.5 mg: Light orange, oval tablet, engraved with “HGH” on one side and “CG” on the other.
160 mg/12.5 mg: Dark red, oval tablet, engraved with “HHH” on one side and “CG” on the other.
160 mg/25 mg: Brown, oval tablet, engraved with “HXH” on one side and “NVR” on the other.
320 mg/12.5 mg: Pink, oval tablet with beveled edges, engraved with “NVR” on one side and “HIL” on the other.
320 mg/25 mg: Yellow, oval tablet with beveled edges, engraved with “NVR” on one side and “CTI” on the other side.

4. CLINICAL DATA

4.1 Therapeutic indications

Treatment of essential hypertension in adults.

The fixed-dose combination Co-Diovan is indicated in patients whose blood pressure is not adequately controlled with valsartan or hydrochlorothiazide alone.

4.2 Dosage and method of administration

Dosage

The recommended dose of Co-Diovan is one film-coated tablet once daily. Individual dose adjustment with the monocomponents is recommended. In each case, individual adjustment of the monocomponents should be done up to the next dose in order to reduce the risk of hypotension and other adverse reactions.

When clinically appropriate, a direct change from monotherapy to the fixed combination may be considered in patients whose blood pressure is not adequately controlled with valsartan or hydrochlorothiazide monotherapy, and when provided that the individual dose adjustment of the monocomponents is titrated according to the recommended sequence.

Clinical response to Co-Diovan should be tested after initiation of treatment and if blood pressure remains

uncontrolled, the dose may be increased by increasing any of the components up to a maximum dose of 320 mg/25 mg Co-Diovan.

The antihypertensive effect is substantially present within 2 weeks.
In most patients, maximum effects are seen within 4 weeks. However, in some patients 4-to 8 weeks of treatment may be needed. This should be considered during dose titration.

Co-Diovan (320 mg/25 mg only)
If no relevant additional effect is seen after 8 weeks of Co-Diovan Forte 320 mg/25 mg treatment, an additional or alternative antihypertensive medicinal product should be considered (see sections 4.3, 4.4, 4.5 and 5.1).

Method of delivery

Co-Diovan may be taken with or without food and should be administered with water.

Special populations

Patients with renal failure
No dosage titration is required in patients with mild to moderate renal failure (Glomerular Filtration Rate (GFR) ≥30 mL/min). Due to the hydrochlorothiazide component, Co-Diovan is contraindicated in patients with severe renal failure (GFR <30 mL/min) and anuria (see sections 4.3, 4.4 and 5.2).

Patients with liver failure
In patients with mild to moderate liver failure without cholestasis, the dose of valsartan should not exceed 80 mg (see section 4.4). No dose titration of hydrochlorothiazide is required in patients with mild to moderate liver failure. Due to the valsartan component, Co-Diovan is contraindicated in patients with severe liver failure together or biliary cirrhosis and cholestasis (see sections 4.3, 4.4 and 5.2).

Elderly patients
No dosage titration is required in elderly patients.

Pediatric patients
Co-Diovan is not recommended for use in children under 18 years of age due to a lack of data on safety and efficacy.

4.3 Contraindications

- Hypersensitivity to the active substances, other drugs derived from sulfonamide or to any of the excipients listed in section 6.1.
- Second and third trimesters of pregnancy (see sections 4.4 and 4.6).
- Severe liver failure, biliary cirrhosis and cholestasis.
- Severe renal failure (creatinine clearance <30 mL/min), anuria.
- 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 failure (GFR <60 mL/min/1.73 m^2) (see sections 4.5 and 5.1).

4.4 Special warnings and precautions for use

Serum electrolyte abnormalities
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
Hypokalemia has been reported during treatment with thiazide diuretics, including hydrochlorothiazide. Frequent monitoring of serum potassium is recommended.
Hyponatremia and hypochloremic alkalosis have been associated with treatment with thiazide diuretics, including hydrochlorothiazide. Thiazides, including hydrochlorothiazide, boost urinary excretion of magnesium, which may lead to hypomagnesemia. The excretion of calcium is reduced with thiazide diuretics, which may lead to hypercalcemia.
In patients 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.

Patients who are severely sodium and/or volume depleted, such as those receiving high doses of diuretics, may in rare cases experience symptomatic hypotension after initiation of therapy with Co-Diovan. Sodium and/or volume depletion should be corrected before treatment with Co-Diovan.

Patients with severe chronic heart failure or other clinical 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 azotemia and in rare cases with acute renal failure and/or death. Evaluation of patients with heart failure or myocardial infarction should always include assessment of renal function. The use of Co-Diovan has not been established in patients with severe chronic heart failure.

Therefore, it cannot be excluded that due to the inhibition of the renin-angiotensin-aldosterone system, the delivery of Co-Diovan may also be associated with impaired renal function. Co-Diovan should not be used in these patients.

Renal artery stenosis
Co-Diovan should not be used to treat hypertension in patients with bilateral or unilateral renal artery stenosis in patients with a single kidney since blood urea and serum creatinine may increase in such patients.

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

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

Renal failure
No dose titration is necessary in patients with renal failure with creatinine clearance ≥30 mL/min (see section 4.2). Periodic monitoring of serum potassium, creatinine and uric acid levels is recommended when Co-Diovan is used in patients with renal failure.

Renal transplant
To date, there is no experience on the safe use of Co-Diovan in patients who have had a recent kidney transplantation.

Liver failure
In patients with mild to moderate liver failure without cholestasis, Co-Diovan should be used with caution (see sections 4.2 and 5.2). Thiazides should be used with caution in patients with impaired liver function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate ammoniagenic 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. Co-Diovan should be discontinued immediately in patients who develop angioedema, and Co-Diovan should not be re-administered in these patients (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 titrations of insulin or oral hypoglycemic agents may be required.

Thiazides may decrease urinary calcium excretion and cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evidence of underlying hyperparathyroidism. Thiazides should be discontinued before performing parathyroid function tests.

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

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

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

Choroidal Effusion, Acute Myopia and Secondary Acute Angle-Closure Glaucoma
Hydrochlorothiazide is a sulfonamide which has been associated with an idiosyncratic reaction resulting in choroidal effusion with visual field defect, acute transient myopia and acute angle-closure glaucoma. Symptoms include acute development of decreased visual acuity or ocular pain and typically occur over a period of time ranging from several hours to several weeks from baseline delivery of the drug. Untreated acute angle-closure glaucoma can lead to permanent loss of vision.

The main treatment is immediate discontinuation of hydrochlorothiazide. Medical or surgical treatment may need to be considered promptly if 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 antagonists or aliskiren increases the risk of hypotension, hyperkalemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE inhibitors, angiotensin II receptor antagonists or aliskiren is therefore not recommended (see sections 4.5 and 5.1).
If dual blockade therapy is considered essential, 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 antagonists 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 exposure of hydrochlorothiazide has been observed in two epidemiological studies based on the Danish National Cancer Registry. Photosensitizing effects 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 are to be advised to the patients in order to minimize the risk of skin cancer. Suspicious skin lesions should be promptly evaluated, including histological analyzes of biopsies. In addition, the use of hydrochlorothiazide may need to be reconsidered in patients who have previously experienced NMSC (see also section 4.8).

Acute respiratory toxicity
Very rare severe cases of acute respiratory toxicity, including acute respiratory distress syndrome (ARDS) have been reported after taking hydrochlorothiazide. Pulmonary edema usually occurs within minutes to a few hours after taking hydrochlorothiazide. At the initiation of treatment, symptoms include dyspnea, fever, pulmonary failure and hypotension. If a diagnosis of ARDS is suspected, Co-Diovan should be discontinued and appropriate treatment given. Patients who have previously experienced ARDS should not be given hydrochlorothiazide after taking this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Interactions related to valsartan and hydrochlorothiazide

Concomitant use not recommended
Lithium
Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant delivery of lithium with ACE inhibitors, angiotensin II receptor antagonists or thiazides, including hydrochlorothiazide. Since renal clearance of lithium is reduced by thiazides, the risk of lithium toxicity may presumably be increased further with Co-Diovan. If the combination proves necessary, careful monitoring of serum lithium levels is recommended.

Concomitant use requiring caution
Other antihypertensive agents
Co-Diovan may increase the effects of other agents with antihypertensive properties (e.g., guanethidine, methyldopa, vasodilators, ACE inhibitor, AIIRAs, beta blockers, calcium channel blockers, and dopamine reuptake inhibitors).

Pressor amino-functional compounds (e.g., noradrenaline, adrenaline)
Potential decrease in response to pressor amino-functional compounds. The clinical relevance of this effect is uncertain and not sufficient to preclude their use.

Non-steroidal anti-inflammatory medicinal products (NSAIDs), including selective COX-2 inhibitors, acetylsalicylic acid (>3 g/day), and non-selective NSAIDs
NSAIDs may down-regulate the antihypertensive effect of angiotensin II antagonists and hydrochlorothiazide when administered simultaneously. In addition, concomitant use of Co-Diovan and NSAIDs may result in compromised renal function and an increase in serum potassium. Therefore, monitoring of renal function at the initiation 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 AIIRAs, ACE inhibitors or aliskiren
Clinical trial data has shown that dual blockade of the renin-angiotensin-aldosterone system (RAAS) through the combined use of ACE inhibitors, angiotensin II receptor antagonists or aliskiren is associated with a higher incidence of adverse events such as hypotension, hyperkalemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent (see sections 4.3, 4.4 and 5.1).

Concomitant use not recommended
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 indicate that valsartan is a substrate of the hepatic uptake transporter OATP1B1/OATP1B3 and the hepatic efflux transporter MRP2. The clinical relevance of this finding is unknown. Co-administration of inhibitors of the uptake transporter (e.g., rifampicin, cyclosporine) or efflux transporter (e.g., ritonavir) may increase the systemic exposure to valsartan. Exercise due care when initiating or ending concomitant treatment with these drugs.

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

Interactions related to hydrochlorothiazide

Concomitant use requiring caution
Medicinal products affecting serum potassium levels
The hypokalemic effect of hydrochlorothiazide may be enhanced by concomitant delivery of kaliuretic diuretics, corticosteroids, laxatives, ACTH, amphotericin, carbenoxolone, penicillin G, salicylic acid and their derivatives.
Monitoring of serum potassium is recommended if these medicinal products are to be prescribed with the hydrochlorothiazide-valsartan combination (see section 4.4).

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

Medicinal products affecting serum sodium levels
The hyponatremic effect of diuretics may be intensified by concomitant delivery of medicinal products such as antidepressants, antipsychotics, antiepileptics, etc. Caution is recommended during long-term delivery of these medicinal products.

Digitalis glycosides
Thiazide-induced hypokalemia or hypomagnesemia may occur as undesirable effects, favoring the onset of digitalis-induced cardiac arrhythmias (see section 4.4).

Calcium and vitamin D salts
Administration of thiazide diuretics, including hydrochlorothiazide, with vitamin D or with calcium salts may enhance the rise in serum calcium levels. Concomitant use of thiazide-type diuretics with calcium salts may cause hypercalcemia in patients predisposed to hypercalcemia (e.g., hyperparathyroidism, tumors or vitamin D-mediated conditions) by increasing tubular calcium reabsorption.

Antidiabetic agents (oral agentsand insulin)
Thiazides may alter glucose tolerance. The dose titration of the antidiabetic medicinal product may be necessary.
Metformin should be used with caution due to 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 hyperglycemia. Thiazide diuretics, including hydrochlorothiazide, may increase the hyperglycemic effect of diazoxide.

Medicines used to treat gout (probenecid, sulfinpyrazone and allopurinol)
Dose titration of uricosuric medication may be necessary as hydrochlorothiazide may raise the level of serum uric acid. Increase in 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 that may alter 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, prokinetic medicinal products such as cisapride are anticipated to 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 and colestipol. This could lead to a sub-therapeutic effect of thiazide diuretics. However, by spacing doses of hydrochlorothiazide and resins by administering hydrochlorothiazide at least 4 hours before or between 4 and 6 hours after the administration of resins, this interaction could potentially be minimized.

Cytotoxic agents
Thiazides, including hydrochlorothiazide, may reduce the renal excretion of cytotoxic agents (e.g., cyclophosphamide, methotrexate) and enhance their myelosuppressive effects.

Non-depolarizing skeletal muscle relaxants (e.g., tubocurarine)
Thiazides, including hydrochlorothiazide, enhance the action of musculoskeletal relaxants such as curare derivatives.

Cyclosporine
Concomitant treatment with cyclosporine may increase the risk of hyperuricemia and gout-type complications.

Alcohol, barbiturates or narcotics
Concomitant delivery of thiazide diuretics with substances that lower blood pressure (e.g., by reducing sympathetic nervous system activity or direct vasodilatation activity) may enhance postural hypotension.

Methyldopa
There have been isolated reports of hemolytic anemia in patients receiving concomitant methyldopa and hydrochlorothiazide.

Iodinated contrast agents
In case of diuretic-induced dehydration, there is an increased risk of acute renal failure, especially with high doses of the iodinated product. Patients must be rehydrated prior to administration.

4.6 Fertility, pregnancy and lactation

Pregnancy

Valsartan

The use of AIIRAs is not recommended during the first trimester of pregnancy (see section 4.4). The use of AIIRAs is contraindicated during the second and third trimesters of pregnancy (see sections 4.3 and 4.4).

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

AIIRAs therapy exposure during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalemia); (see section 5.3).
Should exposure to AIIRAs have occurred from the second trimester of pregnancy, an ultrasound check of renal function and skull is recommended.

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

Hydrochlorothiazide
There is limited experience with hydrochlorothiazide during pregnancy, especially during the first trimester. Animal studies are not sufficient. Hydrochlorothiazide crosses the placenta. Based on the pharmacological mechanism of action of hydrochlorothiazide, its use during the second and third trimesters may compromise placental perfusion of the fetus and may cause fetal and neonatal effects such as jaundice, electrolyte balance disturbances and thrombocytopenia.

Lactation

There is no information regarding the use of valsartan during lactation. Hydrochlorothiazide is excreted in human milk. Therefore, it is recommended that Co-Diovan is not administered during this period. It is preferable to switch to a treatment which is known to have a better safety profile during nursing, especially in newborns or preterm infants.

4.7 Effects on ability to drive and use machines

No studies of the effects of Co-Diovan on the ability to drive and use machines have been performed. When driving vehicles or operating machines it should be taken into account that occasionally dizziness or fatigue may occur.

4.8 Adverse reactions

Adverse drug reactions are listed below by system organ class and the most common laboratory findings reported with valsartan plus hydrochlorothiazide versus placebo or from individual post-marketing case reports. Adverse drug reactions may occur during treatment with valsartan/hydrochlorothiazide due to the delivery of only one of the components, even if not observed in clinical trials.

Adverse drug reactions

The following adverse reactions are classified based on incidence, with the most common first, according to the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100); (≥1/10,000 to <1/1,000), very rare (<1/10,000) or incidence not known (cannot be estimated from the available data).

Within each incidence range, adverse drug reactions are listed in decreasing order of severity.

Table 1. Incidence of adverse reactions with valsartan/hydrochlorothiazide

Metabolism and nutrition disorders	
Uncommon	Dehydration
Nervous system disorders	
Very rare	Dizziness
Uncommon	Paresthesia
Incidence not known	Loss of consciousness
Eye disorders	
Uncommon	Blurred vision
Ear and labyrinth disorders	
Uncommon	Tinnitus
Vascular disorders	
Uncommon	Hypotension
Respiratory, thoracic and mediastinal disorders	
Uncommon	Cough
Incidence not known	Pulmonary edema of noncardiogenic origin
Gastrointestinal disorders	
Very rare	Diarrhea
Musculoskeletal and connective tissue disorders	
Uncommon	Myalgia
Very rare	Arthralgia
Kidney and urinary disorders	
Incidence not known	Compromised renal function
General disorders and delivery site conditions	
Uncommon	Fatigue
Complementary examinations	
Incidence not known	Increased serum uric acid levels, increased serum creatinine and bilirubin, hypokalemia, hyponatremia, increased blood urea nitrogen, neutropenia

Additional information on the individual components

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

Table 2. Incidence of adverse reactions with valsartan

Blood and lymphoid system disorders	
Incidence not known	Decreased hemoglobin levels, decreased hematocrit, thrombocytopenia
Immune system disorders	
Incidence not known	Other hypersensitivity/allergic reactions including serum sickness
Metabolism and nutrition disorders	
Incidence not known	Increased serum potassium levels, hyponatremia
Ear and labyrinth disorders	
Uncommon	Vertigo
Vascular disorders	
Incidence not known	Vasculitis
Gastrointestinal disorders	
Uncommon	Abdominal pain
Hepatobiliary disorders	
Incidence not known	Elevation of liver function values
Skin and subcutaneous tissue disorders	
Incidence not known	Angioedema, bullous dermatitis, rash, itching
Kidney and urinary disorders	
Incidence not known	Renal failure

Table 3. Incidence of adverse reactions with hydrochlorothiazide

Hydrochlorothiazide has been widely prescribed for many years, commonly at higher doses than those administered with Co-Diovan. The following adverse reactions have been reported in patients treated with thiazide diuretics alone, including hydrochlorothiazide:

Benign, malignant and unspecified neoplasms (including cysts and polyps)	
Incidence not known	Non-melanoma skin cancer (basal cell carcinoma and squamous cell carcinoma)
Blood and lymphoid system disorders	
Rare	Thrombocytopenia, sometimes with purpura
Very rare	Agranulocytosis, leucopenia, hemolytic anemia, bone marrow failure
Incidence not known	Aplastic anemia
Immune system disorders	
Very rare	Hypersensitivity reactions
Metabolism and nutrition disorders	
Very common	Hypokalemia increased lipids in the blood (mostly at high doses)
Common	Hyponatremia, hypomagnesemia, hyperuricemia
Rare	Hypercalcemia, hyperglycemia, glycosuria and worsening of diabetic metabolic state
Very rare	Hypochloremic alkalosis
Psychiatric disorders	
Rare	Depression, sleep disorders
Nervous system disorders	
Rare	Headache, dizziness, paresthesia
Eye disorders	
Rare	Vision impairment
Incidence not known	Choroidal effusion, Acute angle-closure glaucoma
Heart disorders	
Rare	Cardiac arrhythmias

Vascular disorders	
Common	Postural hypotension
Respiratory, thoracic and mediastinal disorders	
Very rare	Acute Respiratory Distress Syndrome (ARDS) (see section 4.4), respiratory distress including pneumonitis and pulmonary edema
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
Kidney and urinary disorders	
Incidence not known	Renal impairment, Acute renal failure
Skin and subcutaneous tissue disorders	
Common	Urticaria and other forms of skin rash
Rare	Photosensitization
Very rare	Necrotizing vasculitis and toxic epidermal necrolysis, cutaneous lupus erythematosus-like reactions, reactivation of cutaneous lupus erythematosus
Incidence not known	Erythema multiforme
General disorders and delivery site conditions	
Incidence not known	Pyrexia, asthenia
Musculoskeletal and connective tissue disorders	
Incidence not known	Muscle spasms
Reproductive system and breast disorders	
Common	Impotence

Description of selected adverse reactions

Non-melanoma skin cancer: based on available data from epidemiological studies, cumulative dose-dependent association between hydrochlorothiazide and NMSC has been observed (see also sections 4.4 and 5.1).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after clearance of the medicinal product is important. It allows continued monitoring of the benefit/risk ratio of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Sistema Español de Farmacovigilancia de Medicamentos de Uso Humano [Spanish Pharmacovigilance System for Medicinal Products for Human Use] https://www.notificaram.es.

4.9 Overdose

Symptoms

Overdose with valsartan may result in marked hypotension, which could lead to a 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, hypovolemia, 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; stabilization of the circulatory condition is of the utmost importance.

If hypotension occurs, the patient should be placed in a supine position, and salt and volume supplements should be given promptly.

Valsartan cannot be removed by hemodialysis because of its strong plasma protein binding, but hydrochlorothiazide can be removed by dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Valsartan/hydrochlorothiazide

80 mg/12.5 mg only:
In a double-blind, randomized, active-controlled study in patients not adequately controlled with 12.5 mg hydrochlorothiazide, significantly greater reductions in mean systolic/diastolic BP were seen with valsartan/hydrochlorothiazide 80/12.5 mg (14.9/11.3 mmHg) compared to hydrochlorothiazide 12.5 mg (5.2/2.9 mmHg) and hydrochlorothiazide 25 mg (6.8/5.7 mmHg). In addition, a significantly higher percentage of patients responded to treatment (diastolic BP <90 mmHg or ≥10 mmHg reduction) with valsartan/hydrochlorothiazide 80/12.5 mg (60%) compared to hydrochlorothiazide 12.5 mg (25%) and hydrochlorothiazide 25 mg (27%).

In a double-blind, randomized, active-controlled study in patients not adequately controlled with 80 mg of valsartan, significantly greater reductions in mean systolic/diastolic BP were seen with the combination of valsartan/hydrochlorothiazide 80/12.5 mg (9.8/8.2 mmHg) compared to valsartan 80 mg (3.9/5.1 mmHg) and valsartan 160 mg (6.5/6.2 mmHg). In addition, a significantly higher percentage of patients responded (diastolic BP <90 mmHg or ≥10 mmHg reduction) with valsartan/hydrochlorothiazide 80/12.5 mg (51%) compared to valsartan 80 mg (36%) and valsartan 160 mg (37%).

In a double-blind, randomized, placebo-controlled, factorial-design trial comparing various doses of valsartan/hydrochlorothiazide combinations with their respective components, significantly greater reductions in mean systolic/diastolic BP were observed with valsartan/hydrochlorothiazide 80/12.5 mg (16.5/11.8 mmHg) compared to placebo (1.9/4.1 mmHg) and with hydrochlorothiazide 12.5 mg (7.3/7.2 mmHg) and valsartan 80 mg (8.8/8.6 mmHg). In addition, a significantly higher percentage of patients responded (diastolic BP <90 mmHg or ≥10 mmHg reduction) with valsartan/hydrochlorothiazide 80/12.5 mg (64%) compared to placebo (29%) and hydrochlorothiazide (41%).

160 mg/12.5 mg and 160 mg/25 mg only:
In a double-blind, randomized, active-controlled study in patients not adequately controlled with 12.5 mg hydrochlorothiazide, significantly greater reductions in mean systolic/diastolic BP were seen with valsartan/hydrochlorothiazide 160/12.5 mg (12.4/7.5 mmHg) compared to hydrochlorothiazide 25 mg (5.6/2.1 mmHg). In addition, a significantly higher percentage of patients responded (BP <140/90 mmHg or SBP reduction ≥20 mmHg or DBP reduction ≥10 mmHg) with valsartan/hydrochlorothiazide 160/12.5 mg (50%) compared to hydrochlorothiazide 25 mg (25%).

In a double-blind, randomized, active-controlled study in patients not adequately controlled with 160 mg valsartan, significantly greater reductions in mean systolic/diastolic BP were seen with the combination of valsartan/hydrochlorothiazide 160/25 mg (14.6/11.9 mmHg) and valsartan/hydrochlorothiazide 160/12.5 mg (12.4/10.4 mmHg) compared to valsartan 160 mg (8.7/8.8 mmHg). The difference in BP reductions between the 160/25 mg and 160/12.5 mg doses also reached statistical significance. In addition, a significantly higher percentage of patients responded (diastolic BP <90 mmHg or ≥10 mmHg reduction) with valsartan/hydrochlorothiazide 160/25 mg (68%) and 160/12.5 mg (62%) compared to valsartan 160 mg (49%).

In a double-blind, randomized, placebo-controlled, factorial-design trial comparing various doses of valsartan/hydrochlorothiazide combinations with their respective components, significantly greater reductions in mean systolic/diastolic BP were observed with the combination of valsartan/hydrochlorothiazide 160/12.5 mg (17.8/13.5 mmHg) and 160/25 mg (22.5/15.3 mmHg) compared to placebo (1.9/4.1 mmHg) and the respective monotherapies, for example, hydrochlorothiazide 12.5 mg (7.3/7.2), hydrochlorothiazide 25 mg (12.7/9.3 mmHg) and valsartan 160 mg (12.1/9.4 mmHg). In addition, a significantly higher percentage of patients responded (diastolic BP <90 mmHg or ≥10 mmHg reduction) with valsartan/hydrochlorothiazide 160/25 mg (81%) and valsartan/hydrochlorothiazide 160/12.5 mg (76%) compared to placebo (29%) and the respective monotherapies, e.g., hydrochlorothiazide 12.5 mg (41%), hydrochlorothiazide 25 mg (54%), and valsartan 160 mg (59%).

320 mg/12.5 mg and 320 mg/25 mg only:
In a double-blind, randomized, active-controlled study in patients not adequately controlled with 320 mg valsartan, significantly greater reductions in mean systolic/diastolic BP were seen with the combination of valsartan/hydrochlorothiazide 320/25 mg (15.4/10.4 mmHg) and valsartan/hydrochlorothiazide 320/12.5 mg (13.6/9.7 mmHg) compared to valsartan 320 mg (6.1/5.8 mmHg). The difference in BP reductions between the 320/25 mg and 320/12.5 mg doses also reached statistical significance. In addition, a significantly higher percentage of patients responded (diastolic BP <90 mmHg or ≥10 mmHg reduction) with valsartan/hydrochlorothiazide 320/25 mg (75%) and 320/12.5 mg (69%) compared to valsartan 320 mg (53%).

In a double-blind, randomized, placebo-controlled, factorial-design trial comparing various doses of valsartan/hydrochlorothiazide combinations with their respective components, significantly greater reductions in mean systolic/diastolic BP were observed with the combination of valsartan/hydrochlorothiazide 320/12.5 mg (21.7/15.0 mmHg) and 320/25 mg (24.7/16.6 mmHg) compared to placebo (7.0/5.9 mmHg) and the respective monotherapies, for example, hydrochlorothiazide 12.5 mg (11.1/9.0 mmHg), hydrochlorothiazide 25 mg (14.5/10.8 mmHg) and valsartan 320 mg (13.7/11.3 mmHg). In addition, a significantly higher percentage of patients responded (diastolic BP <90 mmHg or ≥10 mmHg reduction) with 320/25 mg (85%) and 320/12.5 mg (83%) of valsartan/hydrochlorothiazide compared to placebo (45%) and the respective monotherapies, e.g., hydrochlorothiazide 12.5 mg (60%), hydrochlorothiazide 25 mg (66%), and valsartan 320 mg (69%).

80 mg/12.5 mg, 160 mg/12.5 mg, 160 mg/25 mg, 320 mg/12.5 mg and 320 mg/25 mg:
Dose-related decreases in serum potassium occurred in controlled clinical trials with valsartan + hydrochlorothiazide. Reduction of serum potassium occurred more frequently in patients receiving 25 mg of hydrochlorothiazide than in those receiving 12.5 mg of hydrochlorothiazide. The potassium-sparing effect of valsartan down-regulated hydrochlorothiazide in controlled clinical trials with valsartan/hydrochlorothiazide.

The beneficial effects of valsartan in combination with hydrochlorothiazide on cardiovascular morbidity and mortality are currently unknown.
Epidemiological studies have shown that long term treatment with hydrochlorothiazide reduces the risk of cardiovascular morbidity and mortality.

Valsartan
Valsartan is an orally active, potent and specific angiotensin II (Ang II) receptor antagonist. It acts selectively on the receptor subtype AT1, which is responsible for the known actions of angiotensin II. The increased plasma levels of Ang II following AT1 receptor blockade with valsartan may stimulate the unblocked AT2 receptor, which appears to offset the effect of the AT1 receptor. Valsartan does not exhibit any partial agonist activity at the AT1 receptor and has much (about 20,000 fold) greater affinity for the AT1 receptor than for the AT2 receptor. Valsartan does not 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 maximization of bradykinin or substance P, angiotensin

II antagonists are unlikely to be associated with coughing. In clinical trials where valsartan was compared with an ACE inhibitor, the incidence of a dry cough was significantly lower (P <0.05) 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 a cough compared to 68.5% of those treated with an ACE inhibitor (P <0.05).

The delivery of valsartan to hypertensive patients down-regulates blood pressure without affecting the heart rate. In most patients, after delivery of a single oral dose, onset of antihypertensive activity occurs in the first 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 delivery, the maximum reduction in blood pressure usually occurs within 2-4 weeks with all doses and is sustained during long-term therapy. If hydrochlorothiazide is added, a significant additional reduction in blood pressure is observed.

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

In hypertensive patients with type 2 diabetes and microalbuminuria, valsartan has been shown to reduce the urinary excretion of albumin. The MARVAL (Micro Albuminuria Reduction with Valsartan) study tested the reduction in urinary albumin excretion (UAE) with valsartan (80-160 mg/once daily) versus amlodipine (5-10 mg/once daily), in 332 type 2 diabetic patients (mean age: 58 years; 265 men) with microalbuminuria (valsartan: 58 µg/min; amlodipine: 55.4 µg/min), normal or high blood pressure and preserved renal function (blood creatinine <120 µmol/l). At 24 weeks, UAE was reduced (p <0.001) by 42% (-24.2 µg/min; 95% CI: -40.4 to -19.1) for valsartan and by approximately 3% (-1.7 µg/min; 95% CI: -5.6 to 14.9) with amlodipine despite similar rates of blood pressure reduction in both groups. The Diovan Reduction of Proteinuria (DROP) study also examined the efficacy of valsartan in reducing UAE in 391 hypertensive patients (BP = 150/88 mmHg) with type 2 diabetes, albuminuria (mean = 102 µg/min; 20-700 µg/min) and preserved renal function (mean serum creatinine = 80 µmol/l). Patients were randomized to one of 3 doses of valsartan (160, 320, and 640 mg/once daily) and treated for 30 weeks. The purpose of the study was to determine the optimal dose of valsartan for reducing UAE in hypertensive patients with type 2 diabetes. At 30 weeks, the percentage change in UAE was significantly reduced by 36% from baseline with valsartan 160 mg (95% CI: 22 to 47%), and by 44% for valsartan 320 mg (95% CI: 31 to 54%). It was concluded that 160-320 mg of valsartan produced clinically relevant reductions in UAE in hypertensive patients with type 2 diabetes.

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

ONTARGET was a study conducted in patients with a history of cardiovascular or cerebrovascular disease, or type 2 diabetes mellitus accompanied by evidence of target organ damage. VA NEPHRON-D was a study in patients with type 2 diabetes mellitus and diabetic nephropathy.
These studies showed no significant benefit on renal and/or cardiovascular findings and mortality, while an increased risk of hyperkalemia, acute kidney injury and/or hypotension compared to monotherapy was observed. Given their similar pharmacodynamic properties, these results are also appropriate for other ACE inhibitors and AIIRAs.
ACE inhibitors and AIIRAs should therefore not be used concomitantly in patients with diabetic nephropathy.

ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints) was a study designed to test the benefit of adding aliskiren to a standard therapy of an ACE inhibitor or an AIIRA in patients with type 2 diabetes mellitus and chronic kidney disease, cardiovascular disease, or both. The study was terminated early due to an increased risk of adverse findings. Cardiovascular death and stroke were both numerically more common in the aliskiren group than in the placebo group, and adverse events

and serious adverse events of interest (hyperkalemia, hypotension and renal impairment) were more frequently reported in the aliskiren group than in the placebo group.

Hydrochlorothiazide
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 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- transport system, perhaps by competing for the Cl- site, thus affecting electrolyte reabsorption mechanisms: directly increasing sodium and chloride excretion to an approximately equal extent, and indirectly by this diuretic action, reducing plasma volume and consequent increases in plasma renin activity, aldosterone secretion, urinary potassium loss and a decrease in serum potassium. Renin-aldosterone binding is mediated by angiotensin II, such that under concomitant delivery of valsartan, the reduction in serum potassium is less pronounced than that observed with hydrochlorothiazide monotherapy.

Non-melanoma skin cancer:
Based on available data from epidemiological studies, cumulative dose-dependent association between hydrochlorothiazide and NMSC has been observed. One study included a population consisting of 71,533 cases of BCC and 8,629 cases of SCC matched to 1,430,833 and 172,462 population controls, respectively. High hydrochlorothiazide use (≥50,000 mg cumulative) was associated with an adjusted Odds Ratio (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 hydrochlorothiazide: 633 cases of lip cancer were matched with 63,067 population controls using a risk-based sampling strategy. A cumulative dose-response relationship was demonstrated with an adjusted OR of 2.1 (95% CI: 1.7-2.6) which increased to an OR of 3.9 (3.0-4.9) for high doses (~25,000 mg) and an OR of 7.7 (5.7-10.5) for the highest cumulative dose (~100,000 mg) (see also section 4.4).

5.2 Pharmacokinetic properties

Valsartan/hydrochlorothiazide
The systemic availability of hydrochlorothiazide is decreased by approximately 30% when co-administered with valsartan. The kinetics of valsartan did not change markedly with concomitant delivery of hydrochlorothiazide. This interaction does not affect the combined use of valsartan and hydrochlorothiazide, because controlled clinical trials have shown an apparent antihypertensive effect, greater than that obtained with each active substance alone or with dosing of placebo.

Valsartan
Absorption
Following oral dosing of valsartan monotherapy, peak plasma concentrations of valsartan are reached in 2-4 hours. Mean absolute bioavailability is 23%. Food decreases the exposure (as measured by AUC) to valsartan by approximately 40% and peak plasma concentration (Cmax) by approximately 50%, although from approximately 8 hours post dosing plasma valsartan concentrations are similar for the groups that were receiving the medicinal product when fasting or with food. This decrease in AUC is not, however, accompanied by a clinically significant decrease in the therapeutic effect, and valsartan can therefore be administered with or without food.

Distribution
The steady-state volume of distribution of valsartan after intravenous delivery is about 17 liters, indicating that valsartan is not distributed 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 (t½α <1 h and t½ß about 9 h). Valsartan is primarily eliminated in feces (about 83% of the dose) and urine (about 13% of the dose), mostly as an unmodified compound. Following intravenous delivery, plasma clearance is approximately 2 l/h and its renal clearance is 0.62 l/h (approximately 30% of total clearance). The half-life of valsartan is 6 hours.

Hydrochlorothiazide
Absorption
Absorption of hydrochlorothiazide is acute (tmax approx. 2 hours) after an oral dose. The increase in mean AUC is linear and dose proportional in the therapeutic range.
The effect of food on the absorption of hydrochlorothiazide, if any, has minimal clinical significance. After oral dosing, the absolute bioavailability of hydrochlorothiazide is 70%.

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 an unchanged compound. Hydrochlorothiazide is eliminated from plasma with a half-life of 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 unmodified compound in the urine. The renal clearance consists of passive filtration and active secretion into the renal tubule.

Special populations

Elderly patients
Some elderly people have somewhat higher systemic exposure to valsartan than younger subjects; however, this has not been shown to have any clinical significance.
Limited findings suggest that the systemic clearance of hydrochlorothiazide is reduced in both healthy and hypertensive elderly subjects when compared to young healthy volunteers.

Renal failure
No dose titration is required in patients with a Glomerular Filtration Rate (GFR) of 30-70 mL/min at the recommended dose of Co-Diovan.

No data are available for Co-Diovan administered in patients with severe renal failure (GFR <30 mL/min) or in patients undergoing dialysis. Valsartan is highly bound to plasma proteins and cannot be removed by dialysis, whereas hydrochlorothiazide can be.

In the presence of renal failure, the 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 failure, a 3-fold higher AUC has been observed for hydrochlorothiazide. In patients with severe renal failure, an 8-fold higher AUC has been observed. Hydrochlorothiazide is contraindicated in patients with severe renal failure (see section 4.3).

Liver failure
In a pharmacokinetic study in patients with mild (n=6) to moderate (n=5) hepatic impairment, valsartan exposure was shown to increase approximately 2-fold compared to healthy volunteers (see sections 4.2 and 4.4).

There are no data available for the use of valsartan in patients with severe liver impairment (see section 4.3). Hepatic disease does not significantly affect the pharmacokinetics of hydrochlorothiazide.

5.3 Preclinical safety data

The potential toxicity of the combination of valsartan - hydrochlorothiazide after oral dosing was investigated in rats and marmoset monkeys in studies of up to six months duration. No findings emerged that excluded its use at therapeutic doses in humans.

The changes caused by the combination in chronic toxicity studies appear to be probably caused by valsartan. The toxicological target organ was the kidney, the reaction being more pronounced in marmoset monkeys than in rats. The combination resulted in renal lesion (nephropathy with tubular basophilia, increases in plasma urea, plasma creatinine and serum potassium, increases in urine volume and urinary electrolytes from valsartan 30 mg/kg/day + hydrochlorothiazide 9 mg/kg/day in rats and 10 + 3 mg/kg/day in marmoset monkeys), likely due to impaired renal hemodynamics. These doses in rats account for respectively 0.9 and 3.5 times the maximum recommended human dose (MRHD) of valsartan and hydrochlorothiazide on a mg/m2 basis. These doses in marmosets account for respectively 0.3 and 1.2 times the maximum recommended human dose (MRHD) of valsartan and hydrochlorothiazide on a mg/m2 basis. (Calculations consider an oral dose of 320 mg/day of valsartan in combination with 25 mg/day of hydrochlorothiazide and a 60 kg patient).

High doses of the valsartan-hydrochlorothiazide combination caused decreases in red blood cell indices (erythrocyte count, hemoglobin, hematocrit, from 100 + 31 mg/kg/day in rats and 30 + 9 mg/kg/day in marmoset monkeys). These doses in rats account for respectively 3.0 and 12 times the maximum recommended human dose (MRHD) of valsartan and hydrochlorothiazide on a mg/m2 basis. These doses in marmosets account for respectively 0.9 and 3.5 times the maximum recommended human dose (MRHD) of valsartan and hydrochlorothiazide on a mg/m2 basis. (Calculations consider an oral dose of 320 mg/day of valsartan in combination with 25 mg/day of hydrochlorothiazide and a 60 kg patient).

In marmoset monkeys, damage to the gastric mucosa was noted (from 30 + 9 mg/kg/day). The combination also resulted in hyperplasia of the renal afferent arterioles (at 600 + 188 mg/kg/day in rats and from 30 + 9 mg/kg/day in marmosets). These doses in marmosets account for respectively 0.9 and 3.5 times the maximum recommended human dose (MRHD) of valsartan and hydrochlorothiazide based on mg/m2. These doses in rats account for respectively 18 and 73 times the maximum recommended human dose (MRHD) of valsartan and hydrochlorothiazide on a mg/m2 basis. (Calculations consider an oral dose of 320 mg/day of valsartan in combination with 25 mg/day of hydrochlorothiazide and a 60 kg patient).

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

The valsartan - hydrochlorothiazide combination was not studied for mutagenicity, chromosome breakage or carcinogenicity since there was no evidence of interaction between the two substances. However, these tests were performed separately with valsartan and hydrochlorothiazide and did not show evidence of mutagenicity, chromosomal breakage or carcinogenicity.

In rats, maternally toxic doses (600 mg/kg/day) during the last days of gestation and lactation led to lower survival, lower weight gain and delayed development (pinna detachment and ear-canal opening) in the offspring (see section 4.6). These doses in rats (600 mg/kg/day) are approximately 18 times the maximum recommended human dose on a mg/m2 basis (calculations assume an oral dose of 320 mg/day and a 60-kg patient). Similar findings were observed with valsartan/hydrochlorothiazide in rats and rabbits. In embryo-fetal development (segment II) studies with valsartan/hydrochlorothiazide in rats and rabbits, there was no evidence of teratogenicity, but fetotoxicity associated with maternal toxicity was observed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Microcrystalline cellulose
Colloidal anhydrous silica
Crospovidone
Magnesium stearate

Coating:

Hypromellose
Macrogol 8000
Talc
Iron oxide red (E 172)
Iron oxide yellow (E172)
Titanium dioxide (E 171)
Iron oxide black (E 172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

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

MARKETING AUTHORIZATION HOLDER

Novartis Pharma AG

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