CO-MIGROBEN®

80/12.5, 160/12.5 mg tablets

(valsartan/hydrochlorothiazide)

Professional Information

Document status: Final

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SCHEDULING STATUS: S3

1. NAME OF THE MEDICINE

CO-MIGROBEN® 80/12,5 TABLET

CO-MIGROBEN® 160/12,5 TABLET

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

CO-MIGROBEN® 80/12,5 TABLET: Each film coated tablet contains 80 mg valsartan and 12,5 mg hydrochlorothiazide.

CO-MIGROBEN® 160/12,5 TABLET: Each film coated tablet contains 160 mg valsartan and 12,5 mg hydrochlorothiazide.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

CO-MIGROBEN® 80/12,5:

Light orange, ovaloid, convex tablet. One side bears the imprint “HGH”, the other “CG”.

CO-MIGROBEN® 160/12,5:

Dark red, ovaloid, convex film-coated tablet. One side bears the imprint “HHH”, the other “CG”.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of mild to moderate hypertension.

CO-MIGROBEN is indicated for the treatment of hypertension in patients whose blood pressure has been stabilized at the same dosages of the individual components given together.

4.2 Posology and method of administration

Posology:

The recommended dose is 1 (one) tablet per day. When clinically appropriate either 80 mg valsartan and 12,5 mg hydrochlorothiazide (CO-MIGROBEN 80/12,5) or 160 mg valsartan and 12,5 mg hydrochlorothiazide (CO-MIGROBEN 160/12,5 mg) may be used. The maximum antihypertensive effect is seen within 2 to 4 weeks.

For initial therapy, the usual starting dose is 160/12,5 mg once daily, the dosage can be increased after 1 – 2 weeks of therapy to a maximum of one 320/25 mg tablet once daily as needed to control blood pressure. CO-MIGROBEN is not recommended as initial therapy in patients with intravascular volume depletion. (see section 4.4).

The maximum daily dose is 320/25 mg.

Renal impairment

No dosage adjustment is required for patients with mild to moderate renal impairment (Glomerular Filtration Rate (GFR) ≥ 30 mL/min). Due to the hydrochlorothiazide component, CO-MIGROBEN is contraindicated in patient with anuria (see section 4.3) and should be used in caution with patients with severe renal impairment (GFR < 30 mL/min) (see section 4.4). Thiazide diuretics are ineffective as monotherapy in severe renal impairment, but may be useful in these patients when used with due caution in combination with a loop diuretic even in patients with GFR < 30 mL/min.

Hepatic Impairment

No dose adjustment is required in patients with mild to moderate hepatic impairment. Due to the hydrochlorothiazide component, CO-MIGROBEN should be used with caution in patients with severe

hepatic impairment. Due to the valsartan component, CO-MIGROBEN should be used with particular caution in patients with biliary obstructive disorders (see section 4.4).

The safety and efficacy of CO-MIGROBEN have not been established in children.

4.3 Contraindications

- Hypersensitivity to valsartan or hydrochlorothiazide or to any of the excipients of CO-MIGROBEN
- A history of angioedema related to previous therapy with ACE inhibitors or angiotensin receptor blockers (ARBs): these patients must never again be given these medicines
- Hereditary or idiopathic angioedema
- Hypertrophic obstructive cardiomyopathy (HOCM)
- Moderate to severe renal function impairment (creatinine clearance less than 30 mL/min)
- Bilateral renal artery stenosis
- Renal artery stenosis in patients with a single kidney
- Aortic stenosis
- Concomitant therapy with potassium sparing diuretics such as spironolactone, triamterene, amiloride (see section 4.5)
- Porphyria
- Lithium therapy: Concomitant administration with CO-MIGROBEN may lead to toxic blood concentrations of lithium (see section 4.5)
- Pregnancy and lactation (see section 4.6)
- Severe hepatic impairment, biliary cirrhosis and cholestasis
- Anuria
- Refractory hypokalaemia, hyponatraemia, hypercalcaemia, and symptomatic hyperuricemia / gout
- Addison’s disease
- The concomitant use of CO-MIGROBEN with renin inhibitors such as aliskiren-containing products is contraindicated (see section 4.4)

- Concomitant use of fluoroquinolones with ACE inhibitors / Angiotensin receptor blockers is contraindicated in patients with moderate to severe renal impairment (creatinine clearance ≤ 30 mL / min) and in elderly patients

4.4 Special warnings and precautions for use

Should a woman become pregnant while receiving CO-MIGROBEN, the treatment should be stopped promptly and switched to a different class of antihypertensive medicines (see section 4.3 and section 4.6).

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)

There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers (ARBs) or aliskiren may increase the risk of hypotension, hyperkalaemia and decreases renal function (including acute renal failure).

Dual blockade of RAAS through the combined use of CO-MIGROBEN and aliskiren is therefore contraindicated (see section 4.3). CO-MIGROBEN should not be used concomitantly with aliskiren (see section 4.3).

Sodium and/or volume-depleted patients:

In sodium depleted and/or volume depleted patients such as those receiving doses of diuretics, and/or patients with moderate to severe renal impairment, symptomatic hypotension may occur after initiation of therapy with CO-MIGROBEN. Sodium and/or volume depletion should be corrected before starting treatment with CO-MIGROBEN.

If hypotension occurs, symptomatic treatment should be given. Treatment can be continued once the blood pressure has been stabilised.

Non-melanoma skin cancer:

An increased risk of non-melanoma skin cancer (NMSC) [basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)] with increasing cumulative dose of hydrochlorothiazide exposure. The risk for NMSC appears to increase with long-term use. Photosensitising actions of hydrochlorothiazide could act as a possible mechanism for NMSC.

Patients taking hydrochlorothiazide should be informed of the risk of NMSC and advised to regularly check their skin for any new lesions and promptly report any suspicious skin lesions. Possible preventive measures such as limited exposure to sunlight and adequate protection when exposed to sunlight should be advised to the patients in order to minimise the risk of skin cancer. Suspicious skin lesions should be promptly examined, potentially including histological examination of biopsies. The use of hydrochlorothiazide may also need to be reconsidered in patients who have previously experienced NMSC.

Serum electrolyte changes:

Concomitant use with potassium supplements, potassium-sparing diuretics, salt substitutes containing potassium, or other medicines that may increase potassium levels (heparin, etc.) should be used with caution. Thiazide diuretics can precipitate new onset hypokalaemia or exacerbate pre-existing hypokalaemia. Thiazide diuretics should be administered with caution in patients with conditions involving enhanced potassium loss, for example salt –losing nephropathies and prerenal (cardiogenic) impairment of kidney function. If hypokalaemia is accompanied by clinical signs (e.g. muscular weakness, paresis, or ECG alterations), CO-MIGROBEN should be discontinued. Correction of hypokalaemia and any hypomagnesemia is recommended prior to the initiation of Thiazides. Frequent monitoring of serum potassium and magnesium levels is recommended.

Treatment with thiazide diuretics have been associated with hyponatraemia and hypochloroaemic alkalosis or exacerbate pre-existing hyponatraemia. Hyponatraemia, accompanied by neurological symptoms (nausea, progressive disorientation, apathy) has been observed in isolated cases.

Regular monitoring of serum sodium concentrations is recommended. Thiazides increase the urinary excretion of magnesium, which may result in hypomagnesaemia.

Renal Artery stenosis:

CO-MIGROBEN should not be used in patients with unilateral or bilateral renal artery stenosis or stenosis to a solitary kidney, aortic valve stenosis or hypertrophic obstructive cardiomyopathy (see section 4.3), since blood urea and serum creatinine may increase in such patients.

Renal impairment:

No dosage adjustment is required for patients with mild renal impairment. CO-MIGROBEN is contraindicated in patients with severe renal function impairment (creatinine clearance less than 30 mL/min) (see section 4.3). Thiazide diuretics may precipitate azotaemia in patients with chronic kidney disease.

Hepatic impairment:

CO-MIGROBEN is mostly eliminated in the bile, patients with mild to moderate hepatic impairment, including patients with biliary obstructive disorders, showed lower valsartan clearance. Care should be exercised in administering CO-MIGROBEN to these patients.

Systemic Lupus erythematosus:

CO-MIGROBEN has been reported to exacerbate or activate systemic lupus erythematosus.

Other metabolic disturbances:

Thiazide diuretics may alter the glucose tolerance and raise serum levels of cholesterol and triglycerides.

Like other diuretics, hydrochlorothiazide may raise the serum uric acid level due to the reduced clearance of uric acid and may cause or exacerbate hyperuricaemia and precipitate gout in susceptible patients.
Thiazides may decrease the urinary calcium excretion. Thiazides may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcaemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

General:

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

Concomitant use of fluoroquinolones and ACE-inhibitors / angiotensin receptor blockers may precipitate acute kidney injury in patients, especially those with moderate to severe renal impairment and elderly patients (see section 4.3) Renal function should be assessed before initiating treatment and monitored during treatment with fluoroquinolones or ACE inhibitors / angiotensin receptor blockers whether used separately and / or concomitantly.

Angioedema:

Angioedema, including swelling of the larynx and glottis, causing airway obstruction and/or swelling of the face, lips, pharynx and/or tongue have been reported in patients treated with valsartan; some of these patients previously experience angioedema with other drugs including ACE inhibitors. CO-MIGROBEN should immediately be discontinued in patients who develop angioedema, and CO-MIGROBEN should not be re-administered.

Acute angle-closure glaucoma:

Hydrochlorothiazide, a sulphonamide, has been associated with an idiosyncratic reaction resulting in acute transient myopia and acute angle-closure glaucoma.

Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of a drug initiation. Untreated acute-angle closure glaucoma can lead to permanent vision loss.

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

Patients with heart failure / post-myocardial infarction

In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (e.g. patients with severe congestive heart failure), treatment with angiotensin converting enzyme inhibitors or angiotensin receptor antagonists has been associated with oliguria and/or progressive azotemia, and in rare cases with acute renal failure and/or death. Evaluation of patients with heart failure or post-myocardial infarction should always include assessment of renal function.

Intestinal angioedema

Intestinal angioedema has been reported in patients treated with angiotensin II receptor antagonists, including valsartan (see section 4.8). These patients presented with abdominal pain, nausea, vomiting and diarrhoea. Symptoms resolved after discontinuation of angiotensin II receptor antagonists. If intestinal angioedema is diagnosed, CO-MIGROBEN should be discontinued, and appropriate monitoring should be initiated until complete resolution of symptoms has occurred.

4.5 Interaction with other medicines and other forms of interaction

Valsartan – hydrochlorothiazide

The following interactions may occur due to both components (valsartan and/or hydrochlorothiazide) of CO-MIGROBEN:

Lithium: Reversible increases in serum lithium concentrations and toxicity have been reported during concurrent use of ACE inhibitors and thiazides.

Since renal clearance of lithium is reduced by thiazides, the risk of lithium toxicity may be increased further with CO-MIGROBEN. Therefore, careful monitoring of serum lithium concentrations is recommended during concomitant use (see section 4.3).

Valsartan

The following potential drug interactions may occur due to the valsartan component for CO-MIGROBEN:

Dual blockade of the RAAS with ARBs, ACE inhibitors or aliskiren

Clinical trial data has shown that dual blockade or the renin-angiotensin-aldosterone-system (RAAS) through the combined use of ace inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (see section 4.3 and 4.4).

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

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

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

Transporters: the results from an *in vitro* study with human liver tissue indicate that valsartan is a substrate of the hepatic uptake transporter OATP1B1 and the hepatic efflux transporter MRP2. Co-administration of inhibitors of the uptake transporter (e.g., rifampin, ciclosporin) or efflux transporter (e.g. ritonavir) may increase the systemic exposure to valsartan.

Under monotherapy with DIOVAN, no drug interactions of clinical significance have been found with the following drugs: cimetidine, warfarin, furosemide, atenolol, indomethacin, hydrochlorothiazide, amlodipine, glibenclamide.

Concomitant use of fluoroquinolones and ACE inhibitors / angiotensin receptor blockers may precipitate acute kidney injury. The mechanism of the possible interaction between the different classes of medicines, over and above different mechanisms of kidney damage, is unknown (see section 4.3).

Hydrochlorothiazide:

The following potential drug interactions may occur due to the thiazide component of CO-MIGROBEN: thiazides potentiate the action of curare derivatives.

Other anti-hypertensive drugs: Thiazides potentiate the antihypertensive action of other antihypertensive drugs (e.g. guanethidine, methyldopa, beta-blockers, vasodilators, calcium channel blockers, ACE inhibitors, Angiotensin Receptor Blockers (ARBs) and Direct Renin Inhibitors (DRIs)).

Skeletal muscle relaxants: thiazides potentiate the action of skeletal muscle relaxants such as curare derivatives.

NSAIDs and COX-2 Selective inhibitors: Concomitant administration of non-steroidal anti-inflammatory agents (e.g. salicylic acid derivative, indomethacin) may weaken the diuretic and antihypertensive activity of the thiazide component of CO-MIGROBEN. Concurrent hypovolemia may induce acute renal failure.

Medicinal products affecting serum potassium levels: The hypokalaemic effect of diuretics may be increased by kaliuretic diuretics, corticosteroids, ACTH, amphotericin, carbenoxolone, penicillin G, salicylic acid derivatives.

Medicinal products affecting serum sodium levels: The hyponatraemic effect of diuretics may be intensified by concomitant administration of medicines such as anti-depressants, antipsychotics, antiepileptics, etc. Caution is advised in long term administration of these medicines (see section 4.4).

Digitalis glycosides: Thiazide-induced hypokalaemia or hypomagnesaemia may occur as unwanted effects, favouring the onset of digitalis-induced cardiac dysrhythmia.

Antidiabetic agents: Thiazides may alter glucose tolerance. It may prove necessary to readjust the dose 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.

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

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

Methyldopa: There have been reports in the literature 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. However, staggering the dose of hydrochlorothiazide and resin such that hydrochlorothiazide is administered at least 4 hours before or 4-6 hours after administration of resins would potentially minimise the interaction.

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

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

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

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

Alcohol, barbiturates or narcotics: Alcohol, barbiturates and narcotics may potentiate orthostatic hypotension.

4.6 Fertility, pregnancy and lactation

CO-MIGROBEN is contraindicated in pregnancy and lactation.

CO-MIGROBEN treatment may cause congenital abnormalities. Should a woman become pregnant while receiving CO-MIGROBEN, the treatment must be stopped promptly and switched to a different medicine. Should a woman contemplate pregnancy, the doctor should consider alternative medication.

Safety in pregnancy and lactation has not been established (see section 4.3). When pregnancy is planned or confirmed CO-MIGROBEN should be discontinued.

Medicines affecting the renin-angiotensin system, such as CO-MIGROBEN, can cause embryonal toxicity, foetal and neonatal morbidity and mortality when administered to pregnant women.

There have been reports of spontaneous abortion, oligohydramnios and newborn renal dysfunction, when pregnant women have inadvertently taken valsartan.

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

Lactation:

Hydrochlorothiazide crosses the placenta and is excreted in human milk. Thus, it is not advisable to use CO-MIGROBEN in lactating mothers.

Females and males of reproductive potential

CO-MIGROBEN should not be used 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.

4.7 Effects on ability to drive and use machines

It is advisable to exercise caution when driving and operating machinery.

4.8 Undesirable effects

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

Adverse reactions have been ranked under headings of frequency using the following convention:

very common (> 1/10); common (> 1/100, < 1/10); uncommon (> 1/1 000, < 1/100); rare (> 1/10 000, < 1/1 000); very rare (< 1/10 000), not known (cannot be estimated form the available data). Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.

Table 1: frequency of adverse drug reactions with valsartan/hydrochlorothiazide

Blood and lymphatic system disorders	
Not known	Neutropenia
Metabolism and nutrition disorders	
Uncommon Not known	Dehydration Hypokalaemia, hyponatraemia
Nervous system disorders	
Very rare Uncommon Not known	Dizziness Parasthaesia Syncope

Eye Disorders	
Uncommon	Blurred vision
Ear and Labyrinth disorders	
Uncommon	Tinnitus
Vascular disorders	
Uncommon	Hypotension
Respiratory, thoracic and mediastinal disorders	
Uncommon Not known	Cough Non-cardiogenic pulmonary oedema
Gastrointestinal disorders	
Very rare	Diarrhoea
Musculoskeletal and connective tissue disorders	
Uncommon Very rare	Myalgia Arthralgia
Renal and urinary disorders	
Not known	Renal impairment
General disorders and administration site conditions	
Uncommon	Fatigue
Investigations	
Not known	Increased blood uric acid, increased blood bilirubin and blood creatinine, increased blood urea

The following events have also been observed during clinical trials: Abdominal pain, upper abdominal pain, anxiety, arthritis, asthenia, back pain, bronchitis, acute bronchitis, chest pain, postural dizziness, dyspepsia, dyspnoea, dry mouth, epistaxis, erectile dysfunction, gastroenteritis, headache, hyperhydrosis, hypoesthesia, influenza, insomnia, ligament sprain, muscle spasms, muscle strain, nasal congestion,

nasopharyngitis, nausea, neck pain, oedema, peripheral oedema, otitis media, pain in extremity, palpitations, pharyngolaryngal pain, pollakiuria, pyrexia, rash, sinusitis, sinus congestion, somnolence tachycardia, upper respiratory tract infections, urinary tract infections, vertigo, viral infections, vision disturbance.

Post-marketing data revealed cases of angioneurotic oedema, rash, pruritus, and other hypersensitivity/ allergic reactions including serum sickness, and vasculitis.

Cases of renal impairment and myalgia have also been reported.

There have also been reported cases of hydrochlorothiazide-induced pulmonary oedema with granulocytic infiltration and IgG deposition in alveolar membranes. Non-cardiogenic pulmonary oedema may be an immunologically mediated idiosyncratic reaction to hydrochlorothiazide.

Additional Information on the individual components

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

Valsartan

Table 2 Frequency of adverse drug reactions with Valsartan

Infections and infestations	
Less frequent	Pharyngitis, rhinitis, sinusitis, upper respiratory tract infection, viral infections
Blood and lymphatic system disorders	
Not known	Decreased haemoglobin, decreased haematocrit, thrombocytopenia

Immune system disorders	
Not known	Hypersensitivity including serum sickness, angioedema
Metabolism and nutrition disorders	
Not known	Increased blood potassium
Psychiatric disorders	
Less frequent	Insomnia, decreased libido
Nervous system disorders	
Less frequent	Dizziness, headache
Ear and labyrinth disorders	
Less frequent	Vertigo
Vascular	
Not known	Vasculitis
Gastrointestinal disorders	
Less frequent	Abdominal pain, diarrhoea
Very rare	Intestinal angioedema
Hepatobiliary disorders	
Not known	Abdominal liver function test
Skin and subcutaneous tissue disorders	
Less frequent	Rash, dermatitis bullous, pruritus
Musculoskeletal and connective tissue disorders	
Less frequent	Arthralgia, asthenia, back pain
Renal and urinary disorders	
Less frequent	Renal failure

Hydrochlorothiazide

Table 3 Frequency of adverse reactions with Hydrochlorothiazide

Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	
Not known:	Non-melanoma skin cancer (basal cell carcinoma and squamous cell carcinoma)
Blood and lymphatic disorders	
Rare: Less frequent: Not known:	Thrombocytopenia sometimes with purpura Leucopenia, agranulocytosis, bone marrow failure and haemolytic anaemia Aplastic anaemia
Immune system disorders	
Less frequent:	Necrotizing vasculitis, vascular disorders, hypersensitivity reactions – respiratory distress including pneumonitis and pulmonary oedema, respiratory disorders
Metabolism and nutrition disorders	
Frequent: Less frequent:	Mainly at higher doses, increased blood lipids, hypomagnesaemia, hyperuricaemia, decreased appetite. Hypercalcaemia, hyperglycaemia, glucosuria and worsening of diabetic metabolic state, hypochloraemia alkalosis, metabolic alkalosis
Psychiatric disorder	
Less frequent:	Sleep disorders, depression
Nervous System disorders	
Less frequent:	Headache, dizziness, and paraesthesia
Eye disorders	

Less frequent: Not known:	Visual impairment Angle-closure glaucoma
Cardiac disorder	
Less frequent:	Dysrhythmias
Vascular disorders	
Frequent:	Orthostatic hypotension, which may be aggravated by alcohol, anaesthetics or sedatives
Gastrointestinal disorders	
Frequent: Rare: Less frequent:	Nausea, vomiting Abdominal discomfort, constipation and diarrhoea Pancreatitis
Hepatobiliary disorders	
Less frequent:	Cholestasis or jaundice
Skin or subcutaneous tissue disorders	
Frequent:	Urticaria and other forms of rash
Rare:	Photosensitivity reaction
Less frequent:	Toxic epidermal necrolysis, cutaneous lupus-erythematosus-like reactions, reactivation of cutaneous lupus erythematosus
Not known:	Erythema multiforme
Musculoskeletal and connective tissue disorders	
Not known:	Muscle spasms
Renal and urinary disorders	
Not known:	Acute renal failure, renal disorder
Reproductive system and breast disorders	
Common:	Erectile dysfunction

General disorders and administration site conditions	
Not known:	Pyrexia, asthenia

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

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

Pharmacological classification (ATC Code): C09DA03

A 7.1.3 Vascular medicines – other hypotensives

Valsartan in an orally active, specific angiotensin II (Ang II) receptor antagonist. It acts selectively on the angiotensin 1 receptor subtype, which is responsible for the known actions of the angiotensin II. Valsartan does not exhibit any partial agonist activity at the angiotensin 1 receptor and has much (about 20 000-fold) greater affinity for the angiotensin 1 receptor than for the angiotensin 2 receptor.

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 action is achieved within 4 to 6 hours.

The 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 the diuretic effect 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 mechanisms of the antihypertensive effects of the thiazide diuretics are not fully known.

5.2 Pharmacokinetic properties

Pharmacokinetic Properties:

Valsartan:

Valsartan is absorbed after oral administration, although the amount is absorbed varies widely. Mean absolute bioavailability for Diovan is 23 %. Valsartan shows multi-exponential decay kinetics (T½ α < 1 h and t½ β about 9 h).

The pharmacokinetics of valsartan is linear in the dose range tested. There is no change in the kinetics of valsartan on repeated administration and little accumulation when dosed once daily. Plasma concentrations were observed to be similar in males and females.

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 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 h 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 h). The distribution and elimination kinetics is described by a bi-exponential decay function, with a terminal half-life of 6 to 15 h.

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 is not markedly affected by the co-administration of hydrochlorothiazide. This observed interaction has no impact on the combined use of valsartan and hydrochlorothiazide.

Elderly:

A significantly higher systemic exposure to valsartan was observed in 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:

At the recommended dose of CO-MIGROBEN no dose adjustment is required for patients with mild renal impairment.

In patients with moderate to severe renal impairment (creatinine clearance < 70 mL/min) and patients undergoing dialysis no data is available for CO-MIGROBEN. Valsartan is highly bound to plasma protein and is not removed by dialysis whereas clearance of hydrochlorothiazide will be achieved by dialysis.

Renal clearance of hydrochlorothiazide id 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 marked effect on the kinetics of hydrochlorothiazide (see section 4.3).

Hepatic impairment:

In patients with mild to moderate hepatic dysfunction, exposure to valsartan is increased approximately 2-fold. There is no data available on the use of valsartan in patients with severe hepatic dysfunction.

Valsartan/hydrochlorothiazide combination should be used with particular caution in patients with biliary obstructive orders and severe hepatic impairment (see section 4.3 and 4.4).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal silicon dioxide; crospovidone; hydroxypropyl-methylcellulose; magnesium stearate; microcrystalline cellulose; polyethylene glycol; talc; titanium dioxide (E171) (CO-MIGROBEN 80/12,5 and CO-MIGROBEN 160/12,5); red iron oxide (E172) (CO-MIGROBEN 80/12,5 and CO-MIGROBEN 160/12,5); yellow iron oxide (E172) (CO-MIGROBEN 80/12,5).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Protect from moisture and, store below 30 °C.

Keep containers well closed.

6.5 Nature and contents of container

CO-MIGROBEN® 80:

28 tablets in PA/Al/PVC blisters or PVC/PVDC blisters.

CO-MIGROBEN® 160:

28 tablets in PA/Al/PVC blisters or PVC/PVDC blisters.

Blisters are packed into an outer carton.

6.6 Special precautions for disposal and other handling

No special instructions for disposal.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Novartis South Africa (Pty) Ltd.

Magwa Crescent West

Waterfall City

Jukskei view

Johannesburg

2090

+27 11 347 6600

8. REGISTRATION NUMBERS

CO-MIGROBEN® 80/12,5: 43/7.1.3/0083

CO-MIGROBEN® 160/12,5: 43/7.1.3/0084

9. DATE OF FIRST AUTHORISATION

23 July 2010

10. DATE OF REVISION OF THE TEXT

17 March 2026