NOVARTIS

# CO-COPALIA 5 mg/160 mg/12.5 mg
# CO-COPALIA 10 mg/160 mg/12.5 mg
# CO-COPALIA 5 mg/160 mg/25 mg
# CO-COPALIA10 mg/160 mg/25 mg
# CO-COPALIA 10 mg/320 mg/25 mg

## Film-coated tablets

**(amlodipine/valsartan/hydrochlorothiazide)**

Professional Information

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**SCHEDULING STATUS S3**

## 1. NAME OF THE MEDICINE

CO-COPALIA 5 mg/160 mg/12,5 mg film-coated tablets

CO-COPALIA 10 mg/160 mg/12,5 mg film-coated tablets

CO-COPALIA 5 mg/160 mg/25 mg film-coated tablets

CO-COPALIA 10 mg/160 mg/25 mg film-coated tablets

CO-COPALIA 10 mg/320 mg/25 mg film-coated tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

CO-COPALIA 5 mg/160 mg/12,5 mg:

Each film-coated tablet contains 6,94 mg amlodipine besylate (equivalent to 5 mg of amlodipine base), 160 mg of valsartan and 12,5 mg hydrochlorothiazide.

CO-COPALIA 10 mg/160 mg/12,5 mg:

Each film-coated tablet contains 13,87 mg amlodipine besylate (equivalent to 10 mg of amlodipine base), 160 mg of valsartan and 12,5 mg hydrochlorothiazide.

CO-COPALIA 5 mg/160 mg/25 mg:

Each film-coated tablet contains 6,94 mg amlodipine besylate (equivalent to 5 mg of amlodipine base), 160 mg of valsartan and 25 mg hydrochlorothiazide.

CO-COPALIA 10 mg/160 mg/25 mg:

Each film-coated tablet contains 13,87 mg amlodipine besylate (equivalent to 10 mg of amlodipine base), 160 mg of valsartan and 25 mg hydrochlorothiazide.

CO-COPALIA 10 mg/320 mg/25 mg:

Each film-coated tablet contains 13,87 mg amlodipine besylate (equivalent to 10 mg of amlodipine base), 320 mg of valsartan and 25 mg hydrochlorothiazide.

Sugar free.

For the full list of excipients, see section 6.1.

**3. PHARMACEUTICAL FORM**

CO-COPALIA 5 mg/160 mg/12,5 mg:

White film-coated tablet, ovaloid, biconvex with bevelled edges. Debossed with “NVR” on one side and “VCL” on the other. Length approx. 15 mm and width approx. 5,9 mm.

CO-COPALIA 10 mg/160 mg/12,5 mg:

Pale yellow film-coated tablet, ovaloid, biconvex with bevelled edges. Debossed “NVR” on one side and “VDL” on the other. Length approx. 15 mm and width approx. 5,9 mm.

CO-COPALIA 5 mg/160 mg/25 mg:

Yellow film-coated tablet, ovaloid, biconvex with bevelled edges. Debossed “NVR” on one side and “VEL” on the other. Length approx. 15 mm and width approx. 5,9 mm.

CO-COPALIA 10 mg/160 mg/25 mg:

Brown-yellow film-coated tablet, ovaloid, biconvex with bevelled edges. Debossed “NVR” on one side and “VHL” on the other. Length approx. 15 mm and width approx. 5,9 mm.

CO-COPALIA 10 mg/320 mg/25 mg:

Brown-yellow film-coated tablet, ovaloid, biconvex with bevelled edges. Debossed “NVR” on one side and “VFL” on the other. Length approx. 19 mm and width approx. 7,5 mm.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Treatment of essential hypertension in patients stabilised on individual components given at the same doses.

CO-COPALIA is not indicated for the initial therapy of hypertension (see section 4.2*)*.

### 4.2 Posology and method of administration

The recommended dose is one tablet per day (the 5 strengths are listed under section 2).

If a tablet shows signs of cracking the tablet should not be taken.

Patients stabilised with valsartan, amlodipine and hydrochlorothiazide from separate tablets may be switched to CO-COPALIA containing the same component doses.

The maximum antihypertensive effect of CO-COPALIA is reached within two weeks after a change in dose. The maximum recommended dose of CO-COPALIA is 10/320/25 mg.

CO-COPALIA can be taken with or without food. It is recommended to take CO-COPALIA with water.

**In elderly > 65 years**

Starting with the lowest available dose of amlodipine should be considered. The lowest strength of CO-COPALIA contains 5 mg of amlodipine (see section 2).

**Paediatric population (below 18 years)**

*Children and adolescents (below 18 years):*

CO-COPALIA is not recommended for use in patients aged below 18 years due to a lack of data on safety and efficacy.

**Renal impairment:**

- No dosage adjustment is required for patients with mild to moderate renal impairment (see section 4.8 and section 4.4).
- Due to the hydrochlorothiazide component, CO-COPALIA is not recommended in patients with anuria and severe renal impairment (creatinine clearance < 30 ml/min) (see section 4.3 and section 5.2).

**Hepatic impairment:**

Due to the valsartan, hydrochlorothiazide and amlodipine components, particular caution should be exercised when administering CO-COPALIA in patients with hepatic impairment or biliary obstructive disorders. Starting with the lowest avaliable dose of amlodipine should be considered. The lowest strength of CO-COPALIA contains 5 mg of amlodipine.

CO-COPALIA is contraindicated in patients with severe hepatic impairment (Child Pugh C) (see section 4.3).

**4.3 Contraindications**

- Hypersensitivity to amlodipine, valsartan, hydrochlorothiazide and other sulfonamides or to any of the excipients of CO-COPALIA.
- The use of CO-COPALIA during pregnancy and lactation is contra-indicated (see section 4.6). CO-COPALIA should be discontinued as soon as possible when pregnancy is suspected.
- A history of angioedema related to previous therapy with angiotensin receptor blockers (ARBs): These patients must never again be given these medicines.
- Hereditary or idiopathic angioedema.
- Severe hepatic impairment (Child Pugh C).
- CO-COPALIA should not be given to patients with Addison’s disease.
- Anuria, severe renal impairment (creatinine clearance less than 30 mL/min).

- Lithium therapy: Concomitant administration with CO-COPALIA may lead to toxic blood concentrations of lithium (see section 4.5).
- Refractory hypokalaemia, hyponatraemia, hypercalcaemia and symptomatic hyperuricaemia.
- Safety and efficacy have not been established in children less than 18 years of age.
- Safety has not been established in porphyria.
- Hypertrophic obstructive cardiomyopathy (HOCM).
- Bilateral renal artery stenosis.
- Renal artery stenosis in patients with a single kidney.
- Aortic stenosis and mitral valve stenosis.
- Concomitant therapy with potassium sparing diuretics such as spironolactone, triamterene, amiloride.
- Concomitant use of fluoroquinolones with ACE inhibitors/Angiotensin blockers is contraindicated in patients with moderate (creatinine clearance <60 mL/min) to severe renal impairment (creatinine clearance <30 mL/min) and in elderly patients.
- The concomitant use of CO-COPALIA with aliskiren-containing products is contraindicated.
- Patients with a history of previous and/or current basal cell carcinomas and/or squamous cell carcinomas of the skin and lip.

**4.4 Special warnings and precautions for use**

***Sodium- and/or volume depleted patients:***

Excessive hypotension, including orthostatic hypotension was seen in 1,7 % of patients treated with the maximum dose of CO-COPALIA (10/320/25 mg) compared to 1,8 % of valsartan/hydrochlorothiazide (320/25 mg) patients, 0,4 % of amlodipine/valsartan (10/320 mg) patients, and 0,2 % of hydrochlorothiazide/amlodipine (25/10 mg) patients in a controlled trial in patients with moderate to severe uncomplicated hypertension. In patients with an activated renin-angiotensin system, such as volume-and/or salt-depleted patients receiving high doses of diuretics, symptomatic hypotension may occur in patients receiving angiotensin receptor blockers. This condition should be corrected prior to

administration of CO-COPALIA, or the treatment should start under close medical supervision. If excessive hypotension occurs with CO-COPALIA, the patient should be placed in the supine position and, if necessary, given an intravenous infusion of 0,9 % sodium chloride solution. Treatment can be continued once blood pressure has been stabilised.

***Renal impairment:***

No dosage adjustment of CO-COPALIA is required for patients with mild to moderate renal impairment. Due to the hydrochlorothiazide component, CO-COPALIA is not recommended for use in patients with severe renal impairment (creatinine clearance < 30 mL/min) (see section 4.3).
Thiazide diuretics may precipitate azotaemia in patients with chronic kidney disease. When CO-COPALIA is used in patients with renal impairment periodic monitoring of serum electrolytes (including potassium), creatinine and uric acid serum levels is recommended.

***Concomitant use with fluoroquinolones***

The concomitant use of fluoroquinolones with ACE inhibitors/Angiotensin receptor blockers is contraindicated in patients with moderate (creatinine clearance< 60 mL/min) to severe renal impairment (creatinine clearance< 30 mL/min) and in elderly patients.
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.
Patients currently treated with concomitant use of ACE inhibitors/Angiotensin receptor blockers and fluoroquinolones should contact their doctor to re-evaluate their treatment.

***Hepatic impairment:***

Valsartan is mostly eliminated unchanged via the bile whereas amlodipine is extensively metabolised by the liver. Particular caution should be exercised when administering CO-COPALIA to patients with hepatic

impairment or biliary obstructive disorders. Because of hydrochlorothiazide, CO-COPALIA is not recommended in patients with severe hepatic impairment (see section 4.3).

***Serum electrolyte changes:***

*Hydrochlorothiazide:*

Concomitant use with potassium supplements, potassium sparing diuretics, salt substitutes containing potassium, or other medicines that may increase potassium levels (heparin, etc.) could lead to hyperkalaemia and should be used with caution. Hypokalaemia has been reported under treatment with thiazide diuretics including hydrochlorothiazide. Frequent monitoring of potassium is recommended (see section 4.3).

Treatment with thiazide diuretics, including hydrochlorothiazide, has been associated with hyponatraemia and hypochloroaemic alkalosis. Thiazides, including hydrochlorothiazide increase the urinary excretion of magnesium, which may result in hypomagnesaemia. As for any patient receiving diuretic therapy, periodic determination of serum electrolytes and potassium in particular should be performed at appropriate intervals.

*Amlodipine -Valsartan - Hydrochlorothiazide*:

In the controlled trial of CO-COPALIA in moderate to severe hypertensive patients, the incidence of hypokalaemia (serum potassium <3,5 mmol/L) at any time post-baseline with the maximum dose of CO-COPALIA (10/320/25 mg) was 9,9 % compared to 24,5 % with hydrochlorothiazide/amlodipine (25/10 mg), 6,6 % with valsartan/hydrochlorothiazide (320/25 mg), and 2,7 % with amlodipine/valsartan (10/320 mg). One patient (0,2 %) discontinued therapy due to an adverse event of hypokalaemia in each of the CO-COPALIA and hydrochlorothiazide/amlodipine groups. The incidence of hyperkalaemia (serum potassium > 5,7 mmol/L) was 0,4 % with CO-COPALIA compared to 0,2 - 0,7 % with the dual therapies.

In the controlled trial of CO-COPALIA, the opposite effects of valsartan 320 mg and hydrochlorothiazide 25 mg on serum potassium approximately balanced each other in many patients. In other patients, one or

the other effect may be dominant. Periodic determinations of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals.

***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.

Hydrochlorothiazide may raise the serum uric acid level due to reduced clearance of uric acid and may cause or exacerbate hyperuricemia as well as precipitate gout in susceptible patients.

Thiazides decrease urinary calcium excretion and may cause mild elevation of serum calcium in the absence of known disorders of calcium metabolism. Since hydrochlorothiazide can increase serum calcium concentrations, CO-COPALIA is contraindicated in patients with hypercalcaemia (see section 4.3). Marked hypercalcaemia unresponsive to thiazide withdrawal or ≥ 12 mg/dL may be evidence of an underlying thiazide independent hypercalcaemic process. Pathological changes in the parathyroid gland of patients with hypercalcaemia and hypophosphatemia have been observed in a few patients on prolonged thiazide therapy. If hypercalcemia occurs, further diagnostic clarification is necessary.

***Non-melanoma skin cancer:***

An increased risk of non-melanoma skin cancer (NMSC) [basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)] with increasing cumulative dose of hydrochlorothiazide exposure has been observed in two epidemiological studies. 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 minimize the risk of skin cancer. Suspicious skin lesions should be promptly examined, potentially including histological examination of biopsies. CO-COPALIA should not be used by patients who have had previous and/or current basal cell carcinomas of the skin and/or lip (see section 4.3 and 4.8).

***Angioedema:***

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

***Patients with heart failure/post-myocardial infarction:***

In general, calcium channel blockers including amlodipine should be used with caution in patients with serious congestive heart failure (New York Heart Association (NYHA) functional class III-IV).
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 azotaemia, 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.

***Patients with acute myocardial infarction:***

Worsening angina pectoris and acute myocardial infarction can develop after starting or increasing the dose of amlodipine, particularly in patients with severe obstructive coronary artery disease.

***Aortic and mitral valve stenosis:***

As with all other vasodilators, special caution is indicated in patients with mitral stenosis or significant aortic stenosis that is not high grade.

***Primary hyperaldosteronism:***

Patients with primary hyperaldosteronism should not be treated with the angiotensin II antagonist valsartan as their renin-angiotensin system is not activated. Therefore, CO-COPALIA is not recommended in this population.

***Choroidal effusion, acute myopia and secondary acute angle-closure glaucoma:***

Hydrochlorothiazide, a sulfonamide, has been associated with an idiosyncratic reaction resulting in acute transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of a treatment initiation. Untreated acute-angle closure glaucoma can lead to permanent vision loss.

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

***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-COPALIA and aliskiren is therefore contraindicated (see section 4.3).

CO-COPALIA should not be used concomitantly with aliskiren. (see section 4.3).

***Photosensitivity***

Cases of photosensitivity reactions have been reported with thiazide diuretics (see section 4.8). If photosensitivity reaction occurs during treatment with CO-COPALIA, it is recommended to stop the treatment. If a readministration of the diuretic is deemed necessary, it is recommended to protect exposed areas to the sun or to artificial UVA.

**4.5 Interaction with other medicines and other forms of interaction**

**Amlodipine:**

The following potential medicine interactions may occur due to the amlodipine component of CO-COPALIA:

***Simvastatin*:**

Co-administration of multiple doses of 10 mg of amlodipine with 80 mg simvastatin resulted in a 77 % increase in exposure to simvastatin compared to simvastatin alone. It is recommended to limit the dose of simvastatin to 20 mg daily in patients on amlodipine.

***CYP3A4 Inhibitors*:**

Co-administration of a 180 mg daily dose of diltiazem with 5 mg amlodipine in elderly hypertensive patients resulted in a 1.6-fold increase in amlodipine systemic exposure. However, strong inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, ritonavir) may increase the plasma concentrations of amlodipine to a greater extent than diltiazem. Caution should therefore be exercised when co-administering amlodipine with CYP3A4 inhibitors.

***Grapefruit Juice:***

The exposure of amlodipine may be increased when co-administered with grapefruit juice due to CYP3A4 inhibition. Administration of amlodipine with grapefruit or grapefruit juice is not recommended.

***CYP3A4 Inducers:***

No information is available on the quantitative effects of CYP3A4 inducers on amlodipine. Patients should be monitored for adequate clinical effect when amlodipine is co-administered with CYP3A4 inducers (e.g. rifampicin, hypericum perforatum)

In monotherapy, amlodipine has been safely administered with thiazide diuretics, beta-blockers, angiotensin-converting enzyme inhibitors, long-acting nitrates, sublingual nitroglycerin, digoxin, warfarin, atorvastatin, sildenafil, aluminium hydroxide gel, magnesium hydroxide and simeticone, cimetidine, non-steroidal anti-inflammatory drugs, antibiotics, and oral hypoglycaemic medicines.

**Valsartan:**

The following potential medicine interactions may occur due to the amlodipine component of CO-COPALIA:

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

***Inhibitors of the uptake or efflux transporters (rifampicin, ciclosporin) or efflux transporter (ritonavir) Transporters****:*

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

In monotherapy with valsartan, no medicine interactions of clinical significance have been found with the following medicines: cimetidine, warfarin, furosemide, digoxin, atenolol, indomethacin, hydrochlorothiazide, amlodipine, glibenclamide.
Concomitant use with potassium supplements, potassium-sparing diuretics, salt substitutes containing potassium, or other medicines that may increase potassium levels (heparin, etc.) requires caution and frequent monitoring of potassium levels.
Concomitant use of fluoroquinolones and ACE inhibitors/Angiotensin receptor blockers may precipitate acute kidney injury (see section 4.3). The mechanism of the possible interaction between the different classes of medicines, over and above different mechanism of kidney damage, is unknown (see section 4.3).

**Valsartan and hydrochlorothiazide**

Reversible increases in serum lithium concentrations and toxicity have been reported during concurrent administration of lithium with ACE inhibitors, angiotensin II receptor antagonists or thiazides. Since renal clearance of lithium is reduced by thiazides, the risk of lithium toxicity may presumably be increased further with CO-COPALIA. Therefore, concurrent use of CO-COPALIA and lithium is contraindicated (see section 4.3).

**Hydrochlorothiazide:**

The following potential medicine interactions may occur due to the hydrochlorothiazide component of CO-COPALIA:

***Skeletal muscle relaxants:*** Thiazides, including hydrochlorothiazide, potentiate the action of non-depolarising muscle relaxants.

***Non-steroidal anti-inflammatory drugs including Cox-2 inhibitors***:
Concomitant administration of NSAIDs (e.g. salicylic acid derivative, indomethacin) may weaken the diuretic and antihypertensive activity of the thiazide component of CO-COPALIA. Concurrent hypovolaemia may induce acute renal failure.

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

***Digoxin:*** Thiazide (hydrochlorothiazide)-induced hypokalaemia or hypomagnesaemia may occur as unwanted effects, favouring the onset of digoxin-induced cardiac dysrhythmias.

***Antidiabetic medicinal products:*** It may prove necessary to readjust the dosage of insulin and of oral antidiabetic medicines.

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

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

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

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

***Carbamazepine:*** Patients receiving hydrochlorothiazide concomitantly with carbamazepine may develop hyponatraemia. Such patients should therefore be advised about the possibility of hyponatraemic reactions, and should be monitored accordingly.

***Other interactions:*** 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 hyperglycaemic effect of diazoxide, and may reduce the renal excretion of cytotoxic medicines (e.g. cyclophosphamide, methotrexate) and potentiate their myelosuppressive effects.

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

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

***Medicinal products affecting serum sodium level:*** The hyponatraemic effect of diuretics, including hydrochlorothiazide, may be intensified by concomitant administration of medicines such as

antidepressants, antipsychotics, etc. Caution is indicated in long-term administration of these medicines (see section 4.4).

**4.6 Fertility, pregnancy and lactation**

Women of childbearing potential should use effective contraception.

**Pregnancy:**

CO-COPALIA is contraindicated in pregnancy as teratogenicity has been shown in experimental animals (see section 4.3). Medicines affecting the renin-angiotensin system, such as CO-COPALIA, can cause foetal and neonatal morbidity and mortality when administered to pregnant women. When pregnancy is detected, CO-COPALIA should be discontinued as soon as possible.

**Lactation:**

It is not known whether valsartan and/or amlodipine are transferred into human milk. Valsartan was transferred into the milk of lactating rats. Hydrochlorothiazide is transferred into human milk. CO-COPALIA is contra-indicated in women who are breast-feeding.

**4.7 Effects on ability to drive and use machines:**

No studies on the effects on the ability to drive and use machines have been performed.

CO-COPALIA may cause dizziness or weariness and may affect mental and/or physical abilities to perform or execute tasks or activities requiring mental alertness, judgment and/or sound coordination and vision.

Amlodipine can have mild or moderate influence on the ability to drive and use machines. If patients taking CO-COPALIA suffer from dizziness, headache, fatigue or nausea the ability to react may be impaired.

**4.8 Undesirable effects**

The presentation of the safety profile of CO-COPALIA is based on the experience with CO-COPALIA, and the individual components.

***Information on CO-COPALIA:***

The safety of CO-COPALIA has been evaluated at its maximum dose of 10/320/25 mg for safety in one controlled clinical study with 2 271 patients, 582 of whom received valsartan in combination with amlodipine and hydrochlorothiazide.

There were no known adverse reactions which occurred specifically with CO-COPALIA in addition to those known to be associated with the individual components.

***Information on individual components:***

Adverse reactions previously reported with one of the individual components may occur with CO-COPALIA even if not observed in the pivotal clinical trial.

Adverse drug reactions observed are ranked under heading of frequency, the most frequent first, 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), including isolated reports. Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.

| **MedDRA System Organ Class** | **Adverse reactions** | **Frequency** | | | |
|---|---|---|---|---|---|
| | | **CO-COPALIA** | **Amlodipine** | **Valsartan** | **HCT** |
| **Infections and Infestations:** | Viral infections, upper respiratory tract infection, sinusitis, pharyngitis, rhinitis | - | - | Not known | - |
| Neoplasms benign, malignant and unspecified (incl. cysts and polyps) | Non-melanoma skin cancer (Basal cell carcinoma and Squamous cell carcinoma) (see *sections 4.4 and 5.1*) | -- | -- | -- | Not known |
| Blood and lymphatic system disorders | Agranulocytosis, bone marrow failure | -- | -- | -- | Very rare |
| | Haemoglobin and haematocrit decreased | -- | -- | Not known | -- |
| | Haemolytic anaemia | -- | -- | -- | Very rare |
| | Leukopenia | -- | Very rare | -- | Very rare |
| | Neutropenia | -- | -- | Not known | -- |

| MedDRA System Organ Class | Adverse reactions | Frequency | | | |
|---|---|---|---|---|---|
| | | CO-COPALIA | Amlodipine | Valsartan | HCT |
| | Thrombocytopenia, sometimes with purpura | -- | Very rare | Not known | Rare |
| | Aplastic anaemia | -- | -- | -- | Not known |
| Immune system disorders | Hypersensitivity | -- | Very rare | Not known | Very rare |
| Metabolism and nutrition disorders | Anorexia | Uncommon | -- | -- | -- |
| | Hypercalcaemia | Uncommon | -- | -- | Rare |
| | Hyperglycaemia | -- | Very rare | -- | Rare |
| | Hyperlipidaemia | Uncommon | -- | -- | -- |
| | Hyperuricaemia | Uncommon | -- | -- | Common |
| | Hypochloraemic alkalosis | -- | -- | -- | Very rare |
| | Hypokalaemia | Common | -- | -- | Very common |
| | Hypomagnesaemia | -- | -- | -- | Common |
| | Hyponatraemia | Uncommon | -- | -- | Common |
| | Worsening of diabetic metabolic state | -- | -- | -- | Rare |

| MedDRA System Organ Class | Adverse reactions | Frequency | | | |
|---|---|---|---|---|---|
| | | CO-COPALIA | Amlodipine | Valsartan | HCT |
| Psychiatric disorders | Depression | -- | Uncommon | -- | Rare |
| | Insomnia/sleep disorders | Uncommon | Uncommon | -- | Rare |
| | Mood swings | -- | Uncommon | -- | |
| | Confusion | -- | Rare | -- | -- |

| MedDRA System Organ Class | Adverse reactions | Frequency | | | |
|---|---|---|---|---|---|
| | | CO-COPALIA | Amlodipine | Valsartan | HCT |
| Nervous system disorders | Coordination abnormal | Uncommon | -- | -- | -- |
| | Dizziness | Common | Common | -- | Rare |
| | Dizziness postural, dizziness exertional | Uncommon | -- | -- | -- |
| | Dysgeusia | Uncommon | Uncommon | -- | -- |
| | Extrapyramidal syndrome | -- | Not known | -- | -- |
| | Headache | Common | Common | -- | Rare |
| | Hypertonia | -- | Very rare | -- | -- |
| | Lethargy | Uncommon | -- | -- | -- |
| | Paraesthesia | Uncommon | Uncommon | -- | Rare |
| | Peripheral neuropathy, neuropathy | Uncommon | Very rare | -- | -- |
| | Somnolence | Uncommon | Common | -- | -- |
| | Syncope | Uncommon | Uncommon | -- | -- |
| | Tremor | -- | Uncommon | -- | -- |
| | Hypoesthesia | -- | Uncommon | -- | -- |
| Eye disorders | Acute angle-closure glaucoma | -- | -- | -- | Not known |
| | Visual disturbance | -- | Uncommon | -- | -- |
| | Visual impairment | Uncommon | Uncommon | -- | Rare |

| MedDRA System Organ Class | Adverse reactions | Frequency | | | |
|---|---|---|---|---|---|
| | | CO-COPALIA | Amlodipine | Valsartan | HCT |
| | Choroidal effusion | -- | -- | -- | Not known |
| Ear and labyrinth disorders | Tinnitus | -- | Uncommon | -- | -- |
| | Vertigo | Uncommon | -- | Uncommon | -- |
| Cardiac disorders | Palpitations | -- | Common | -- | -- |
| | Tachycardia | Uncommon | -- | -- | -- |
| | Arrhythmias (including bradycardia, ventricular tachycardia, and atrial fibrillation) | -- | Very rare | -- | Rare |
| | Myocardial infarction | -- | Very rare | -- | -- |
| Vascular disorders | Flushing | -- | Common | -- | -- |
| | Hypotension | Common | Uncommon | -- | -- |
| | Orthostatic hypotension | Uncommon | -- | -- | Common |
| | Phlebitis, thrombophlebitis | Uncommon | -- | -- | -- |
| | Vasculitis | -- | Very rare | Not known | -- |

| MedDRA System Organ Class | Adverse reactions | Frequency | | | |
|---|---|---|---|---|---|
| | | CO-COPALIA | Amlodipine | Valsartan | HCT |
| Respiratory, thoracic and mediastinal disorders | Cough | Uncommon | Very rare | Uncommon | -- |
| | Dyspnoea | Uncommon | Uncommon | -- | -- |
| | Respiratory distress, pulmonary oedema, pneumonitis | -- | -- | -- | Very rare |
| | Rhinitis | -- | Uncommon | -- | -- |
| | Throat irritation | Uncommon | -- | -- | -- |

| MedDRA System Organ Class | Adverse reactions | Frequency | | | |
|---|---|---|---|---|---|
| | | CO-COPALIA | Amlodipine | Valsartan | HCT |
| Gastrointestinal disorders | Abdominal discomfort, abdominal pain upper | Uncommon | Common | Uncommon | Rare |
| | Breath odour | Uncommon | -- | -- | -- |
| | Change of bowel habit | -- | Uncommon | -- | -- |
| | Constipation | -- | -- | -- | Rare |
| | Decreased appetite | -- | -- | -- | Common |
| | Diarrhoea | Uncommon | Uncommon | -- | Rare |
| | Dry mouth | Uncommon | Uncommon | -- | -- |
| | Dyspepsia | Common | Uncommon | -- | -- |
| | Gastritis | -- | Very rare | -- | -- |
| | Gingival hyperplasia | -- | Very rare | -- | -- |
| | Nausea | Uncommon | Common | -- | Common |
| | Pancreatitis | -- | Very rare | -- | Very rare |
| | Vomiting | Uncommon | Uncommon | -- | Common |

| MedDRA System Organ Class | Adverse reactions | Frequency | | | |
|---|---|---|---|---|---|
| | | CO-COPALIA | Amlodipine | Valsartan | HCT |
| Hepatobiliary disorders | Liver function test abnormal, including blood bilirubin increase | -- | Very rare** | Not known | -- |
| | Hepatitis | -- | Very rare | -- | -- |
| | Intrahepatic cholestasis, jaundice | -- | Very rare | -- | Rare |

| MedDRA System Organ Class | Adverse reactions | Frequency | | | |
|---|---|---|---|---|---|
| | | CO-COPALIA | Amlodipine | Valsartan | HCT |
| Skin and subcutaneous tissue disorders | Alopecia | -- | Uncommon | -- | |
| | Angioedema | -- | Very rare | Not known | -- |
| | Dermatitis bullous | -- | -- | Not known | -- |
| | Cutaneous lupus erythematosus-like reactions, reactivation of cutaneous lupus erythematosus | -- | -- | -- | Very rare |
| | Erythema multiforme | -- | Very rare | -- | Not known |
| | Exanthema | -- | Uncommon | -- | -- |
| | Hyperhidrosis | Uncommon | Uncommon | -- | -- |
| | Photosensitivity reaction* | -- | Very rare | -- | Rare |
| | Pruritus | Uncommon | Uncommon | Not known | -- |
| | Purpura | -- | Uncommon | -- | Rare |
| | Rash | -- | Uncommon | Not known | Common |
| | Skin discoloration | -- | Uncommon | -- | -- |
| | Urticaria and other forms of rash | -- | Very rare | -- | Common |

| MedDRA System Organ Class | Adverse reactions | Frequency | | | |
|---|---|---|---|---|---|
| | | CO-COPALIA | Amlodipine | Valsartan | HCT |
| | Vasculitis necrotising and toxic epidermal necrolysis | -- | Not known | -- | Very rare |
| | Exfoliative dermatitis | -- | Very rare | -- | -- |
| | Stevens-Johnson syndrome | -- | Very rare | -- | -- |
| | Quincke oedema | -- | Very rare | -- | -- |
| Musculoskeletal and connective tissue disorders | Arthralgia | -- | Uncommon | -- | -- |
| | Back pain | Uncommon | Uncommon | -- | -- |
| | Joint swelling | Uncommon | -- | -- | -- |
| | Muscle spasm | Uncommon | Uncommon | -- | Not known |
| | Muscular weakness | Uncommon | -- | -- | -- |
| | Myalgia | Uncommon | Uncommon | Not known | -- |
| | Pain in extremity | Uncommon | -- | -- | -- |
| | Ankle swelling | -- | Common | -- | -- |

| MedDRA System Organ Class | Adverse reactions | Frequency | | | |
|---|---|---|---|---|---|
| | | CO-COPALIA | Amlodipine | Valsartan | HCT |
| Renal and urinary disorders | Blood creatinine increased | Uncommon | -- | Not known | -- |
| | Micturition disorder | | Uncommon | | |
| | Nocturia | -- | Uncommon | -- | -- |
| | Pollakiuria | Common | Uncommon | | |
| | Renal dysfunction | -- | -- | -- | Not known |
| | Acute renal failure | Uncommon | -- | -- | Not known |
| | Renal failure and impairment | -- | -- | Not known | Rare |
| Reproductive system and breast disorders | Impotence | Uncommon | Uncommon | -- | Common |
| | Gynaecomastia | | Uncommon | -- | -- |
| General disorders and administration site conditions | Abasia, gait disturbance | Uncommon | -- | -- | -- |
| | Asthenia | Uncommon | Uncommon | -- | Not known |
| | Discomfort, malaise | Uncommon | Uncommon | -- | -- |
| | Fatigue | Common | Common | Uncommon | -- |
| | Non cardiac chest pain | Uncommon | Uncommon | -- | -- |
| | Oedema | Common | Common | -- | -- |
| | Pain | -- | Uncommon | -- | -- |
| | Pyrexia | -- | -- | -- | Not known |

| MedDRA System Organ Class | Adverse reactions | Frequency | | | |
|---|---|---|---|---|---|
| | | CO-COPALIA | Amlodipine | Valsartan | HCT |
| Investigations | Lipids increased | | -- | | Very common |
| | Blood urea nitrogen increased | Uncommon | -- | -- | -- |
| | Blood uric acid increased | Uncommon | -- | -- | |
| | Glycosuria | | | | Rare |
| | Blood potassium decreased | Uncommon | -- | -- | -- |
| | Blood potassium increased | -- | -- | Not known | -- |
| | Weight increase | Uncommon | Uncommon | -- | -- |
| | Weight decrease | -- | Uncommon | -- | -- |

**Description of selected adverse reactions**

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

**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**

There is no experience of overdose with CO-COPALIA. The major symptom of overdose with valsartan is possibly pronounced hypotension with dizziness. Overdose with amlodipine may result in excessive peripheral vasodilatation and possibly reflex tachycardia. Marked and potentially prolonged systemic hypotension up to and including shock with fatal outcome have been reported.
Non-cardiogenic pulmonary oedema has rarely been reported as a consequence of amlodipine overdose that may manifest with a delayed onset (24-48 hours post-ingestion) and require ventilatory support. Early resuscitative measures (including fluid overload) to maintain perfusion and cardiac output may be precipitating factors.

Treatment

*Amlodipine*

If the ingestion is recent, gastric lavage may be considered.
Administration of activated charcoal to healthy volunteers immediately or up to two hours after ingestion of amlodipine has been shown to significantly decrease amlodipine absorption.

*Valsartan/Amlodipine/Hydrochlorothiazide*

Clinically significant hypotension due to CO-COPALIA overdose calls for active cardiovascular support including frequent monitoring of cardiac and respiratory function, elevation of extremities, and attention to circulating fluid volume and urine output. A vasoconstrictor may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade.

*Valsartan/Amlodipine*

Both valsartan and amlodipine are unlikely to be removed by haemodialysis whereas clearance of hydrochlorothiazide will be achieved by dialysis.

*Hydrochlorothiazide*

Overdose with hydrochlorothiazide is associated with electrolyte depletion (hypokalaemia, hypochloraemia) and hypovolaemia resulting from excessive diuresis. The most common signs and symptoms of overdose are nausea and somnolence. Hypokalaemia may result in muscle spasms and or accentuate arrhythmia associated with the concomitant use of digitalis glycosides or certain anti-arrhythmic medicinal products.

The degree to which hydrochlorothiazide is removed by haemodialysis has not been established.

## 5 PHARMACOLOGICAL PROPERTIES

### Pharmacotherapeutic group, ATC

Angiotensin II antagonists (valsartan) combinations with dihydropyridine derivatives (amlodipine) and thiazide diuretics (hydrochlorothiazide), ATC code: C09DX01

### 5.1 Pharmacodynamic properties

*Mechanism of action*

CO-COPALIA combines three antihypertensive compounds with complementary mechanisms to control blood pressure in patients with essential hypertension: amlodipine belongs to the calcium antagonist class, valsartan to the angiotensin II (Ang II) antagonist class and hydrochlorothiazide belongs to the thiazide diuretics class of medicines. The combination of these ingredients has an additive antihypertensive effect, reducing blood pressure to a greater degree than either component alone.

***Amlodipine***

*Mechanism of action*

The amlodipine component of CO-COPALIA inhibits the transmembrane entry of calcium ions into cardiac and vascular smooth muscle. The mechanism of the antihypertensive action of amlodipine is due to a direct relaxant effect on vascular smooth muscle, causing a reduction in peripheral vascular resistance and reduction in blood pressure.

*Pharmacodynamic effects*

Experimental data suggest that amlodipine binds to both dihydropyridine and nondihydropyridine binding sites. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels.

Following administration of therapeutic doses to patients with hypertension, amlodipine produces vasodilatation resulting in a reduction of supine and standing blood pressures. These decreases in blood pressure are not accompanied by a significant change in heart rate or plasma catecholamine levels with chronic dosing.

Plasma concentrations correlate with effect in both young and elderly patients.
In hypertensive patients with normal renal function, therapeutic doses of amlodipine resulted in a decrease in renal vascular resistance and an increase in glomerular filtration rate and effective renal plasma flow without change in filtration fraction or proteinuria.
Haemodynamic measurements of cardiac function at rest and during exercise (or pacing) in patients with normal ventricular function treated with amlodipine have generally demonstrated a small increase in cardiac index without significant influence on dP/dt or on left ventricular end diastolic pressure or volume.
In haemodynamic studies, amlodipine has not been associated with a negative inotropic effect when administered in the therapeutic dose range to intact animals and humans, even when co-administered with beta blockers to humans.

***Valsartan:***

*Mechanism of action*

Valsartan is an orally active, and specific angiotensin 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 $AT_2$

receptor, which appears to counterbalance the effect of the $AT_1$ receptor. Valsartan does not exhibit any partial agonist activity at the $AT_1$ receptor and has much (about 20 000-fold) greater affinity for the $AT_1$ receptor than for the $AT_2$ receptor.

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 4-6 hours.

The antihypertensive effect persists over 24 hours after administration. During repeated administration, the maximum reduction in blood pressure with any dose is generally attained within 2-4 weeks and is sustained during long-term therapy. Abrupt withdrawal of Valsartan has not been associated with rebound hypertension or other adverse clinical events.

***Hydrochlorothiazide***

*Mechanism of action*

The site of action of thiazide diuretics is primarily in the renal distal convoluted tubule. It has been shown that there is a high-affinity receptor in the renal cortex as the primary binding site for the thiazide diuretic action and inhibition of sodium chloride 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, thereby affecting electrolyte reabsorption mechanisms: - directly increasing sodium and chloride excretion to an approximately equal extent, and indirectly by this diuretic action reducing plasma volume, with consequent increases in plasma renin activity, aldosterone secretion and urinary potassium loss, and a decrease in serum potassium.

**Non-melanoma skin cancer**

Based on available data from epidemiological studies, cumulative dose-dependent association between HYDROCHLOROTHIAZIDE and NMSC has been observed. One study included a population comprised of 71,533 cases of BCC and of 8,629 cases of SCC matched to 1,430,833 and 172,462 population

controls, respectively. High HYDROCHLOROTHIAZIDE use (≥50,000 mg cumulative) was associated with an adjusted OR of 1.29 (95 % CI: 1.23-1.35) for BCC and 3.98 (95 % CI: 3.68-4.31) for SCC. A clear cumulative dose response relationship was observed for both BCC and SCC. Another study showed a possible association between lip cancer (SCC) and exposure to HYDROCHLOROTHIAZIDE: 633 cases of lip-cancer were matched with 63,067 population controls, using a risk-set sampling strategy. A clear cumulative dose-response relationship was demonstrated with an adjusted OR 2.1 (95 % CI: 1.7-2.6) increasing to OR 3.9 (3.0-4.9) for high use (~25,000 mg) and OR 7.7 (5.7-10.5) for the highest cumulative dose (~100,000 mg). For example: A 100,000 mg cumulative dose corresponds to more than 10 years' daily use with a defined daily dose of 25 mg (see section 4.4 and section 4.8).

**5.2 Pharmacokinetic properties:**

*Linearity:*

Amlodipine, valsartan and hydrochlorothiazide exhibit linear pharmacokinetics.

**Amlodipine**

*Absorption:* After oral administration of therapeutic doses of amlodipine alone, peak plasma concentrations of amlodipine are reached in 6–12 hours. Absolute bioavailability has been calculated as between 64 % and 80 %. Amlodipine bioavailability is unaffected by food ingestion.

*Distribution*: Volume of distribution is approximately 21 l/kg. *In vitro* studies with amlodipine have shown that approximately 97,5 % of circulating compound is bound to plasma proteins.

*Biotransformation*: Amlodipine is extensively (approximately 90 %) metabolised in the liver to inactive metabolites with 10 % of the parent compound and 60 % of the metabolites excreted in the urine.

*Excretion:* Amlodipine elimination from plasma is biphasic with a terminal elimination half-life of approximately 30 to 50 hours. Steady-state plasma levels are reached after continuous administration for 7–8 days. Ten per cent of original amlodipine and 60 % of amlodipine metabolites are excreted in urine.

***Valsartan:***

*Absorption*: Following oral administration of valsartan alone, peak plasma concentrations of valsartan are reached in 2-4 hours. Mean absolute bioavailability is 23 %. Valsartan shows multiexponential decay kinetics ($t_{1/2\alpha}$ <1h and $t_{1/2}$ ß about 9 h). Food decreases the exposure (as measured by AUC) to valsartan by about 40 % and peak plasma concentration ($C_{max}$) by about 50 %, 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, and valsartan can therefore be given either with or without food.

*Distribution:* The steady-state volume of distribution of valsartan after intravenous administration is about 17 litres indicating that valsartan does not distribute into tissues extensively. Valsartan is highly bound to serum proteins (94-97 %), mainly serum albumin.

*Biotransformation:* Valsartan is not transformed to a high extent as only about 20 % of dose is recovered as metabolites. A hydroxy metabolite has been identified in plasma at low concentrations (less than 10 % of the valsartan AUC). This metabolite is pharmacologically inactive.

*Excretion:* Valsartan is primarily eliminated in faeces (about 83 % of dose) and urine (about 13 % of dose) mainly as unchanged compound. Following intravenous administration, plasma clearance of valsartan is about 2 L/h and its renal clearance is 0,62 L/h (about 30 % of total clearance). The half-life of valsartan is 6 hours.

***Hydrochlorothiazide***

*Absorption:* The absorption of hydrochlorothiazide, after an oral dose, is rapid ($T_{max}$ about 2 h). The increase in mean AUC is linear and dose proportional in the therapeutic range. Concomitant administration with food has been reported to both increase and decrease the systemic availability of hydrochlorothiazide compared with the fasted state. The magnitude of these effects is small and has little clinical importance. Absolute bioavailability of hydrochlorothiazide is 60-80 % after oral administration.

*Distribution*: The distribution and elimination kinetics have generally been described as a bi-exponential decay function, with a terminal half-life of 6-15 h. The apparent volume of distribution is 4-8 L/kg. Circulating hydrochlorothiazide is bound to serum proteins (40-70 %), mainly serum albumin. Hydrochlorothiazide also accumulates in erythrocytes at approximately 3 times the level in plasma.
*Biotransformation:* Hydrochlorothiazide is eliminated as unchanged compound.

*Excretion*: 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 being excreted as unchanged compound in the urine.

***Amlodipine/ Valsartan/ Hydrochlorothiazide:***

Following oral administration of CO-COPALIA in normal healthy adults, peak plasma concentrations of amlodipine, valsartan and hydrochlorothiazide are reached in 6-8 hours, 3 hours, and 2 hours, respectively. The rate and extent of absorption of amlodipine, valsartan and hydrochlorothiazide from CO-COPALIA are the same as when administered as individual dosage forms.

***Special populations:***

***Paediatric:***

No pharmacokinetic data are available in the paediatric population for CO-COPALIA.

***Elderly:***

Time to peak plasma amlodipine concentrations is similar in young and elderly patients. In elderly patients, amlodipine clearance tends to decline, causing increases in AUC and elimination half-life. Systemic exposure to valsartan is slightly elevated in the elderly as compared to the young, but 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:***

The pharmacokinetics of amlodipine is not significantly influenced by renal impairment. There is no apparent correlation between renal function (measured by creatinine clearance) and exposure (measured by AUC) to valsartan in patients with different degrees of renal impairment. Patients with mild to moderate renal impairment may therefore receive the usual initial dose (see section 4.2 and section 4.8 and section 4.4).

***Hepatic impairment:***

Patients with hepatic insufficiency have decreased clearance of amlodipine with resulting increase in AUC of approximately 40-60 % in AUC. On average, in patients with mild to moderate chronic liver disease exposure (measured by AUC values) to valsartan is twice that found in healthy volunteers (matched by age, sex and weight). Care should be exercised in patients with liver disease. (see section 4.2, 4.8 and 4.4).

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

CO-COPALIA 5 mg/160 mg/12,5 mg film-coated tablets:

*Tablet core*

Cellulose microcrystalline

Crospovidone

Silica, colloidal anhydrous

Magnesium stearate

*Coating*

Hypromellose

Titanium dioxide (E171)

Macrogol 4000

Talc

CO-COPALIA 10 mg/160 mg/12,5 mg film-coated tablets:

*Tablet core*

Cellulose microcrystalline

Crospovidone

Silica, colloidal anhydrous

Magnesium stearate

*Coating*

Hypromellose

Macrogol 4000

Talc

Titanium dioxide (E171)

Iron oxide, yellow (E172)

Iron oxide, red (E172)

CO-COPALIA 5 mg/160 mg/25 mg film-coated tablets:

*Tablet core*

Cellulose microcrystalline

Crospovidone

Silica, colloidal anhydrous

Magnesium stearate

Coating

Hypromellose

Macrogol 4000

Talc

Titanium dioxide (E171)

Iron oxide, yellow (E172)

CO-COPALIA 10 mg/160 mg/25 mg film-coated tablets:

*Tablet core*

Cellulose microcrystalline

Crospovidone

Silica, colloidal anhydrous

Magnesium stearate

*Coating*

Hypromellose

Macrogol 4000

Talc

Iron oxide, yellow (E172)

CO-COPALIA 10 mg/320 mg/25 mg film-coated tablets:

*Tablet core*

Cellulose microcrystalline

Crospovidone

Silica, colloidal anhydrous

Magnesium stearate

*Coating*

Hypromellose

Macrogol 4000

Talc

Iron oxide, yellow (E172)

**6.2 Incompatibilities**

Not applicable.

**6.3 Shelf life**

2 years.

**6.4 Special precautions for storage**

Store at or below 30 °C. Store in the original package in order to protect from moisture.

**6.5 Nature and contents of container**

7, 14, 28, 56 or 98 film-coated tablets in a colourless, transparent laminated plastic film made of PA/Al/PVC (polyamide/aluminium/polyvinylchloride) blisters with an aluminium foil backing. Not all pack sizes may be marketed.

**6.6 Special precautions for disposal and other handling**

No special requirements.

**7. HOLDER OF CERTIFICATE OF REGISTRATION**

Novartis South Africa (Pty) Ltd

Magwa Crescent West

Waterfall City, Jukskei View

Johannesburg, 2090

South Africa

011 347 6600

**8. REGISTRATION NUMBER(S)**

CO-COPALIA: 5 mg/160 mg /12,5 mg film-coated tablets: 48/7.1.3/0872

CO-COPALIA: 5 mg/160 mg/25 mg film-coated tablets: 48/7.1.3/0873

CO-COPALIA: 10 mg/160 mg/12,5 mg film-coated tablets: 48/7.1.3/0874

CO-COPALIA: 10 mg/160 mg/25 mg film-coated tablets: 48/7.1.3/0875

CO-COPALIA: 10 mg/320 mg/25 mg tablets: 48/7.1.3/0876

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 27 July 2012

**10. DATE OF REVISION OF THE TEXT**

04 February 2026

**11. DOSIMETRY (IF APPLICABLE)**

Not applicable

**12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE)**

Not applicable

| **Namibia** | | |
|---|---|---|
| Co-Copalia 5 mg/160 mg /12,5 mg | 20/7.1.3/0131 | NS2 |
| Co-Copalia 5 mg/160 mg/25 mg | 20/7.1.3/0128 | NS2 |
| Co-Copalia 10 mg/160 mg/12,5 mg | 20/7.1.3/0132 | NS2 |
| Co-Copalia 10 mg/160 mg/25 mg | 20/7.1.3/0129 | NS2 |

**MANUFACTURER**

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