

פורמט עלון זה נקבע ע"י משרד הבריאות ותוכנו נבדק ואושר על ידו במאי 2009.

CO-DIOVAN[®]

(valsartan + hydrochlorothiazide)

80/12.5 mg, 160/12.5 mg, 160/25 mg Film-coated tablets

Prescribing Information

1 Name of the medicinal product

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

2 Qualitative and quantitative composition

Active substances: (S)-N-valeryl-N-{{2'-(1H-tetrazol-5-yl)biphenyl-4-yl}methyl}-valine (INN = valsartan) and 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide-1,1-dioxide (= hydrochlorothiazide).

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.

For a full list of excipients, see section 6.1 List of excipients.

3 Pharmaceutical form

Film-coated tablets 80/12.5 mg, 160/12.5 mg, 160/25 mg.

Co-Diovan 80/12.5 mg: Ovaloid, non-divisible, film-coated tablets measuring approximately 10.2 mm by 5.4 mm and 3.7 mm in thickness, and weighing approximately 156 mg. The tablets are coloured light orange and imprinted with HGH on one side and CG on the other side.

Co-Diovan 160/12.5 mg: Ovaloid, non-divisible, film-coated tablets measuring approximately 15.2 mm by 6.2 mm and 4.4 mm in thickness, and weighing approximately 312 mg. The tablets are coloured dark red and imprinted with HHH on one side and CG on the other side.

Co-Diovan 160/25 mg: Ovaloid, non-divisible, film-coated tablets measuring approximately 14.2 mm by 5.7 mm and 4.5 mm in thickness, and weighing approximately 310 mg. The tablets are colored brown-orange and imprinted with HXH on one side and NVR on the other side.

4 Clinical particulars

4.1 Therapeutic indications

80/12.5 mg:

Treatment of hypertension

Co-Diovan is indicated for the treatment of hypertension in patients whom combination therapy is appropriate.

160/12.5 mg, 160/25 mg:

Treatment of hypertension.

Co-Diovan is indicated for the treatment of hypertension in patients whose blood pressure is not adequately controlled by monotherapy. These fixed dose combinations should be used as second-line therapy.

4.2 Posology and method of administration

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 may be used. When necessary 160 mg valsartan and 25 mg may be used. The maximum antihypertensive effect is seen within 2 to 4 weeks.

No dosage adjustment is required for patients with mild to moderate renal impairment (creatinine clearance > 30 mL/min). No dosage adjustment is required in patients with mild to moderate hepatic insufficiency of non-biliary origin and without cholestasis (see section 4.4 Special warnings and precautions for use).

The safety and efficacy of Co-Diovan have not been established in children.

4.3 Contraindications

Known hypersensitivity to valsartan, hydrochlorothiazide, other sulfonamides or to any of the excipients of Co-Diovan.

Pregnancy (see section 4.6. Pregnancy and lactation).

CO-DIO API MAY09 CL V4

REF CDS 260109

Severe hepatic impairment, biliary cirrhosis and cholestasis.

Anuria, severe renal impairment (creatinine clearance < 30 mL/min).

Refractory hypokalemia, hyponatremia, hypercalcemia, and symptomatic hyperuricemia (gout or uric acid calculi).

4.4 Special warnings and precautions for use

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. Hypokalemia has been reported under treatment with thiazide diuretics. Frequent monitoring of serum potassium is recommended.

Treatment with thiazide diuretics, including hydrochlorothiazide, has been associated with hyponatremia and hypochloremic alkalosis. Thiazides, including hydrochlorothiazide, increase the urinary excretion of magnesium, which may result in hypomagnesemia .

Sodium- and/or volume-depleted patients

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

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.

Renal artery stenosis

In patients with unilateral or bilateral renal artery stenosis or stenosis to a solitary kidney, the safe use of Co-Diovan has not been established.

Renal impairment

No dosage adjustment is required for patients with renal impairment (creatinine clearance > 30 mL/min).

Hepatic impairment

In patients with mild to moderate hepatic impairment without cholestasis, no dosage adjustment is required. However, Co-Diovan should be used with caution. Liver disease does not significantly alter the pharmacokinetics of hydrochlorothiazide.

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.

4.5 Interaction with other medicinal products and other forms of interaction

The antihypertensive effect may be increased with concomitant use of other antihypertensive drugs.

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.

Reversible increases in serum lithium concentrations and toxicity have been reported during concurrent use of ACE inhibitors and thiazides. There is no experience with concomitant use of valsartan and lithium. Therefore, monitoring of serum lithium concentrations is recommended during concurrent use.

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 .

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

Thiazides, including hydrochlorothiazide, potentiate the action of curare derivatives .

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 .

The hypokalemic effect of diuretics may be increased by kaliuretic diuretics, corticosteroids, ACTH, amphotericin, carbenoxolone, penicillin G, salicylic acid derivatives.

Thiazide-induced hypokalemia or hypomagnesemia may occur as unwanted effects, favouring the onset of digitalis-induced cardiac arrhythmias .

It may prove necessary to readjust the dosage of insulin and of oral antidiabetic agents .

Co-administration of thiazide diuretics, including hydrochlorothiazide, may increase the incidence of hypersensitivity reactions to allopurinol, may increase the risk of adverse effects caused by amantadine, may enhance the hyperglycemic effect of diazoxide, and may reduce the renal excretion of cytotoxic drugs (e.g. cyclophosphamide, methotrexate) and potentiate their myelosuppressive effects .

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 .

There have been reports in the literature of haemolytic anaemia occurring with concomitant use of hydrochlorothiazide and methyl dopa .

Absorption of thiazide diuretics, including hydrochlorothiazide, is decreased by cholestyramine .

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

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

Patients receiving hydrochlorothiazide concomitantly with carbamazepine may develop hyponatremia. Such patients should therefore be advised about the possibility of hyponatremic reactions, and should be monitored accordingly.

When administered concomitantly the following drugs may interact with thiazides: alcohol, barbiturates or narcotics. Potentiation of orthostatic hypotension may occur.

4.6 Pregnancy and lactation

Pregnancy

Due to the mechanism of action of angiotensin II antagonists, a risk for the foetus cannot be excluded. In utero exposure to angiotensin converting enzyme (ACE) inhibitors (a specific class of drugs acting on the renin-angiotensin-aldosterone system – RAAS) given to pregnant women during the second and third trimesters has been reported to cause injury and death to the developing foetus. In addition, in retrospective data, first trimester use of ACE inhibitors has been associated with a potential risk of birth defects. Intrauterine exposure to thiazide diuretics, including hydrochlorothiazide, is associated with foetal or neonatal thrombocytopenia, and may be associated with other adverse reactions that have occurred in adults. There have been reports of spontaneous abortion, oligohydramnios and newborn renal dysfunction, when pregnant women have inadvertently taken valsartan . As for any drug that also acts directly on the RAAS, Co-Diovan should not be used during pregnancy (see section 4.3 Contraindications) or in women planning to become pregnant. Healthcare professionals prescribing any agents acting on the RAAS should counsel women of childbearing potential about the potential risk of these agents during pregnancy. If pregnancy is detected during therapy, Co-Diovan should be discontinued as soon as possible .

Lactation

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Co-Diovan has been evaluated for safety in more than 4,300 patients. Adverse experiences have generally been mild and transient in nature.

The following table of adverse experiences is based on three controlled trials involving a total of 7,616 patients. Of the 7,616 patients, 4,372 received valsartan in combination with hydrochlorothiazide. The overall incidence of adverse experiences with Co-Diovan was similar to placebo. All adverse experiences showing an incidence of 1% or more in the Co-Diovan group are included in the following table, irrespective of their causal association with the study drug.

Table 1

	Valsartan/HCTZ (%) N=4372†	Placebo N=262
Headache	3.7	14.5
Dizziness	3.5	3.8
Nasopharyngitis‡	2.4	1.9
Fatigue	1.6	1.5
Upper Respiratory tract Infection	1.2	3.4
Cough	1.2	0.8
Diarrhea	1.1	1.1
Arthralgia	1.0	1.1
Back pain	1.2	2.7

† Includes all combinations of valsartan 80, 160 mg and 320mg with HCTZ 12.5 and 25 mg

‡ Nasopharyngitis including pharyngitis + rhinitis

HCTZ = Hydrochlorothiazide;

Other adverse experiences with a frequency below 1% included abdominal pain, abdominal pain upper, anxiety, arthritis, asthenia, bronchitis, bronchitis acute, chest pain, dizziness postural, dyspepsia, dyspnoea, dry mouth, erectile dysfunction, gastroenteritis, hypersensitivity, hyperhidrosis, hypoaesthesia, hypokalemia, hypotension, influenza, insomnia, muscle spasms, muscle strain, myalgia, nausea, nasal congestion, neck pain, oedema, oedema peripheral, otitis media, pain in extremity, palpitations, paraesthesia, pharyngolaryngeal pain, pollakiuria, pyrexia, rash, sinus congestion, sinusitis, somnolence, ligament sprain, syncope, tachycardia, tinnitus, urinary tract infection, vertigo, viral infection, vision blurred, vision disturbance, dysuria, dehydration, gout. It is unknown whether these effects were causally related to the therapy.

Postmarketing data revealed very rare cases of angioneurotic oedema, rash, pruritus, and other hypersensitivity/allergic reactions including serum sickness, and vasculitis. Very rare cases of renal impairment and myalgia have also been reported. There have also been reported several cases of hydrochlorothiazide-induced pulmonary oedema with granulocytic

infiltration and IgG deposition in alveolar membranes. Non-cardiogenic pulmonary oedema may be an immunologically mediated rare idiosyncratic reaction to hydrochlorothiazide.

Laboratory findings

A greater than 20% decrease in serum potassium was observed in 3.7% of patients receiving Co-Diovan as compared to placebo (3.1%) (see section 4.4 Special warnings and precautions).

Elevations in creatinine and blood urea nitrogen (BUN) occurred in 1.9% and 14.7% respectively, of patients taking Co-Diovan and 0.4% and 6.3% respectively, given placebo in controlled clinical trials.

Neutropenia was observed in 0.1 % of patients treated with Co-Diovan versus 0.4 % of patients treated with placebo.

Valsartan

Other additional adverse experiences reported in clinical trials with valsartan monotherapy, irrespective of their causal association with the study drug, were with a frequency below 1%: libido decreased, renal failure acute, occasional elevations in liver function values.

Hydrochlorothiazide

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

Electrolytes and metabolic disorders

(see section 4.4 Special warnings and precautions).

Others

Common: Urticaria and other forms of rash, decreased appetite, mild nausea and vomiting, orthostatic hypotension, which may be aggravated by alcohol, anaesthetics or sedatives, and erectile dysfunction.

Rare: Photosensitivity reaction, abdominal discomfort, constipation, diarrhoea, cholestasis or jaundice, arrhythmia, headache, dizziness, sleep disorder, depression, paresthesia, visual disturbance, thrombocytopenia, sometimes with purpura.

Very rare: Vasculitis necrotizing and toxic epidermal necrolysis, cutaneous lupus erythematosus-like reactions, reactivation of cutaneous lupus erythematosus, pancreatitis, leukopenia, agranulocytosis, bone marrow depression, haemolytic anaemia, hypersensitivity reactions, respiratory distress including pneumonitis and pulmonary oedema.

4.9 Overdose

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 haemodialysis because of its strong plasma binding behaviour, whereas clearance of hydrochlorothiazide will be achieved by dialysis.

5 Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: angiotensin II antagonists combinations (valsartan) with diuretics (hydrochlorothiazide); ATC code: C09D A03

The active hormone of the RAAS 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 AT₁ receptor subtype, 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 counterbalance 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 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.

5.2 Pharmacokinetic properties

Valsartan

Absorption of valsartan after oral administration is rapid, although the amount absorbed varies widely. Mean absolute bioavailability for Diovan is 23%. Valsartan shows multiexponential decay kinetics ($t_{1/2\alpha} < 1$ hour and $t_{1/2\beta}$ about 9 hours).

The pharmacokinetics of valsartan are 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 .

Valsartan is highly bound to serum protein (94 to 97%), mainly serum albumin. Steady-state volume of distribution is low (about 17 L). Plasma clearance is relatively slow (about 2 L/h) when compared with hepatic blood flow (about 30 L/h). Of the absorbed dose of valsartan, 70% is excreted in the faeces and 30% in the urine, mainly as unchanged compound.

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, however, is not accompanied by a clinically significant reduction in the therapeutic effect.

Hydrochlorothiazide

The absorption of hydrochlorothiazide after an oral dose is rapid ($t_{\max}$ about 2 hours), with similar absorption characteristics for both suspension and tablet formulations. The distribution and elimination kinetics have generally been described by a bi-exponential decay function, with a terminal half-life of 6 to 15 hours.

The increase in mean AUC is linear and dose proportional in the therapeutic range. There is no change in the kinetics of hydrochlorothiazide on repeated dosing, and accumulation is minimal when dosed once daily .

Absolute bioavailability of hydrochlorothiazide is 60 to 80% after oral administration, with > 95% of the absorbed dose being excreted as unchanged compound in the urine, and about 4% as the hydrolysate, 2-amino-4-chloro-*m*-benzenedisulfonamide.

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.

Valsartan/hydrochlorothiazide

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

Elderly

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

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.

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 4.3 Contraindications).

Hepatic impairment

In a pharmacokinetics trial in patients with mild (n=6) to moderate (n=5) hepatic dysfunction, exposure to valsartan was increased approximately two-fold 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.

5.3 Preclinical safety data

In a variety of preclinical safety studies conducted in several animal species with valsartan, hydrochlorothiazide and valsartan:hydrochlorothiazide, there was no evidence of systemic or target organ toxicity. 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, haemoglobin, haematocrit) and evidence of changes in renal haemodynamics (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.

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:hydrochlorothiazide which is synergistic (potentiation is about ten-fold 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. However, both valsartan and hydrochlorothiazide have been tested individually for mutagenicity, clastogenicity and carcinogenicity with negative results.

6 Pharmaceutical particulars

6.1 List of 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).

6.2 Special precautions for storage

Do not store above 30°C, store in the original package.

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

Manufacturer:

Novartis Pharma Stein AG, Switzerland

for: Novartis Pharma AG, Basel, Switzerland

License Holder:

PharmaExcel Ltd.

23 Hasivim St. Petach-Tikva