NOVARTIS

COPALIA®

5/160, 10/160, 5/320, 10/320 mg

Film coated Tablets

(Amlodipine/Valsartan)

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1. NAME OF THE MEDICINE

COPALIA® 5/160 mg film-coated tablets

COPALIA® 10/160 mg film-coated tablets

COPALIA® 5/320 mg film-coated tablets

COPALIA® 10/320 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

COPALIA 5/160 mg:

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

COPALIA 10/160 mg:

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

COPALIA 5/320 mg:

Each film-coated tablet contains 6,94 mg amlodipine besylate (equivalent to 5 mg amlodipine base) and 320 mg valsartan.

COPALIA 10/320 mg:

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

For the full list of excipients, see **section 6.1**

3. PHARMACEUTICAL FORM

Film-coated tablet

COPALIA 5/160 mg film-coated tablet

Dark yellow, ovaloid, film-coated tablets with bevelled edges. Debossed with "NVR" on one side and "ECE" on the other.

Length: 14.2 mm approximately

Width: 5.7 mm approximately

COPALIA 10/160 mg film-coated tablet

Light yellow ovaloid, film-coated tablets with bevelled edges. Debossed with "NVR" on one side and "UIC" on the other.

Length: 14.2 mm approximately

Width: 5.7 mm approximately

COPALIA 5/320 mg film-coated tablet

Dark yellow ovaloid, film-coated tablets with bevelled edges. Debossed with "NVR" on one side and "CSF" on the other.

Length: 19.2 mm approximately

Width: 7.7 mm approximately

COPALIA 10/320 mg film-coated tablet

Dark yellow ovaloid, film-coated tablets with bevelled edges. Debossed with "NVR" on one side and "LUF" on the other.

Length: 19.2 mm approximately

Width: 7.7 mm approximately

COPALIA film-coated tablets are non-divisible and cannot be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of mild to moderate essential hypertension in patients ≥ 18 years old whose blood pressure is normalised with the individual components in the same doses as the proposed fixed dose combination of COPALIA.

4.2 Posology and method of administration

Posology:

Patients receiving valsartan and amlodipine from separate tablets may be switched to COPALIA containing the same component doses.

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

Special populations

In Elderly:

Normal dosage regimens are recommended. The elimination half-life of amlodipine 5 mg oral dose is significantly prolonged (48 vs 35 hours; $p<0.025$), suggesting a decreased oral clearance or increased bioavailability. Therefore, COPALIA should be used with caution in elderly subjects.

Renal impairment:

No dosage adjustment is required for patients with mild to moderate renal impairment. COPALIA is contraindicated in patients with severe renal impairment (see **sections 4.3** and **4.4**).

Hepatic impairment:

Caution should be exercised when administering COPALIA to patients with mild to moderate hepatic impairment or biliary obstructive disorders (see **sections 4.8** and **4.4)**

COPALIA is contraindicated in patients with severe hepatic impairment (Child-Pugh C), biliary cirrhosis or cholestasis. (see **section 4.3**)

Paediatric population

COPALIA is not recommended for use in patients aged below 18 years due to a lack of data on safety and efficacy (see **section 4.4**).

Method of administration:

Oral use

It is recommended to take COPALIA with some water.

4.3 Contraindications

- Hypersensitivity to any of the components and any of the excipients of COPALIA.
- 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)
- Aortic valve stenosis
- Mitral valve stenosis
- Haemodynamically unstable heart failure after acute myocardial infarction
- Severe hepatic impairment (Child-Pugh C), biliary cirrhosis or cholestasis
- Severe renal function impairment (creatinine clearance less than 30 ml/min)
- Bilateral renal artery stenosis.
- Renal artery stenosis in patients with a single kidney
- Concomitant therapy with potassium sparing diuretics such as spironolactone, triamterene, amiloride (see **section 4.5**)
- Concomitant use of COPALIA with aliskiren-containing products in patients with diabetes mellitus or renal impairment (GFR <60 ml/min/1.73 m^2) (see **section 4.5** and **5.1**)
- Porphyria.
- Lithium therapy: Concomitant administration with COPALIA may lead to toxic blood concentrations of lithium.
- Pregnancy and lactation (see **section 4.6**).

4.4 Special warnings and precautions for use

Renal Impairment:

Amlodipine is extensively metabolised to inactive metabolites with 10 % excreted unchanged in the urine. Changes in amlodipine plasma concentrations are not correlated with mild renal impairment. COPALIA may be used in such patients at normal doses. In patients with

moderate renal impairment, COPALIA containing reduced amlodipine dosages (5 mg) may need to be administered in these patients. Amlodipine is not dialysable.

No dosage adjustment of COPALIA is required for patients with mild to moderate renal impairment.

Hepatic impairment:

Amlodipine is extensively metabolised by the liver and its half-life is prolonged (48 hours vs 35 hours) and AUC values are higher in patients with impaired liver function. Dosage recommendations have not been established. COPALIA containing lower amlodipine dosages (5 mg) should therefore be administered in these patients.

Caution should be exercised when administering amlodipine to patients with severe (Child-Pugh Class C) hepatic impairment.

Valsartan is mostly eliminated unchanged via the bile.

Particular caution should be exercised when administering COPALIA to patients with hepatic impairment or biliary obstructive disorders.

In patients with mild to moderate hepatic impairment without cholestasis, the maximum recommended dose is 80 mg valsartan. COPALIA is contraindicated in severe hepatic impairment, biliary cirrhosis or cholestasis (see **section 4.3)**

Sodium- and/or volume depleted patients:

Excessive hypotension was seen in 0,4 % of patients with uncomplicated hypertension treated with COPALIA in placebo-controlled studies. In patients with an activated renin-angiotensin system (such as volume- and/or salt-depleted patients receiving high doses of diuretics) who are receiving angiotensin receptor blockers, symptomatic hypotension may occur. Correction of this condition prior to administration of COPALIA or close medical supervision at the start of treatment is recommended.

If hypotension occurs with COPALIA, the patient should be placed in the supine position and, if necessary, given an i.v. infusion of normal saline. Treatment can be continued once blood pressure has been stabilised.

Hyperkalaemia:

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 and with frequent monitoring of potassium (see **section 4.3**).

Renal artery stenosis:

(See **section 4.3**).

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. COPALIA should be immediately discontinued in patients who develop angioedema, and COPALIA should never be re-administered again.

Patients with heart failure/post-myocardial infarction

In a long-term, placebo-controlled study (Praise-2) of amlodipine in patients with NYHA (New York Heart Association Classification) III and IV heart failure of non-ischaemic aetiology, amlodipine was associated with increased reports of pulmonary oedema despite no significant difference in the incidence of worsening heart failure as compared to placebo.

Calcium channel blockers including amlodipine (as contained in COPALIA) should be used with caution in patients with severe 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 receptor antagonists (e.g. valsartan as contained in COPALIA) has been associated with oliguria and/or progressive uraemia, and with acute renal failure and/or death.

Evaluation of patients with heart failure or with history of recent 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.

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

The concomitant use of ACE-inhibitors, angiotensin II receptor blockers (ARBs) (e.g. valsartan as contained in COPALIA) or renin inhibitors such as aliskiren increases the risk of hypotension, hyperkalaemia and decreases renal function including acute renal failure. Dual blockade of RAAS through the combined use of COPALIA and renin inhibitors such as aliskiren is therefore contraindicated (see **section 4.3**).

COPALIA should not be used concomitantly with renin inhibitors such as aliskiren (see **section 4.3**).

Paediatric population

Children:

Safety and effectiveness of COPALIA in children has not been established.

4.5 Interaction with other medicines and other forms of interaction

Interactions common to the combination

No drug-drug interaction studies have been performed with COPALIA and other medicinal products.

To be taken into account with concomitant use

Other antihypertensive agents

Commonly used antihypertensive agents (e.g. alpha blockers, diuretics) and other medicinal products which may cause hypotensive adverse effects (e.g. tricyclic antidepressants, alpha blockers for treatment of benign prostate hyperplasia) may increase the antihypertensive effect of the combination.

Interactions linked to amlodipine

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:

Concomitant use of amlodipine with strong or moderate CYP3A4 inhibitors (protease inhibitors, azole antifungals, macrolides like erythromycin or clarithromycin, verapamil or diltiazem) may give rise to significant increase in amlodipine exposure. The clinical translation of these pharmacokinetic variations may be more pronounced in the elderly. Clinical monitoring and dose adjustment may thus be required.

Grapefruit Juice:

- The exposure of amlodipine may be increased when co-administered with grapefruit juice due to CYP3A4 inhibition. However, co-administration of 240 mℓ of grapefruit juice with a single oral dose of amlodipine 10 mg in 20 healthy volunteers had no significant effect on the pharmacokinetics of amlodipine.

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, Maalox® (Aluminium hydroxide gel,*

Magnesium hydroxide and Simeticone), cimetidine, non-steroidal anti-inflammatory drugs, antibiotics, and oral hypoglycaemic medicines.

Studies have indicated that the co-administration of monotherapy amlodipine with digoxin did not change serum digoxin levels or digoxin renal clearance in renal clearance in normal volunteers, and that co-administration of cimetidine did not alter the pharmacokinetics of amlodipine.

In vitro data from studies with human plasma indicate that monotherapy amlodipine has no effect on protein binding of the medicines tested (digoxin, phenytoin, warfarin, or indomethacin).

In healthy male volunteers, the co-administration of monotherapy amlodipine does not significantly alter the effect of warfarin on prothrombin response time.

Pharmacokinetics studies with cyclosporin have demonstrated that monotherapy amlodipine does not significantly alter the pharmacokinetics of cyclosporin.

Dantrolene (infusion)

In animals, lethal ventricular fibrillation and cardiovascular collapse have been observed in association with hyperkalaemia after administration of verapamil and intravenous dantrolene. Due to the risk of hyperkalaemia, it is recommended that the co-administration of calcium channel blockers such as amlodipine be avoided in patients susceptible to malignant hyperthermia and in the management of malignant hyperthermia.

Interactions linked to valsartan

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

Clinical trial data has shown that dual blockade of the renin-angiotensin-aldosterone-system (RAAS) through the combined use of ACE inhibitors, angiotensin II receptor blockers or renin inhibitors such as 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 concomitant use of COPALIA - including valsartan is contraindicated in patients with severe renal impairment (GFR < 30 mℓ/min) (see **section 4.3**).

Potassium:

Concomitant use of potassium-sparing diuretics (e.g. spironolactone, triamterene, amiloride), potassium supplements, or salt substitutes containing potassium that may lead to increases in serum potassium, and to increase in serum creatinine, are contraindicated.

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 elderly patients, 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 worsening of renal function.
- Therefore, monitoring of renal function is essential when initiating or modifying treatment in patients on COPALIA who are taking NSAIDs concomitantly.

Lithium:

Reversible increases in serum lithium concentrations and toxicity have been reported. Concurrent use of lithium and valsartan as contained in COPALIA, is contraindicated. Therefore, monitoring of serum lithium levels is recommended, if needed (see **section 4.3**).

Inhibitors of the uptake transporter or efflux transporter:

- 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., rifampicin, ciclosporin) or efflux transporter (e.g., ritonavir) may increase the systemic exposure to valsartan.

Others

In monotherapy with valsartan, no interactions of clinical significance have been found with the following medicines: cimetidine, warfarin, furosemide, digoxin, atenolol, indomethacin, hydrochlorothiazide, amlodipine, glibenclamide.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

COPALIA must not be used in women planning to become pregnant. Healthcare professionals prescribing any products acting on the RAAS should counsel women of childbearing potential about the potential risk of these agents during pregnancy. Suitable contraception must be used.

Pregnancy

ACE-inhibitors, as in COPALIA, pass through the placenta and can be presumed to cause disturbance in foetal blood pressure regulatory mechanisms. Oligohydramnios as well as hypotension, oliguria and anuria in newborns, have been reported after administration of ACE-inhibitors in the second and third trimester.

COPALIA acts directly on the renin-angiotensin-aldosterone system therefore it is a risk to the foetus. When pregnancy is detected during therapy, COPALIA must be discontinued as soon as possible. COPALIA must not be used during pregnancy as teratogenicity has been shown with valsartan in experimental animals (see **section 4.3**).

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

Breastfeeding

COPALIA is contra-indicated for women who are breast-feeding (see **section 4.3**).

It is not known whether valsartan is excreted in human milk. It is reported that amlodipine is excreted in human milk. The proportion of the maternal dose received by the infant has been estimated with an interquartile range of 3 – 7 %, with a maximum of 15 %. The effect of amlodipine on infants is unknown. Valsartan was excreted in the milk of lactating rats. COPALIA is contra-indicated for women who are breast-feeding (see **section 4.3**).

Fertility

There is no information on the effects of amlodipine or valsartan on human fertility. Studies in rats did not show any effects of amlodipine or valsartan on fertility (see **section 5.3**).

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. When driving vehicles or using machines it should be taken into account that occasionally dizziness or weariness may occur.

4.8 Undesirable effects

The safety of COPALIA has been evaluated in five controlled clinical studies with 5 175 patients, 2 613 of whom received valsartan in combination with amlodipine at variable dosage combinations.

Adverse reactions 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.

Tabulated list of adverse reactions

MedDRA System organ class	**Adverse reactions**	**Frequency**		
		COPALIA	**Amlodipine**	**Valsartan**
Infections and infestations	Nasopharyngitis	Common	--	--
	Influenza	Common	--	--
Blood and lymphatic system disorders	Haemoglobin and haematocrit decreased	--	--	Not known
	Leucopenia	--	Very rare	--
	Neutropenia	--	--	Not known
	Thrombocytopenia	--	Very rare	Not known
Immune system disorders	Hypersensitivity	Rare	Very rare	Not known
Metabolism and	Hyperglycaemia	--	Very rare	--

MedDRA System organ class	**Adverse reactions**	**Frequency**		
		COPALIA	**Amlodipine**	**Valsartan**
nutrition disorders	Blood potassium increased	--		Not known
Psychiatric disorders	Anxiety	Rare	--	**--**
	Insomnia	--	Uncommon	**--**
	Mood changes	--	Uncommon	**--**
Nervous system disorders	Dizziness	Uncommon	Common	--
	Dysgeusia	--	Uncommon	
	Headache	Common	Common	--
	Hypertonia	--	Very rare	--
	Hypoesthesia	--	Uncommon	--
	Paraesthesia	Uncommon	Uncommon	--
	Peripheral neuropathy	--	Very rare	--
	Postural dizziness	Uncommon	--	--
	Somnolence	Uncommon	Common	--
	Tremor	--	Uncommon	--
Eye disorders	Visual disturbances	Rare	Uncommon	---
Ear and labyrinth disorders	Tinnitus	Rare	--	--
	Vertigo	Uncommon	--	Uncommon
Cardiac disorders	Palpitations	Uncommon	--	--
	Syncope	Rare	--	--
	Tachycardia	Uncommon	--	--
	Dysrhythmias, bradycardia, atrial fibrillation, ventricular tachycardia	--	Very rare	--

MedDRA System organ class	Adverse reactions	Frequency		
		COPALIA	Amlodipine	Valsartan
	Myocardial infarction	--	Very rare	--
Vascular disorders	Angioedema	--	--	--
	Hypotension	Rare	--	--
	Orthostatic hypotension	Uncommon	--	--
	Vasculitis	--	Very rare	Not known
Respiratory, thoracic and mediastinal disorders	Cough	Uncommon	--	Uncommon
	Dyspnoea	--	Uncommon	--
	Pharyngolaryngeal pain	Uncommon	--	--
	Rhinitis	--	Uncommon	--
Gastro-intestinal disorders	Abdominal pain	Uncommon	--	Uncommon
	Altered bowel habits	--	--	--
	Constipation	Uncommon	--	--
	Diarrhoea	Uncommon	--	--
	Dry mouth	Uncommon	--	--
	Dyspepsia	--	Uncommon	--
	Gastritis	--	Very rare	--
	Gingival hyperplasia	--	Very rare	--
	Nausea	Uncommon	--	
	Pancreatitis	--	Very rare	--
	Vomiting	Uncommon	Uncommon	--
Hepato-biliary disorders	Liver function test abnormal, including serum bilirubin	--	--	Not known

MedDRA System organ class	Adverse reactions	Frequency		
		COPALIA	Amlodipine	Valsartan
	increase			
	Hepatitis	--	Very rare	--
	Jaundice	--	Very rare	--
Skin and subcutaneous tissue disorders	Alopecia	--	Uncommon	--
	Angioedema	--	Very rare	Not known
	Dermatitis bullous	--	--	Not known
	Erythema	Uncommon	--	--
	Erythema multiforme	--	Very rare	--
	Exanthema	Rare	--	--
	Hyperhidrosis	Rare	Uncommon	--
	Photosensitivity reaction	--	Uncommon	--
	Pruritus	Rare	Uncommon	--
	Purpura	--	Uncommon	--
	Rash	Uncommon	Uncommon	
	Skin discolouration	--	Uncommon	--
	Urticaria,	--	Very rare	
	Steven-Johnson syndrome	--	Very rare	--
Musculo-skeletal and connective tissue disorders	Arthralgia	Uncommon	Uncommon	--
	Back pain	Uncommon	Uncommon	--
	Joint swelling	Uncommon	--	--
	Muscle spasm	Rare	Uncommon	--

MedDRA System organ class	Adverse reactions	Frequency		
		COPALIA	Amlodipine	Valsartan
	Myalgia	--	Uncommon	Not known
	Sensation of heaviness	Rare	--	--
Renal and urinary disorders	Serum creatinine increased	--	--	Not known
	Micturition disorder	--	Uncommon	--
	Nocturia	--	Uncommon	--
	Pollakiuria,	Rare	--	--
	Polyuria	Rare	--	
	Renal failure and impairment	--	--	Not known
Reproductive system and breast disorders	Erectile dysfunction	Rare	--	--
	Impotence	--	--	--
	Gynaecomastia,	--	Uncommon	--
General disorders and administration site conditions	Asthenia	Common	--	--
	Malaise	--	Uncommon	--
	Fatigue	Common	--	Uncommon
	Facial oedema	Common	--	--
	Flushing, hot flush	Common	--	--
	Non cardiac chest pain	--	Uncommon	--
	Oedema	Common	--	--
	Oedema peripheral	Common	--	--
	Pain	--	Uncommon	--
	Pitting oedema	Common	--	--
Investigations	Hepatic enzyme increased (mostly	--	Very rare	--

MedDRA System organ class	Adverse reactions	Frequency		
		COPALIA	Amlodipine	Valsartan
	consistent with cholestasis)			
	Weight increased	--	Uncommon	--
	Weight decreased	--	Uncommon	--

Additional information on the combination

In double-blind, active- or placebo-controlled completed clinical trials, the incidence of peripheral oedema was statistically lower in patients treated with the combination (5,8 %) than in patients treated with amlodipine monotherapy (9 %).

Additional information on individual components

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

In a long-term, placebo controlled study (PRAISE-2) of amlodipine in patients with NYHA Class III and IV heart failure of non-ischaemic aetiology, amlodipine was associated with increased reports of pulmonary oedema despite no significant difference in the incidence of worsening heart failure as compared to placebo.

Laboratory findings:

Valsartan may be associated with decreases in haemoglobin and haematocrit.

Neutropenia was observed in 1,9 % of patients treated with valsartan versus 1,6 % of patients treated with an ACE inhibitor.

Hypertensive patients:

In controlled clinical trials in hypertensive patients, significant increases in serum creatinine, potassium and total bilirubin were observed, respectively, in 0,8 %, 4,4 %, and 6 % of patients treated with valsartan versus 1,6 %, 6,4 % and 12,9 % of those treated with an ACE inhibitor.

No special monitoring of laboratory parameters is necessary for patients with essential hypertension receiving valsartan therapy.

Occasional elevations of liver function values were reported in hypertensive patients treated with valsartan.

Heart failure patients:

In heart failure patients, increases in serum creatinine greater than 50 % were observed in 3,9 % of valsartan-treated patients compared to 0,9 % of placebo-treated patients. In post-myocardial infarction patients, doubling of serum creatinine was observed in 4,2% of valsartan-treated patients and 3,4 % of captopril-treated patients.

In heart failure patients, increases in serum potassium greater than 20 % were observed in 10 % of valsartan-treated patients compared to 5,1 % of placebo-treated patients.

In heart failure patients, increases in serum urea greater than 50 % were observed in 16,6 % of valsartan-treated patients compared to 6,3 % of placebo-treated patients.

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 asked to report any suspected adverse reactions to SAHPRA via the “6.04 Adverse Drug Reactions Reporting Form”, found online under SAHPRA’s publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

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.

If the ingestion is recent, induction of vomiting 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. Clinically significant

hypotension due to COPALIA overdose calls for early and 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 to reverse the effects of calcium channel blockade.

Both valsartan and amlodipine are unlikely to be removed by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification

A 7.1.3 Vascular medicines – other hypotensives

COPALIA combines two antihypertensive compounds with separate mechanisms of action: amlodipine belongs to the calcium channel antagonist class and valsartan to the angiotensin II (Ang II) receptor antagonist class of medicines.

Amlodipine:

The amlodipine component of COPALIA inhibits the transmembrane entry of calcium ions into cardiac and vascular smooth muscle cells. The mechanism of the antihypertensive action of amlodipine is due to a direct relaxant effect on vascular smooth muscle cells, causing a reduction in peripheral vascular resistances and a reduction in blood pressure. Experimental data suggest that amlodipine binds to both dihydropyridine and nondihydropyridine binding sites. The contractile processes of cardiac muscle cells and vascular smooth muscle cells are dependent upon the movement of extracellular calcium ions into these cells through specific ion-gated 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 elderly and younger 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.

Amlodipine has minimal effect on sinoatrial nodal function or atrioventricular conduction.

Valsartan:

Valsartan is an orally active, and specific angiotensin II receptor antagonist. It acts selectively on the angiotensin 1 (AT1) receptor subtype, which is responsible for the known actions of angiotensin II. The increased plasma levels of angiotensin II following AT1 receptor blockade with valsartan may stimulate the unblocked AT2 receptor, which appears to counterbalance the effect of the AT1 receptor. Valsartan does not exhibit any partial agonist activity at the AT1 receptor and has much (about 20,000 fold) greater affinity for the AT1 receptor than for the AT2 receptor.

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.

Valsartan has been demonstrated to significantly reduce hospitalisations in patients with chronic heart failure (NYHA class II-IV). The benefits were greatest in patients not receiving either an ACE inhibitor or a beta blocker. Valsartan has also been shown to reduce cardiovascular mortality in clinically stable patients with left ventricular failure or left ventricular dysfunction following myocardial infarction.

Valsartan/Amlodipine:

The antihypertensive effect of a single dose of COPALIA persists for 24 hours.

Age, gender and race did not influence the response to COPALIA.

5.2 Pharmacokinetic properties

Linearity:

Valsartan and amlodipine 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. (See absorption of combination tablet below).

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 in hypertensive patients. Amlodipine crosses the placenta and is excreted into breast milk.

Biotransformation

Amlodipine is extensively (approximately 90 %) metabolised in the liver to inactive metabolites.

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 percent 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 multi-exponential decay kinetics (t1/2 α <1 h and t1/2 ß about 9 h). Food decreases the exposure (as measured by AUC) to valsartan by about 40 % and peak plasma concentration (Cmax) 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. (See absorption of combination tablet below).

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 unchanged 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.

Valsartan/Amlodipine

Following oral administration of COPALIA peak plasma concentrations of valsartan and amlodipine are reached in 3 and 6-8 hours, respectively. The rate and extent of absorption of COPALIA are equivalent to the bioavailability of valsartan and amlodipine when administered as individual tablets. (See absorption of individual tablets above).

Special populations:

Paediatric:

No pharmacokinetic data are available in the paediatric population.

Elderly:

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. Since the two components are equally well tolerated in younger and elderly patients, normal dose regimens are recommended (see **section 4.2**).

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, 4.8** and **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**).

5.3 Preclinical safety data

Valsartan

Preclinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity, carcinogenic potential and effects on fertility.

Safety pharmacology and Long-term toxicity: In a variety of preclinical safety studies conducted in several animal species, there were no findings that would exclude the use of therapeutic doses of valsartan in humans.

In preclinical safety studies, high doses of valsartan (200 to 600 mg/kg/day body weight) caused in rats a reduction of red blood cell parameters (erythrocytes, haemoglobin, haematocrit) and evidence of changes in renal haemodynamics (slightly raised blood urea nitrogen, and renal tubular hyperplasia and basophilia in males). These doses in rats (200 and 600 mg/kg/day) are approximately 6 and 18 times the maximum recommended human dose on a mg/m2 basis (calculations assume an oral dose of 320 mg/day and a 60-kg patient). In marmosets at comparable doses, the changes were similar though more severe, particularly in the kidney where the changes developed to a nephropathy including raised blood urea nitrogen and creatinine. Hypertrophy of the renal juxtaglomerular cells was also seen in both species. All changes were considered to be caused by the pharmacological action of valsartan which produces prolonged hypotension, particularly in marmosets. For therapeutic doses of valsartan in humans, the hypertrophy of the renal juxtaglomerular cells does not seem to have any relevance.

Reproductive toxicity: In a rat fertility study, Valsartan had no adverse effects on the reproductive performance of male or female rats at oral doses up to 200 mg/kg/day,

approximately 18 times the maximum recommended human dose on a mg/m2 basis (calculations assume an oral dose of 320 mg/day and a 60-kg patient).

Mutagenicity: Valsartan was devoid of mutagenic potential at either the gene or chromosome level when investigated in various standard in vitro and in vivo genotoxicity studies.

Carcinogenicity: There was no evidence of carcinogenicity when valsartan was administered in the diet to mice and rats for 2 years at doses up to 160 and 200 mg/kg/day, respectively.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

COPALIA 5/160 mg film-coated tablets

Tablet core

Microcrystalline cellulose

Crospovidone

Colloidal silicon dioxide, anhydrous

Magnesium stearate

Coating

Hypromellose

Polyethylene glycol 4000

Talc

Titanium dioxide (E171)

Iron oxide, yellow (E172).

COPALIA 10/160 mg:

Tablet core

Microcrystalline cellulose

Crospovidone

Colloidal silicon dioxide, anhydrous

Magnesium stearate

Coating

Hypromellose

Polyethylene glycol 4000

Talc

Titanium dioxide (E171)

Iron oxide, yellow (E172)

Iron oxide, red (E172).

COPALIA 5/320 mg:

Tablet core

Microcrystalline cellulose

Sodium starch glycolate

Crospovidone

Colloidal silicon dioxide, anhydrous

Magnesium stearate

Coating

Hypromellose

Polyethylene glycol 4000

Talc

Titanium dioxide (E171)

Iron oxide, yellow (E172);

Iron oxide, red (E172).

COPALIA 10/320 mg

Tablet core

Microcrystalline cellulose

Sodium starch glycolate,

Crospovidone

Colloidal silicon dioxide, anhydrous

Magnesium stearate

Coating

Hypromellose

Polyethylene glycol 4000

Talc

Titanium dioxide (E171)

Iron oxide, yellow (E172)

Iron oxide, red (E172).

6.2 Incompatibilities

Not applicable

6.3 Shelf life

COPALIA 5/160 and 10/160 mg: 3 years

COPALIA 5/320 and 10/320 mg: 2 years

6.4 Special precautions for storage

Do not store above 30 °C, store in the original package in order to protect from moisture.
Keep out of the reach and sight of children.

6.5 Nature and contents of container

7, 14, 28, 56, 90 or 98 film-coated tablets in PA/Al/PVC (polyamide/aluminium/polyvinylchloride) blisters with an aluminium foil backing.

Not all pack sizes may be marketed.

The blister foil is imprinted with the proprietary name, company name, batch number and expiry date.

6.6 Special precautions for disposal and other handling

No specific requirements for disposal

7. HOLDER OF CERTIFICATE OF REGISTRATION

Novartis South Africa (Pty) Ltd.

Magwa Crescent West,

Waterfall City,

Jukskei view,

Johannesburg,

2090

8. REGISTRATION NUMBERS

COPALIA® 5/160 mg tablet: 45/7.1.3/0850

COPALIA® 10/160 mg tablet: 45/7.1.3/0851

COPALIA® 5/320 mg tablet: 45/7.1.3/1013

COPALIA® 10/320 mg tablet: 45/7.1.3/1014

9. DATE OF FIRST AUTHORISATION

11 June 2015

10. DATE OF REVISION OF THE TEXT

07 February 2022