NOVARTIS

# Co-Diovan®

## Composition
*Active substances*: Valsartan, 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; hydroxypropylmethylcellulose;
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).
Co-Diovan 320/12.5 mg: Colloidal silicon dioxide; crospovidone; hydroxypropylmethylcellulose;
magnesium stearate; microcrystalline cellulose; polyethylene glycol; talc;
black iron oxide (E172), titanium dioxide (E171); red iron oxide (E172);.
Co-Diovan 320/25 mg: Colloidal silicon dioxide; crospovidone; hydroxypropylmethylcellulose;
magnesium stearate; microcrystalline cellulose; polyethylene glycol; talc;
titanium dioxide (E171); yellow iron oxide (E172).
Information might differ in some countries.

## Pharmaceutical form and quantity of active substance per unit
*Co-Diovan 80/12.5*
Film-coated tablets containing 80 mg valsartan and 12.5 mg hydrochlorothiazide.
Ovaloid, non-divisible, light orange film-coated tablets imprinted with HGH on one side and CG on the other side.

*Co-Diovan 160/12.5*
Film-coated tablets containing 160 mg valsartan and 12.5 mg hydrochlorothiazide.
Ovaloid, non-divisible, dark red film-coated tablets imprinted with HHH on one side and CG on the other side.

*Co-Diovan 160/25*
Film-coated tablets containing 160 mg valsartan and 25 mg hydrochlorothiazide.
Ovaloid, non-divisible, brown-orange film-coated tablets imprinted with HXH on one side and NVR on the other side.

*Co-Diovan 320/12.5*
Film-coated tablets containing 320 mg valsartan and 12.5 mg hydrochlorothiazide.
Ovaloid, non-divisible, pink film-coated tablets imprinted with HIL on one side and NVR on the other side.

*Co-Diovan 320/25*
Film-coated tablets containing 320 mg valsartan and 25 mg hydrochlorothiazide.
Ovaloid, non-divisible, yellow film-coated tablets imprinted with CTI on one side and NVR on the other side.

## Indications/Potential uses
Treatment of mild and moderate essential hypertension in patients whose blood pressure is not adequately controlled by monotherapy.

## Dosage/Administration
The recommended dose is one Co-Diovan 80/12.5 film-coated tablet per day. If blood-pressure reduction is inadequate after 3-4 weeks' treatment, it may be necessary to continue treatment with one Co-Diovan 160/12.5 film-coated tablet per day. Use of one Co-Diovan 160/25 film-coated tablet per day is restricted to those patients in whom adequate reduction of blood pressure is not achieved with Co-Diovan 160/12.5. If blood-pressure reduction remains inadequate with Co-Diovan 160/25, treatment may need to be continued with one Co-Diovan 320/12.5 film-coated tablet per day. Use of one Co-Diovan 320/25 film-coated tablet per day is restricted to those patients in whom adequate reduction of blood pressure is not achieved with Co-Diovan 320/12.5. The maximum antihypertensive effect is seen within 2 to 4 weeks.
Co-Diovan may be taken without regard to meals. It should be swallowed with liquid.

*Elderly patients (over 65 years)*
Co-Diovan may be taken by patients of any age.

*Renal impairment*
Dose reduction may be necessary in patients with renal impairment. Due to the hydrochlorothiazide component, Co-Diovan is contraindicated in patients with anuria (see "**Contraindications**") and should be used with particular caution in patients with severe renal impairment (GFR <30 ml/minute) (see "**Warnings and precautions**").
There is no experience regarding the use of valsartan in patients with end-stage renal failure (GFR <10 ml/minute) and patients undergoing dialysis.

*Hepatic impairment*
Dose reduction may be necessary in patients with hepatic impairment. Due to the hydrochlorothiazide component, Co-Diovan should be used with caution in patients with hepatic impairment (see "**Warnings and precautions**"). Due to the valsartan component, Co-Diovan is contraindicated in patients with biliary cirrhosis and cholestasis.

*Use in children and adolescents*
There have been no studies of the efficacy and safety of Co-Diovan in the treatment of children and adolescents.

## Contraindications
- Hypersensitivity to valsartan, hydrochlorothiazide, sulfonamide derivatives or to any of the excipients of Co-Diovan.
- Co-Diovan is contraindicated in patients with hereditary angioedema, or in those who have developed angioedema during previous treatment with an ACE inhibitor or angiotensin II receptor antagonist.
- Pregnancy and lactation (see "**Pregnancy/Lactation**").
- Biliary cirrhosis or cholestasis.
- Anuria.
- Concomitant use of angiotensin receptor antagonists (ARBs) – including Co-Diovan – or of angiotensin-converting enzyme inhibitors (ACEIs) with aliskiren in patients with diabetes mellitus (type 1 or type 2) and patients with renal impairment (GFR <60 ml/minute) (see "**Dual RAAS blockade**" under "**Interactions**").

## Warnings and precautions
*Electrolytes*
*Potassium*
Thiazide diuretics can cause hypokalaemia or exacerbate pre-existing hypokalaemia. Thiazides should be administered with caution and regular monitoring of serum potassium in patients with conditions involving enhanced potassium loss.
Correction of hypokalaemia is recommended prior to the initiation of thiazide therapy. Coexisting hypomagnesaemia may make hypokalaemia more difficult to correct. As Co-Diovan contains an angiotensin II receptor antagonist, any supplementation of potassium on treatment with Co-Diovan should be carefully considered, and undertaken with caution. Potassium and magnesium serum concentrations should be monitored regularly. All patients receiving thiazide diuretics should be monitored for imbalances in electrolytes.

*Sodium*
Thiazide diuretics can precipitate new-onset hyponatraemia or exacerbate pre-existing hyponatraemia. This may be accompanied by neurological symptoms (vomiting, confusion, apathy). Thiazide diuretics should only be used after correction of any pre-existing hyponatraemia. Serum sodium concentrations should be monitored regularly.

*Calcium*
Thiazide diuretics decrease urinary calcium excretion and may cause elevation of serum calcium. Thiazide diuretics should only be started after correcting pre-existing hypercalcaemia or treating the condition responsible for it. Serum calcium concentrations should be monitored regularly.

*Volume depletion*
In patients with significant volume depletion, symptomatic hypotension may occur after initiation of therapy with Co-Diovan. Existing volume depletion should be corrected before the start of treatment.
*Renal artery stenosis*
There is no experience with Co-Diovan in patients with unilateral or bilateral renal artery stenosis or stenosis of a solitary kidney.

*Renal impairment*
Caution is required when treating patients with renal impairment. Thiazide diuretics can lose their diuretic efficacy in patients with severe renal impairment (GFR <30 ml/minute). Co-Diovan should thus only be administered to such patients after close examination of the risk-benefit ratio and with monitoring of clinical and laboratory parameters.
Concomitant use of ARBs – including Co-Diovan – or of ACEIs with aliskiren is contraindicated in patients with renal impairment (GFR <60 ml/minute) (see "**Dual RAAS blockade**" under "**Interactions**").
There is no experience regarding the use of valsartan in patients with end-stage renal failure (GFR <10 ml/minute) and patients undergoing dialysis.

*Hepatic impairment*
Caution is required when treating patients with hepatic impairment. Thiazides may cause electrolyte imbalance, hepatic encephalopathy and hepatorenal syndrome in these patients. Co-Diovan should thus only be administered to such patients after close examination of the risk-benefit ratio and with monitoring of clinical and laboratory parameters. Co-Diovan is contraindicated in patients with biliary cirrhosis or cholestasis.

*Systemic lupus erythematosus*
Thiazide diuretics, including hydrochlorothiazide, may trigger or exacerbate systemic lupus erythematosus.

*Metabolic effects*
Co-Diovan may raise the serum uric acid level due to reduced clearance of uric acid and may cause or exacerbate hyperuricaemia and precipitate gout in susceptible patients. Co-Diovan is therefore not recommended for use in patients with hyperuricaemia and/or gout.
Thiazide diuretics, including hydrochlorothiazide, may alter glucose tolerance and worsen diabetic metabolic state. Serum levels of cholesterol and triglycerides may rise during hydrochlorothiazide use.
*Other*

Hypersensitivity reactions to hydrochlorothiazide are more likely in patients with allergy and asthma.

*Acute myopia and secondary angle-closure glaucoma*
Hydrochlorothiazide, a sulfonamide contained in Co-Diovan, can cause idiosyncratic reactions resulting in acute transient myopia or acute angle-closure glaucoma. This presents as acute onset of decreased visual acuity or ocular pain, which typically occur within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue the drug as rapidly as possible. Surgical and medical measures must be considered if intraocular pressure cannot be controlled by other means. A pre-existing sulfonamide or penicillin allergy may be a risk factor for developing angle-closure glaucoma on treatment with hydrochlorothiazide.

*Dual renin-angiotensin-aldosterone system (RAAS) blockade*
Co-administration of ARBs, including Co-Diovan, with other agents that block the RAAS, such as ACEIs or aliskiren, is not recommended. In certain patients this combination is contraindicated (see "**Contraindications**" and "**Dual RAAS blockade**" under "**Interactions**").

## Interactions
*Interactions affecting both components*
*Non-steroidal anti-inflammatory drugs (NSAIDs), including selective cyclooxygenase-2 (COX2) inhibitors*:

Concomitant administration of NSAIDs and COX2 inhibitors may attenuate the antihypertensive effect of angiotensin II receptor antagonists (AIIRAs). In patients who are elderly, volume depleted (including those on diuretic therapy), or have compromised renal function, concomitant use of NSAIDs (or COX2 inhibitors) with an AIIRA may increase the risk of worsening of renal function, including possible acute renal failure. These drugs should therefore be combined in such patients only with caution and monitoring of renal function.

*Other antihypertensive drugs*: Co-Diovan potentiates the antihypertensive action of other antihypertensive drugs (e.g. beta blockers, vasodilators, calcium channel blockers, ACE inhibitors, angiotensin receptor blockers (ARBs) and direct renin inhibitors (DRIs).

*Valsartan*
In monotherapy with valsartan, no drug interactions of clinical significance have been found with the following drugs: cimetidine, warfarin, furosemide, digoxin, atenolol, indometacin, hydrochlorothiazide, amlodipine and glibenclamide.

*Dual renin-angiotensin-aldosterone system blockade with ARBs, ACEIs or aliskiren*: Co-administration of ARBs, including Co-Diovan, with other medicinal products acting on the RAAS is associated with an increased incidence of hypotension, hyperkalaemia and impaired renal function (including acute renal failure) compared to monotherapy. Regular monitoring of blood pressure, renal function and electrolyte status is recommended in patients taking Co-Diovan or other medicinal products acting on the RAAS (see "**Warnings and precautions**").
Concomitant use of ARBs – including Co-Diovan – or of ACEIs with aliskiren is contraindicated in patients with renal impairment (GFR <60 ml/minute) (see "**Warnings and precautions**" and "**Contraindications**").
Concomitant use of ARBs – including Co-Diovan – or of ACEIs with aliskiren is contraindicated in patients with type 1 or type 2 diabetes (see "**Contraindications**").

*Potassium*: Concomitant use of angiotensin II receptor antagonists with other medicinal products capable of increasing serum potassium (e.g. potassium-sparing diuretics, potassium-containing preparations, heparin) may increase the risk of hyperkalaemia. In such cases, valsartan – an ingredient of Co-Diovan – should be used with caution and with monitoring of potassium levels.

*Hydrochlorothiazide*
*Lithium:* Reversible increases in serum lithium concentrations, and increased lithium toxicity, have been reported during concurrent use of lithium with ACE inhibitors and thiazide diuretics. Regular monitoring of serum lithium concentrations is therefore recommended during concurrent use of lithium and Co-Diovan. There is no experience with concomitant use of valsartan and lithium.

*Medicinal products affecting serum potassium or serum magnesium levels*: Potassium and/or magnesium loss may be intensified by concomitant administration of hydrochlorothiazide with kaliuretic diuretics (e.g. furosemide), glucocorticoids, ACTH, amphotericin B, carbenoxolone, penicillin G, salicylic acid derivatives or antiarrhythmics.

*Cardiac glycosides (digitalis)*: Thiazide-induced hypokalaemia or hypomagnesaemia may favour the onset of digitalis-induced cardiac arrhythmias.

*Skeletal muscle relaxants*: Thiazide diuretics, including hydrochlorothiazide, potentiate the action of curare-type skeletal muscle relaxants.

*Antidiabetic agents*: Thiazides may alter glucose tolerance. It may be necessary to adjust the dosage of insulin and of oral antidiabetic agents.
*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.

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

*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 diuretics may be increased by concomitant administration of anticholinergic agents (e.g. atropine, biperiden), probably due to a decrease in gastrointestinal motility and stomach emptying rate. Conversely, prokinetic drugs such as cisapride may decrease the bioavailability of thiazide diuretics.

*Methyldopa*: There have been isolated reports of haemolytic anaemia occurring with concomitant use of hydrochlorothiazide and methyldopa.
*Ion exchange resins*: Absorption of thiazide diuretics, including hydrochlorothiazide, is decreased by cholestyramine or colestipol. Administration of hydrochlorothiazide and an ion exchange resin should thus be staggered, with as large a time interval as possible to minimize interactions.

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

*Ciclosporin*: Concomitant treatment with ciclosporin may increase the risk of hyperuricaemia and give rise to symptoms of gout.

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

*Medicinal products affecting serum sodium level*: The hyponatraemic effect of diuretics may be intensified by concomitant administration of drugs such as antidepressants, antipsychotics or antiepileptics. Caution is advised in long-term administration of these drugs.
*Alcohol, barbiturates or narcotics*: Concomitant use of thiazide diuretics with alcohol, barbiturates or narcotics can potentiate orthostatic hypotension.

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

## Pregnancy/Lactation
*Pregnancy*
Co-Diovan must not be used during pregnancy.
Due to the mechanism of action of angiotensin II receptor antagonists, embryonic and fetal risk cannot be excluded. In retrospective data, first-trimester use of ACE inhibitors has been associated with a potential risk of birth defects. In addition, fetal injury and death have been reported in association with the use during the second and third trimesters of drugs that directly act on the renin-angiotensin-aldosterone system (RAAS). In humans, fetal renal perfusion, which is dependent on the development of the RAAS, begins during the second trimester. The risks associated with valsartan treatment are therefore higher during the second and third trimesters. There have been reports of spontaneous abortion, oligohydramnios and neonatal renal dysfunction when pregnant women have inadvertently taken valsartan.
As for any drug that acts directly on the RAAS, Co-Diovan should not be used during pregnancy (see "**Contraindications**") or in women planning to become pregnant. Healthcare professionals prescribing any RAAS-acting agents should counsel women of childbearing potential about the potential risk of these agents during pregnancy.
All neonates exposed to the drug *in utero* should be carefully checked for adequate urine output, hyperkalaemia and blood pressure. If necessary, appropriate medical steps (e.g. rehydration) must be taken to remove the drug from the circulation.
Intrauterine exposure to thiazide diuretics, including hydrochlorothiazide, can cause 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 must be discontinued.

*Lactation*
Valsartan was excreted in the milk of lactating rats. Hydrochlorothiazide crosses the placenta and is excreted in human milk. There have been no studies in breastfeeding women and Co-Diovan should therefore not be used in breastfeeding women.

## Effects on ability to drive and use machines
Like other antihypertensive agents, Co-Diovan may impair reactions, ability to drive and ability to use tools and machines. Caution is recommended.

## Adverse effects
The following adverse effects were reported in five controlled clinical trials involving 7616 patients, 4372 of whom received valsartan in combination

with hydrochlorothiazide:
*Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10 000 to <1/1000), very rare (<1/10 000).*

*Infections and infestations*
*Uncommon*: Viral infections, fever.

*Metabolic disorders*
*Uncommon*: Hypokalaemia.

*Nervous system disorders*
*Common*: Headache, fatigue, light-headedness.
*Uncommon*: Asthenia, dizziness, insomnia, anxiety, paraesthesia.
*Rare*: Depression.

*Eye disorders*
*Uncommon*: Visual disturbances.
*Rare*: Conjunctivitis.

*Ear and labyrinth disorders*
*Uncommon*: Otitis media, tinnitus.

*Cardiac disorders*
*Uncommon*: Palpitations, tachycardia.

*Vascular disorders*
*Uncommon*: Oedema, hypotension, hyperhidrosis.

*Respiratory disorders*
*Common*: Cough, rhinitis, pharyngitis, upper respiratory tract infection.
*Uncommon*: Bronchitis, dyspnoea, sinusitis, pharyngolaryngeal pain, dry mouth.
*Very rare*: Epistaxis.

*Gastrointestinal disorders*
*Common*: Diarrhoea.
*Uncommon*: Abdominal pain, indigestion, nausea, gastroenteritis.

*Musculoskeletal disorders*
*Common*: Back pain, arthralgia.
*Uncommon*: Arm or leg pain, chest pain, neck pain, arthritis, sprains and strains, muscle cramps.
*Very rare*: Myalgia.

*Renal and urinary disorders*
*Uncommon*: Frequent urination, urinary tract infection.
*Very rare*: Renal impairment.

*Reproductive system and breast disorders*
*Common*: Erectile dysfunction.

*Laboratory findings*
A decrease of more than 20% in serum potassium was observed in 3.7% of patients treated with Co-Diovan and 3.1% of patients who received placebo.
Elevations in creatinine and blood urea nitrogen (BUN) occurred in 1.9% and 14.7%, respectively, of patients taking Co-Diovan, and in 0.4% and 6.3%, respectively, of patients given placebo in controlled clinical trials.
The following findings have been associated with valsartan monotherapy, but not observed with Co-Diovan:
In rare cases, valsartan therapy may be associated with a reduction in haemoglobin and haematocrit. In controlled clinical trials, significant (>20%) reductions in haematocrit and haemoglobin were reported, respectively, in 0.8% and 0.4% of patients. In contrast, 0.1% of patients receiving placebo showed a reduction in levels of haematocrit or haemoglobin.
Neutropenia was observed in 1.9% of patients treated with valsartan and 1.6% of patients treated with ACE inhibitors.
In controlled clinical trials, significant increases in serum creatinine, potassium and total bilirubin were observed, respectively, in 0.8%, 4.4% and 6% of patients treated with valsartan, and 1.6%, 6.4% and 12.9% of patients treated with an ACE inhibitor.
There were uncommon reports of elevated liver function values in patients treated with valsartan.
No special monitoring of laboratory parameters is necessary in patients with essential hypertension receiving valsartan therapy.
There have been post-marketing reports of syncope and of very rare cases of angioedema, rash, pruritus and other hypersensitivity reactions such as serum sickness and vasculitis. There have also been very rare reports of renal dysfunction.

*Valsartan*
Other adverse events reported in clinical trials with valsartan, irrespective of their causal association, were as follows:
*Common*: Arthralgia.
*Uncommon*: Oedema, asthenia, insomnia, rash, reduced libido, dizziness.
*Rare*: Gastroenteritis, neuralgia.
*Very rare*: Thrombocytopenia, arrhythmia, acute renal failure.
A single case of angioedema has been reported.

*Hydrochlorothiazide*
*Blood and lymphatic system disorders*
*Rare*: Thrombocytopenia, occasionally with purpura.
*Very rare*: Leukopenia, agranulocytosis, bone-marrow depression, haemolytic anaemia.

*Immune system disorders*
*Very rare*: Hypersensitivity reactions.

*Metabolism and nutrition disorders*
*Very common*: Hypokalaemia, blood lipids increased.
*Common*: Hyponatraemia, hypomagnesaemia and hyperuricaemia.
*Rare*: Hypercalcaemia, hyperglycaemia, glycosuria and worsening of diabetic metabolic state.
*Very rare*: Hypochloraemic alkalosis.

*Nervous system disorders*
*Rare*: Headache, dizziness or light-headedness, sleep disorders, depression, paraesthesia.

*Eye disorders*
*Rare*: Visual impairment, particularly in the first few weeks of treatment.
*Cardiac disorders*
*Common*: Orthostatic hypotension, which may be aggravated by alcohol, anaesthetics or sedatives.
*Rare*: Arrhythmias.

*Respiratory disorders*
*Very rare*: Respiratory distress including pneumonitis and pulmonary oedema.

*Gastrointestinal disorders*
*Common*: Loss of appetite, mild nausea and vomiting.
*Rare*: Abdominal discomfort, constipation, diarrhoea.
*Very rare*: Pancreatitis.

*Hepatobiliary disorders*
*Rare*: Cholestasis or jaundice.
*Skin and subcutaneous tissue disorders*
*Common*: Urticaria and other forms of rash.
*Rare*: Photosensitivity.
*Very rare*: Necrotizing vasculitis and toxic epidermal necrolysis, lupus-erythematosus-like reactions, reactivation of cutaneous lupus erythematosus.

*Reproductive system and breast disorders*
*Common*: Impotence.

*Post-marketing adverse effects*
The following adverse effects have been identified based on post-marketing experience. Because these effects are reported voluntarily from a population of unknown size, it is not always possible to reliably estimate their frequencies.
Frequency not known: Acute renal failure, renal disorder, aplastic anaemia, erythema multiforme, pyrexia, muscle spasm, asthenia, acute myopia and acute angle-closure glaucoma.

## Overdose
Overdose with valsartan may result in marked hypotension, which could lead to a depressed level of consciousness, circulatory collapse and/or shock.
The following signs and symptoms may also occur as a result of hydrochlorothiazide overdose: nausea, drowsiness, hypovolaemia and electrolyte disturbances, associated with arrhythmias and muscle cramps.
General supportive measures should be initiated in all cases of overdose. This may involve close monitoring of, and measures to stabilize, cardiovascular function.
Valsartan cannot be eliminated by means of haemodialysis because of its strong plasma protein binding, whereas clearance of hydrochlorothiazide can be achieved by dialysis.

## Properties/Actions
*ATC code*: C09DA03

*Valsartan*
The active hormone of the renin-angiotensin-aldosterone system (RAAS) is angiotensin II, which is formed from angiotensin I through angiotensin-converting enzyme (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 effect. In addition, it promotes sodium retention and stimulates aldosterone secretion.
Valsartan is an orally active and specific angiotensin (AT) 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 angiotensin II following $AT_1$ receptor blockade with valsartan may stimulate the unblocked $AT_2$ receptors, which appears to further 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 (= kininase II), the enzyme that converts angiotensin I to angiotensin II and degrades bradykinin. Angiotensin II antagonists are unlikely to cause cough since they have no effect on ACE and do not potentiate bradykinin or substance P.
In clinical trials comparing valsartan with an ACE inhibitor, the incidence of dry cough was significantly ($p < 0.05$) lower in patients treated with valsartan than in those treated with an ACE inhibitor (2.6% versus 7.9%). In a clinical trial involving patients with a history of dry cough during ACE inhibitor therapy, 19.5% of patients receiving valsartan and 19.0% of those receiving a thiazide diuretic experienced cough, compared to 68.5% of those treated with an ACE inhibitor ($p < 0.05$). In controlled clinical trials, the frequency of cough in patients treated with a combination of valsartan and hydrochlorothiazide was 2.9%.
Valsartan does not affect other hormone receptors or ion channels known to be important in cardiovascular regulation.
Valsartan reduces blood pressure in patients with hypertension without affecting pulse rate.
In most patients, after administration of a single oral dose, onset of antihypertensive effect occurs within 2 hours, and the peak reduction of blood pressure is achieved within 4-6 hours. The antihypertensive effect persists over 24 hours after dosing. The maximum reduction in blood pressure is generally attained 2-4 weeks after the start of treatment and is sustained during long-term therapy. Combined with hydrochlorothiazide, a significant additional reduction in blood pressure is achieved.
Withdrawal of valsartan does not bring about rebound hypertension or other adverse effects.
Valsartan does not alter fasting levels of total cholesterol, triglycerides, serum glucose or uric acid in hypertensive patients.

*Hydrochlorothiazide*
The principal site of action of thiazide diuretics is the early distal tubule. It has been shown that a high-affinity receptor in the renal cortex acts as the primary binding site and site of action of thiazide diuretics, which inhibit NaCl transport in the early distal tubule. The action of thiazides involves inhibition of the $Na^+Cl^-$ symporter, competition for the $Cl^-$ binding site possibly affecting electrolyte reabsorption. This results directly in equivalent increases in sodium and chloride excretion, and indirectly in a reduction of plasma volume, with consequent increases in plasma renin activity, aldosterone secretion and potassium excretion, and a fall in serum potassium.
The renin-aldosterone link is mediated by angiotensin II, so co-administration of an angiotensin II receptor antagonist results in a reduction of the potassium loss associated with thiazides.

## Pharmacokinetics
*Valsartan*
*Absorption*
Absorption of valsartan after oral administration is rapid, although the amount absorbed varies widely. The mean absolute bioavailability of valsartan is 23% (range 23 ± 7). Its pharmacokinetics are linear in the dose range studied. When given once daily, valsartan shows little accumulation.
Plasma concentrations were similar in males and females.
When valsartan is given with food, the area under the plasma concentration curve (AUC) is reduced by 48%, and $C_{max}$ by 59%, although from eight hours post dosing, plasma valsartan concentrations are similar for ingestion with or without food. The reductions in AUC and $C_{max}$ do not result in a clinically significant reduction in therapeutic effect, and valsartan can therefore be taken without regard to meals.

*Distribution*
Valsartan is extensively bound to serum proteins (94-97%), mainly serum albumin. Steady state is reached within 1 week. The steady-state volume of distribution is about 17 litres.
Plasma clearance is relatively slow (about 2 litres/hour), compared with hepatic blood flow (about 30 litres/hour).

*Elimination*
Valsartan shows multiexponential decay kinetics (primary half-life <1 hour, terminal (beta) half-life about 9 hours). Of the absorbed dose of valsartan, approximately 70% is excreted in the faeces and 30% in the urine, mainly as unchanged compound.

*Hydrochlorothiazide*
*Absorption*
The absorption of hydrochlorothiazide after an oral dose is rapid ($t_{max}$ approx. 2 hours). The increase in mean AUC is linear and dose-proportional in the therapeutic range. Concomitant administration with food may 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 around 70% after oral administration.

*Distribution/Elimination*
The distribution and elimination kinetics have generally been described as a bi-exponential decay function.
The apparent volume of distribution is 4-8 litres/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.
Hydrochlorothiazide is eliminated predominantly as unchanged drug. Hydrochlorothiazide is eliminated from plasma with a mean 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 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 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 either drug given alone.

*Pharmacokinetics in special patient populations*
*Elderly patients*
A somewhat higher systemic exposure to valsartan was observed in some elderly patients (>65 years) compared to younger volunteers, but this was not found to be clinically relevant.
Steady-state concentrations of hydrochlorothiazide are higher – and systemic clearance considerably slower – in elderly patients than in young patients. Close monitoring is therefore necessary in elderly patients receiving treatment with hydrochlorothiazide.

*Renal impairment*
*Valsartan*
As may be expected for a compound with renal clearance accounting for only 30% of total plasma clearance, no correlation was found between renal function and systemic exposure to valsartan. Dose adjustment is therefore not required in patients with renal dysfunction (for severe renal impairment, see "**Contraindications**"). No studies have been performed in dialysis patients. However, as valsartan is highly bound to plasma proteins, it is unlikely to be removed by dialysis.

*Hydrochlorothiazide*
Renal clearance of hydrochlorothiazide occurs by both passive filtration and active secretion into the renal tubule. As may be expected for a compound that is cleared almost exclusively via the kidneys, renal function has a considerable influence on the kinetics of hydrochlorothiazide (see "**Contraindications**").
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, mean elimination half-life is almost doubled owing to the clear reduction in renal clearance.
Hydrochlorothiazide can be cleared by dialysis.

*Hepatic impairment*
In a pharmacokinetics study in patients with mild to moderate hepatic dysfunction, the concentration of valsartan was approximately double that observed in healthy volunteers. There are no data available in patients with severe hepatic dysfunction (see "**Contraindications**").
In general, hepatic disease with mild to moderate hepatic dysfunction does not significantly affect the pharmacokinetics of hydrochlorothiazide.

## Preclinical data
*Valsartan*
In a variety of preclinical safety studies conducted in several animal species, there was no evidence of systemic or target organ toxicity, apart from fetotoxicity. The offspring of rats given 600 mg/kg during the last trimester and during lactation showed a slightly reduced survival rate and a slight developmental delay (see "**Pregnancy/Lactation**"). The main preclinical safety findings are attributable to the pharmacological action of the compound.
There was no evidence of mutagenicity, clastogenicity or carcinogenicity.

*Hydrochlorothiazide*
Mutagenic and tumorigenic potential: The results of *in vitro* and *in vivo* mutagenicity testing of hydrochlorothiazide were negative for induction of genetic and chromosomal mutations.
Long-term studies with hydrochlorothiazide in rats and mice showed no relevant increase in the number of tumours in the dosage groups.
Reproductive toxicity: In animal studies, hydrochlorothiazide crosses the placenta. Studies in three animal species (rats, mice, rabbits) showed no evidence of teratogenicity.
There have been no preclinical studies of the fixed combination used in Co-Diovan.

## Other information
*Shelf life*
Do not use after the expiry date (= EXP) printed on the pack.

*Special precautions for storage*
See folding box.
Keep out of the reach of children.

## Pack sizes
Country specific pack sizes.

## Manufacturer
See folding box.

## Information last revised
May 2013

® = registered trademark
**Novartis Pharma AG, Basle, Switzerland**

**This is a medicament**
– A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.
– Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
– The doctor and the pharmacist are experts in medicine, its benefits and risks.
– Do not by yourself interrupt the period of treatment prescribed for you.
– Do not repeat the same prescription without consulting your doctor.

Keep medicaments out of reach of children

Council of Arab Health Ministers
Union of Arab Pharmacists