SUMMARY OF PRODUCT CHARACTERISTICS

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1. NAME OF THE MEDICINAL PRODUCT

ValNor Combi 5 mg/160 mg film-coated tablets.
ValNor Combi 10 mg/160 mg film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ValNor Combi 5 mg/160 mg film-coated tablets:

Each film-coated tablet contains 5 mg of amlodipine (such as amlodipine besylate) and 160 mg of valsartan.

ValNor Combi 10 mg/160 mg film-coated tablets:

Each film-coated tablet contains 10 mg of amlodipine (such as amlodipine besylate) and 160 mg of valsartan.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

ValNor Combi 5 mg/160 mg film-coated tablets:

Dark yellow film-coated tablets, oblong, biconvex, and engraved with ‘AV5’ on one side and anonymous on the other side.

ValNor Combi 10 mg/160 mg film-coated tablets:

Light yellow film-coated tablets, oblong, biconvex, and engraved with ‘AV10’ on one side and anonymous on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of essential hypertension.

Amlodipine/valsartan is indicated in adults whose blood pressure is not adequately controlled on amlodipine or valsartan monotherapy

4.2 Posology and method of administration

4.2.1 Posology

The recommended dose of amlodipine/valsartan is one tablet per day.

Amlodipine/valsartan 5 mg/160 mg may be administered in patients whose blood pressure is not adequately controlled on amlodipine 5 mg or valsartan 160 mg alone.

Amlodipine/valsartan 10 mg/160 mg may be administered in patients whose blood pressure is not adequately controlled on amlodipine 10 mg or valsartan 160 mg alone, or with amlodipine/valsartan 5 mg/160 mg.

Amlodipine/valsartan be administered with or without food.

Individual dose titration with the components (i.e. amlodipine and valsartan) is recommended before changing to the fixed dose combination. When clinically appropriate, direct change from monotherapy to the fixed-dose combination may be considered.

For convenience, patients receiving valsartan and amlodipine from separate tablets/capsules may be switched to amlodipine/valsartan containing the same component doses.

Renal impairment

There are no available clinical data in severely renally impaired patients. No dosage adjustment is required for patients with mild to moderate renal impairment. Monitoring of potassium levels and creatinine is advised in moderate renal impairment.

Hepatic impairment

Amlodipine/valsartan is contraindicated in patients with serious hepatic failure (see section 4.3).

Caution should be exercised when administering amlodipine/valsartan to patients with hepatic impairment or biliary obstructive disorders (see section 4.4). In patients with mild to moderate hepatic impairment without cholestasis, the maximum recommended dose is 80 mg valsartan. Amlodipine dosage recommendations have not been established in patients with mild to moderate hepatic impairment. When switching eligible hypertensive patients (see section 4.1) with hepatic

impairment to amlodipine or amlodipine/valsartan, the lowest available dose of amlodipine monotherapy or of the amlodipine component, respectively, should be used.

Elderly patients (65 years or over)

In elderly patients, caution is required when increasing the dosage. When switching eligible elderly hypertensive patients (see section 4.1) to amlodipine or amlodipine/valsartan, the lowest available dose of amlodipine monotherapy or of the amlodipine component, respectively, should be used.

Paediatric population

The safety and efficacy of amlodipine/valsartan in children aged below 18 years have not been established. No data are available.

4.2.2 Method of administration

Amlodipine/valsartan is for oral administration.

It is recommended to take amlodipine/valsartan with some water.

4.3 Contraindications

- Hypersensitivity to the active substances, to dihydropyridine derivatives, or to any of the excipients listed in section 6.1.
- Severe hepatic impairment, biliary cirrhosis, or cholestasis.
- Concomitant use of amlodipine/valsartan with aliskiren-containing products in patients with diabetes mellitus or renal impairment (GFR <60 ml/min/1.73 m^2) (see sections 4.5 and 5.1).
- Second and third trimesters of pregnancy (see sections 4.4 and 4.6).
- Severe hypotension.
- Shock (including cardiogenic shock).
- Obstruction of the outflow tract of the left ventricle (e.g. hypertrophic obstructive cardiomyopathy and high-grade aortic stenosis).

- Hemodynamically unstable heart failure after acute myocardial infarction.

4.4 Special warnings and precautions for use

The safety and efficacy of amlodipine in hypertensive crisis has not been established.

Pregnancy

Angiotensin II Receptor Antagonists (AIIRAs) should not be initiated during pregnancy. Unless continued AIIRA therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with AIIRAs should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

Sodium- and/or volume-depleted patients

Excessive hypotension was seen in 0.4% of patients with uncomplicated hypertension treated with amlodipine/valsartan 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 amlodipine/valsartan or close medical supervision at the start of treatment is recommended.

If hypotension occurs with amlodipine/valsartan, the patient should be placed in the supine position and, if necessary, given an intravenous 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 medicinal products that may increase potassium levels (heparin, etc.) should be undertaken with caution and with frequent monitoring of potassium levels.

Renal artery stenosis

Amlodipine/valsartan should be used with caution to treat hypertension in patients with unilateral or bilateral renal artery stenosis or stenosis to a solitary kidney since blood urea and serum creatinine may increase in such patients.

Kidney transplantation

To date there is no experience of the safe use of amlodipine/valsartan in patients who have had a recent kidney transplantation.

Hepatic impairment

Valsartan is mostly eliminated unchanged via the bile. The half-life of amlodipine is prolonged and AUC values are higher in patients with impaired liver function; dosage recommendations have not been established. Particular caution should be exercised when administering amlodipine/valsartan to patients with mild to moderate hepatic impairment or biliary obstructive disorders.

In patients with mild to moderate hepatic impairment without cholestasis, the maximum recommended dose is 80 mg valsartan.

Renal impairment

No dosage adjustment of amlodipine/valsartan is required for patients with mild to moderate renal impairment (GFR >30 ml/min/1.73 m^2). Monitoring of potassium levels and creatinine is advised in moderate renal impairment.

Primary hyperaldosteronism

Patients with primary hyperaldosteronism should not be treated with the angiotensin II antagonist valsartan as their renin-angiotensin system is affected by the primary disease.

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 medicinal products, including ACE inhibitors. Amlodipine/valsartan should be discontinued immediately in patients who develop angioedema and should not be re-administered.

Heart failure/post-myocardial infarction

As a consequence of the inhibition of the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose

renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotaemia and (rarely) with acute renal failure and/or death. Similar outcomes have been reported with valsartan. Evaluation of patients with heart failure or post-myocardial infarction should always include assessment of renal function.

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, should be used with caution in patients with congestive heart failure, as they may increase the risk of future cardiovascular events and mortality.

Aortic and mitral valve stenosis

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

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

There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended (see sections 4.5 and 5.1).

If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes, and blood pressure.

ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

Amlodipine/valsartan has not been studied in any patient population other than hypertension.

4.5 Interaction with other medicinal products and other forms of interaction

Interactions common to the combination

No drug-drug interaction studies have been performed with amlodipine/valsartan 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

Concomitant use not recommended

Grapefruit or grapefruit juice

Administration of amlodipine with grapefruit or grapefruit juice is not recommended as bioavailability may be increased in some patients, resulting in increased blood pressure lowering effects.

Caution required with concomitant use

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 PK variations may be more pronounced in the elderly. Close observation of patients is recommended, and dose adjustment may thus be required.

CYP3A4 inducers (anticonvulsant agents [e.g. carbamazepine, phenobarbital, phenytoin, fosphenytoin, primidone], rifampicin, Hypericum perforatum)

Upon coadministration of known inducers of the CYP3A4, the plasma concentration of amlodipine may vary. Therefore, blood pressure should be monitored, and dose regulation considered both during and after concomitant medication particularly with strong CYP3A4 inducers (e.g. rifampicin, *Hypericum perforatum* [St. John's Wort]).

Simvastatin

Co-administration of multiple doses of 10 mg 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.

Dantrolene (infusion)

In animals, lethal ventricular fibrillation and cardiovascular collapse are observed in association with hyperkalaemia after administration of verapamil and intravenous dantrolene. Due to risk of hyperkalaemia, it is recommended to avoid the co-administration of calcium channel antagonists such as amlodipine in patients susceptible to malignant hyperthermia and in the treatment of malignant hyperthermia.

To be taken into account with concomitant use

Other

In clinical interaction studies, amlodipine did not affect the pharmacokinetics of atorvastatin, digoxin, warfarin, or cyclosporine.

Interactions linked to valsartan

Concomitant use not recommended

Lithium

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin converting enzyme inhibitors or angiotensin II receptor antagonists, including valsartan. Therefore, careful monitoring of serum lithium levels is recommended during concomitant use. If a diuretic is also used, the risk of lithium toxicity may presumably be increased further with amlodipine/valsartan.

Potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium and other substances that may increase potassium levels

If a medicinal product that affects potassium levels is to be prescribed in combination with valsartan, monitoring of potassium plasma levels is advised.

Caution required with concomitant use

Non-steroidal anti-inflammatory medicines (NSAIDs), including selective COX-2 inhibitors, acetylsalicylic acid >3 g/day), and non-selective NSAIDs

When angiotensin II antagonists are administered simultaneously with NSAIDs attenuation of the antihypertensive effect may occur. Furthermore, concomitant use of angiotensin II antagonists and NSAIDs may lead to an increased risk of worsening of renal function and an increase in serum potassium. Therefore, monitoring of renal function at the beginning of the treatment is recommended, as well as adequate hydration of the patient.

Inhibitors of the uptake transporter (rifampicin, ciclosporin) or efflux transporter (ritonavir)

The results of an *in vitro* study with human liver tissue indicate that valsartan is a substrate of the hepatic uptake transporter OATP1B1 and of the hepatic efflux transporter MRP2. Co-administration of inhibitors of the uptake transporter (rifampicin, ciclosporin) or efflux transporter (ritonavir) may increase the systemic exposure 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 aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent (see sections 4.3, 4.4 and 5.1).

Other

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

4.6 Fertility, pregnancy, and lactation

Pregnancy

Amlodipine

The safety of amlodipine in human pregnancy has not been established. In animal studies, reproductive toxicity was observed at high doses (see section 5.3). Use in pregnancy is only recommended when there is no safer alternative and when the disease itself carries greater risk for the mother and foetus.

Valsartan

The use of AIIRAs is not recommended during the first trimester of pregnancy (see section 4.4). The use of AIIRAs is contraindicated during the second and third trimesters of pregnancy (see sections 4.3 and 4.4).

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however, a small increase in risk cannot be excluded. Whilst there is no controlled epidemiological data on the risk with Angiotensin II Receptor Antagonists (AIIRAs), similar risks may exist for this class of drugs. Unless continued AIIRA therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with AIIRAs should be stopped immediately, and, if appropriate, alternative therapy should be started.

AIIRAs therapy exposure during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (see also section 5.3).

Should exposure to AIIRAs have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.

Infants whose mothers have taken AIIRAs should be closely observed for hypotension (see also sections 4.3 and 4.4).

Breast-feeding

Amlodipine is excreted in breast 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. It is recommended not to administer amlodipine/valsartan throughout this period. Alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a new-born or preterm infant.

Fertility

There are no clinical studies on fertility with amlodipine/valsartan.

Valsartan

Valsartan had no adverse effects on the reproductive performance of male or female rats at oral doses up to 200 mg/kg/day. This dose is 6 times the maximum recommended human dose on a mg/m^2 basis (calculations assume an oral dose of 320 mg/day and a 60-kg patient).

Amlodipine

Reversible biochemical changes in the head of spermatozoa have been reported in some patients treated by calcium channel blockers. Clinical data are insufficient regarding the potential effect of amlodipine on fertility. In one rat study, adverse effects were found on male fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Patients taking amlodipine/valsartan and driving vehicles or using machines should take into account that dizziness or weariness may occasionally occur.
Amlodipine can have minor or moderate influence on the ability to drive and use machines. If patients taking amlodipine suffer from dizziness, headache, fatigue, or nausea the ability to react may be impaired.

4.8 Undesirable effects

Summary of the safety profile

The safety of amlodipine/valsartan has been evaluated in five controlled clinical studies with 5,175 patients, 2,613 of whom received valsartan in combination with amlodipine. The following adverse reactions were found to be the most frequently occurring or the most significant or severe:

nasopharyngitis, influenza, hypersensitivity, headache, syncope, orthostatic hypotension, oedema, pitting oedema, facial oedema, oedema peripheral, fatigue, flushing, asthenia and hot flush.

Tabulated list of adverse reactions

Adverse reactions have been ranked under headings of frequency using the following convention: Very common (≥ 1/10); common (≥1/100 and <1/10); uncommon (≥1/1,000 and <1/100); rare (≥1/10,000 and <1/1,000); very rare (<1/10,000); not known (they cannot be estimated nor extrapolated from the available data).

MedDRA System Organ Class	**Undesirable effects**	**Frequency**		
		Amlodipine - Valsartan	**Amlodipine**	**Valsartan**
Infections and infestations	Nasopharyngitis	Common	--	--
	Influenza	Common	--	--
Blood and lymphatic system disorders	Haemoglobin and haematocrit decreased	--	--	Not known
	Leukopenia	--	Very rare	--
	Neutropenia	--	--	Not known
	Thrombocytopenia, sometimes with purpura	--	Very rare	Not known
Immune system disorders	Hypersensitivity	Rare	Very rare	Not known
Metabolism and nutrition disorders	Anorexia	Uncommon	--	--
	Hypercalcemia	Uncommon	--	--
	Hyperglycaemia	--	Very rare	--
	Hyperlipidaemia	Uncommon	--	--
	Hyperuricemia	Uncommon	--	--
	Hypokalaemia	Common	--	--
	Hyponatremia	Uncommon	--	--
Psychiatric disorders	Depression	--	Uncommon	--
	Anxiety	Rare	--	--
	Insomnia/sleep	--	Uncommon	--

	disorders			
	Mood swings	--	Uncommon	--
	Confusion	--	Rare	--
Nervous system disorders	Coordination abnormal	Uncommon	--	--
	Dizziness	Uncommon	Common	--
	Postural dizziness	Uncommon	--	--
	Dysgeusia	--	Uncommon	--
	Extrapyramidal syndrome	--	Not known	--
	Headache	Common	Common	--
	Hypertonia	--	Very rare	--
	Paraesthesia	Uncommon	Uncommon	--
	Peripheral neuropathy, neuropathy	--	Very rare	--
	Drowsiness	Uncommon	Common	--
	Syncope	--	Uncommon	--
	Tremors	--	Uncommon	--
	Hypesthesia	--	Uncommon	--
Eye disorders	Vision disorder	Rare	Uncommon	--
	Vision impairment	Uncommon	Uncommon	--
Ear and labyrinth disorders	Tinnitus	Rare	Uncommon	--
	Vertigo	Uncommon	--	Uncommon
Cardiac disorders	Palpitations	Uncommon	Common	--
	Syncope	Rare	--	--
	Tachycardia	Uncommon	--	--
	Arrhythmias (including bradycardia, ventricular tachycardia, and atrial fibrillation)	--	Very rare	--
	Myocardial infarction	--	Very rare	--
Vascular disorders	Flushing	--	Common	--
	Hypotension	Rare	Uncommon	--

	Orthostatic hypotension	Uncommon	--	--
	Vasculitis	--	Very rare	Not known
Respiratory, thoracic, and mediastinal disorders	Cough	Uncommon	Very rare	Uncommon
	Dyspnoea	--	Uncommon	--
	Pharyngolaryngeal pain	Uncommon	--	--
	Rhinitis	--	Uncommon	--
Gastrointestinal disorders	Abdominal discomfort, abdominal pain upper	Uncommon	Common	Uncommon
	Alteration of bowel habits	--	Uncommon	--
	Constipation	Uncommon	--	--
	Diarrhoea	Uncommon	Uncommon	--
	Dry mouth	Uncommon	Uncommon	--
	Dyspepsia	--	Uncommon	--
	Gastritis	--	Very rare	--
	Gingival hyperplasia	--	Very rare	--
	Nausea	Uncommon	Common	--
	Pancreatitis	--	Very rare	--
	Vomiting	--	Uncommon	--
Hepatobiliary disorders	Liver function test abnormal, including blood bilirubin increase	--	Very rare*	Not known
	Hepatitis	--	Very rare	--
	Intrahepatic cholestasis, 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	--

	Rash	Rare	Uncommon	--
	Hyperhidrosis	Rare	Uncommon	--
	Photosensitivity reactions	--	Uncommon	--
	Pruritus	Rare	Uncommon	Not known
	Purpura	--	Uncommon	--
	Skin rash	Uncommon	Uncommon	Not known
	Skin discolouration	--	Uncommon	--
	Urticaria and other forms of rash	--	Very rare	--
	Exfoliative dermatitis	--	Very rare	--
	Stevens-Johnson syndrome	--	Very rare	--
	Quincke's oedema	--	Very rare	--
	Toxic epidermal necrolysis		Not known	
Musculoskeletal and connective tissue disorders	Arthralgia	Uncommon	Uncommon	--
	Back pain	Uncommon	Uncommon	--
	Inflammation of the joints	Uncommon	--	--
	Muscle twitching	Rare	Uncommon	--
	Myalgia	--	Uncommon	Not known
	Ankle swelling	--	Common	--
	Sensation of heaviness	Rare	--	--
Renal and urinary disorders	Blood creatinine increased	--	--	Not known
	Micturition disorder	--	Uncommon	--
	Nocturia	--	Uncommon	--
	Pollakiuria	Rare	Uncommon	--
	Polyuria	Rare	--	--
	Renal failure and impairment	--	--	Not known
Reproductive system	Impotence	--	Uncommon	--

and breast disorders	Erectile dysfunction	Rare	--	--
	Gynecomastia	--	Uncommon	--
General disorders and administration site conditions	Asthenia	Common	Uncommon	--
	Discomfort, malaise	--	Uncommon	--
	Fatigue	Common	Common	Uncommon
	Facial oedema	Common	--	--
	Flushing, hot flush	Common	--	--
	Non cardiac chest pain	--	Uncommon	--
	Oedema	Common	Common	--
	Peripheral oedema	Common	--	--
	Pain	--	Uncommon	--
	Pitting oedema	Common	--	--
Complementary tests	Blood potassium increased	--	--	Not known
	Weight gain	--	Uncommon	--
	Weight loss	--	Uncommon	--

* Mostly consistent with cholestasis

Additional information on the combination

Peripheral oedema, a recognised side effect of amlodipine, was generally observed at a lower incidence in patients who received the amlodipine/valsartan combination than in those who received amlodipine alone. In double-blind, controlled clinical trials, the incidence of peripheral oedema by dose was as follows:

% of patients who experienced peripheral oedema		**Valsartan (mg)**				
		0	40	80	160	320
Amlodipine (mg)	0	3.0	5.5	2.4	1.6	0.9
	2.5	8.0	2.3	5.4	2.4	3.9
	5	3.1	4.8	2.3	2.1	2.4
	10	10.3	N/A	N/A	9.0	9.5

The mean incidence of peripheral oedema evenly weighted across all doses was 5.1% with the amlodipine/valsartan combination.

Additional information on the individual components

Adverse reactions previously reported with one of the individual components (amlodipine or valsartan) may be potential adverse reactions with amlodipine/valsartan as well, even if not observed in clinical trials or during the post-marketing period.

Amlodipine

Common	Somnolence, dizziness, palpitations, abdominal pain, nausea, ankle swelling.
Uncommon	Insomnia, mood changes (including anxiety), depression, tremor, dysgeusia, syncope, hypoesthesia, visual disturbance (including diplopia), tinnitus, hypotension, dyspnoea, rhinitis, vomiting, dyspepsia, alopecia, purpura, skin discolouration, hyperhidrosis, pruritus, exanthema, myalgia, muscle cramps, pain, micturition disorder, increased urinary frequency, impotence, gynaecomastia, chest pain, malaise, weight increase, weight decrease.
Rare	Confusion.
Very rare	Leukocytopenia, thrombocytopenia, allergic reactions, hyperglycaemia, hypertonia, peripheral neuropathy, myocardial infarction, arrhythmia (including bradycardia, ventricular tachycardia, and atrial fibrillation), vasculitis, pancreatitis, gastritis, gingival hyperplasia, hepatitis, jaundice, hepatic enzymes increased*, angioedema, erythema multiforme, urticaria, exfoliative dermatitis, Stevens-Johnson syndrome, Quincke oedema, photosensitivity.

* mostly consistent with cholestasis

Exceptional cases of extrapyramidal syndrome have been reported.

Valsartan

Not known	Decrease in haemoglobin, decrease in haematocrit, neutropenia, thrombocytopenia, increase of serum potassium, elevation of liver

function values including increase of serum bilirubin, renal failure and impairment, elevation of serum creatinine, angioedema, myalgia, vasculitis, hypersensitivity including serum sickness.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Spanish Pharmacovigilance System of Medicinal Products for Human Use website: https://www.notificaram.es.

4.9 Overdose

Symptoms

There is no experience of overdose with amlodipine/valsartan. The major symptom of overdose with valsartan is possibly pronounced hypotension with dizziness. Overdose with amlodipine may result in excessive peripheral vasodilation 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

If ingestion is recent, induction of vomiting or 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. Clinically significant hypotension due to amlodipine/valsartan 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.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Agents acting on the renin-angiotensin system; angiotensin II antagonists, combinations; angiotensin II antagonists and calcium channel blockers, ATC code: C09DB01

Amlodipine/valsartan combines two antihypertensive compounds with complementary mechanisms to control blood pressure in patients with essential hypertension: amlodipine belongs to the calcium antagonist class and valsartan to the angiotensin II antagonist class of medicines. The combination of these substances has an additive antihypertensive effect, reducing blood pressure to a greater degree than either component alone.

Amlodipine/valsartan

The combination of amlodipine and valsartan produces dose-related additive reduction in blood pressure across its therapeutic dose range. The antihypertensive effect of a single dose of the combination persisted for 24 hours.

Placebo-controlled trials

Over 1,400 hypertensive patients received amlodipine/valsartan once daily in two placebo-controlled trials. Adults with mild to moderate uncomplicated essential hypertension (mean sitting diastolic blood pressure ≥95 and <110 mmHg) were enrolled. Patients with high cardiovascular risks – heart failure, type I and poorly controlled type II diabetes and history of myocardial infarction or stroke within one year – were excluded.

Active-controlled trials in patients who were non-responders to monotherapy

A multicentre, randomised, double-blind, active-controlled, parallel-group trial showed normalisation of blood pressure (trough sitting diastolic blood pressure <90 mmHg at the end of the trial) in patients not adequately controlled on valsartan 160 mg in 75% of patients treated with amlodipine/valsartan 10 mg/160 mg and 62% of patients treated with amlodipine/valsartan 5 mg/160 mg, compared to 53% of patients remaining on valsartan 160 mg. The addition of amlodipine 10 mg and 5 mg produced an additional reduction in systolic/diastolic blood pressure

of 6.0/4.8 mmHg and 3.9/2.9 mmHg, respectively, compared to patients who remained on valsartan 160 mg only.

A multicentre, randomised, double-blind, active-controlled, parallel-group trial showed normalisation of blood pressure (trough sitting diastolic blood pressure <90 mmHg at the end of the trial) in patients not adequately controlled on amlodipine 10 mg in 78% of patients treated with amlodipine/valsartan 10 mg/160 mg, compared to 67% of patients remaining on amlodipine 10 mg. The addition of valsartan 160 mg produced an additional reduction in systolic/diastolic blood pressure of 2.9/2.1 mmHg compared to patients who remained on amlodipine 10 mg only.

Amlodipine/valsartan was also studied in an active-controlled study of 130 hypertensive patients with mean sitting diastolic blood pressure ≥110 mmHg and <120 mmHg. In this study (baseline blood pressure 171/113 mmHg), an amlodipine/valsartan regimen of 5 mg/160 mg titrated to 10 mg/160 mg reduced sitting blood pressure by 36/29 mmHg as compared to 32/28 mmHg with a regimen of lisinopril/hydrochlorothiazide 10 mg/12.5 mg titrated to 20 mg/12.5 mg.

In two long-term follow-up studies the effect of amlodipine/valsartan was maintained for over one year. Abrupt withdrawal of amlodipine/valsartan has not been associated with a rapid increase in blood pressure.

Age, gender, race, or body mass index (≥30 kg/m^2, <30 kg/m^2) did not influence the response to amlodipine/valsartan.

Amlodipine/valsartan has not been studied in any patient population other than hypertension. Valsartan has been studied in patients with post myocardial infarction and heart failure. Amlodipine has been studied in patients with chronic stable angina, vasospastic angina and angiographically documented coronary artery disease.

Amlodipine

The amlodipine component of amlodipine/valsartan 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 reductions in peripheral vascular resistance and in blood pressure. Experimental data suggest that amlodipine binds to both dihydropyridine and non-dihydropyridine 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 vasodilation, 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.

As with other calcium channel blockers, 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.

Amlodipine does not change sinoatrial nodal function or atrioventricular conduction in intact animals or humans. In clinical studies in which amlodipine was administered in combination with beta blockers to patients with either hypertension or angina, no adverse effects on electrocardiographic parameters were observed.

Use in patients with hypertension

A randomised double-blind morbidity-mortality study called the Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT) was performed to compare newer therapies: amlodipine 2.5-10 mg/day (calcium channel blocker) or lisinopril 10-40 mg/day (ACE-inhibitor) as first-line therapies to that of the thiazide-diuretic, chlorthalidone 12.5-25 mg/day in mild to moderate hypertension.

A total of 33,357 hypertensive patients aged 55 or older were randomised and followed for a mean of 4.9 years. The patients had at least one additional coronary heart disease risk factor, including: previous myocardial infarction or stroke (>6 months prior to enrolment) or documentation of other atherosclerotic cardiovascular disease (overall 51.5%), type 2 diabetes (36.1%), high density

lipoprotein - cholesterol <35 mg/dl or <0.906 mmol/l (11.6%), left ventricular hypertrophy diagnosed by electrocardiogram or echocardiography (20.9%), current cigarette smoking (21.9%).

The primary endpoint was a composite of fatal coronary heart disease or non-fatal myocardial infarction. There was no significant difference in the primary endpoint between amlodipine-based therapy and chlorthalidone-based therapy: risk ratio (RR) 0.98 95% CI (0.90-1.07) p=0.65. Among secondary endpoints, the incidence of heart failure (component of a composite combined cardiovascular endpoint) was significantly higher in the amlodipine group as compared to the chlorthalidone group (10.2% versus 7.7%, RR 1.38, 95% CI [1.25-1.52] p<0.001). However, there was no significant difference in all-cause mortality between amlodipine-based therapy and chlorthalidone-based therapy RR 0.96 95% CI [0.89-1.02] p=0.20.

Valsartan

Valsartan is an orally active, potent, and specific angiotensin II receptor antagonist. It acts selectively on the receptor subtype AT_1, 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 receptor subtype AT_2, 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.

Valsartan does not inhibit ACE, also known as kininase II, which converts angiotensin I to angiotensin II and degrades bradykinin. Since there is no effect on ACE and no potentiation of bradykinin or substance P, angiotensin II antagonists are unlikely to be associated with coughing. In clinical trials where valsartan was compared with an ACE inhibitor, the incidence of dry cough was significantly (p <0.05) lower in patients treated with valsartan than in those treated with an ACE inhibitor (2.6% versus 7.9%, respectively). In a clinical trial of patients with a history of dry cough during ACE inhibitor therapy, 19.5% of trial subjects receiving valsartan and 19.0% of those receiving a thiazide diuretic experienced coughing, compared to 68.5% of those treated with an ACE inhibitor (p <0.05). Valsartan is not known to bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

Administration of valsartan to patients with hypertension results in a drop in 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 drop in 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.

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

Two large randomised, controlled trials (ONTARGET [ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial] and VA NEPHRON-D [The Veterans Affairs Nephropathy in Diabetes]) have examined the use of the combination of an ACE inhibitor with an angiotensin II receptor antagonist.

ONTARGET was a study conducted in patients with a history of cardiovascular or cerebrovascular disease, or type 2 diabetes mellitus accompanied by evidence of end-organ damage. VA NEPHRON-D was a study in patients with type 2 diabetes mellitus and diabetic nephropathy.

These studies have shown no significant beneficial effect on renal and/or cardiovascular outcomes and mortality, while an increased risk of hyperkalaemia, acute kidney injury and/or hypotension as compared to monotherapy was observed. Given their similar pharmacodynamic properties, these results are also relevant for other ACE-inhibitors and angiotensin II receptor blockers.

ACE inhibitors and angiotensin II receptor blockers should therefore not be used concomitantly in patients with diabetic nephropathy (see section 4.4).

ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints) was a study designed to test the benefit of adding aliskiren to a standard therapy of an ACE-inhibitor or an angiotensin II receptor blocker in patients with type 2 diabetes mellitus and chronic kidney disease, cardiovascular disease, or both. The study was terminated early because of an increased risk of adverse outcomes. Cardiovascular death and stroke were both numerically more frequent in the aliskiren group than in the placebo group and adverse events and serious adverse events of interest (hyperkalaemia, hypotension, and renal dysfunction) were more frequently reported in the aliskiren group than in the placebo group.

5.2 Pharmacokinetic properties

Linearity

Amlodipine and valsartan exhibit linear pharmacokinetics.

Amlodipine/valsartan

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

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 drug is bound to plasma proteins.

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

Elimination: 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%. Food decreases 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 groups. This reduction in AUC is not, however, 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.

Elimination: Valsartan shows multiexponential decay kinetics ($t_{½\alpha}$ <1 h and $t_{½\beta}$ about 9 h). Valsartan is primarily eliminated in faeces (about 83% of dose) and urine (about 13% of dose), mainly as unchanged drug. 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.

Special populations

Paediatric population (age below 18 years)

Pharmacokinetic data in the paediatric population are not available.

Elderly patients (65 years or over)

Time to peak plasma amlodipine concentrations is similar in young and elderly patients. In elderly patients, amlodipine clearance tends to decline, causing increases in the area under the curve (AUC) and elimination half-life. Mean systemic AUC of valsartan is higher by 70% in the elderly than in the young, therefore caution is required when increasing the dosage.

Renal impairment

The pharmacokinetics of amlodipine are not significantly influenced by renal impairment. As expected for a compound where renal clearance accounts for only 30% of total plasma clearance, no correlation was seen between renal function and systemic exposure to valsartan.

Hepatic impairment

Very limited clinical data are available regarding amlodipine administration in patients with hepatic impairment. Patients with hepatic impairment have decreased clearance of amlodipine with resulting increase 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). Caution should be exercised in patients with liver disease (see section 4.2).

5.3 Preclinical safety data

Amlodipine/valsartan

Adverse reactions observed in animal studies with possible clinical relevance were as follows:

Histopathological signs of inflammation of the glandular stomach were seen in male rats at an exposure of about 1.9 (valsartan) and 2.6 (amlodipine) times the clinical doses of 160 mg valsartan and 10 mg amlodipine. At higher exposures, there were ulceration and erosion of the stomach mucosa in both females and males. Similar changes were also seen in the valsartan alone group (exposure 8.5–11.0 times the clinical dose of 160 mg valsartan).

An increased incidence and severity of renal tubular basophilia/hyalinisation, dilation, and casts, as well as interstitial lymphocyte inflammation and arteriolar medial hypertrophy were found at an exposure of 8–13 (valsartan) and 7–8 (amlodipine) times the clinical doses of 160 mg valsartan and 10 mg amlodipine. Similar changes were found in the valsartan alone group (exposure 8.5–11.0 times the clinical dose of 160 mg valsartan).

In an embryo-foetal development study in the rat, increased incidences of dilated ureters, malformed sternebrae, and unossified forepaw phalanges were noticed at exposures of about 12 (valsartan) and 10 (amlodipine) times the clinical doses of 160 mg valsartan and 10 mg amlodipine. Dilated ureters were also found in the valsartan alone group (exposure 12 times the clinical dose of 160 mg valsartan). There were only modest signs of maternal toxicity (moderate reduction of body weight) in this study. The no-observed-effect-level for developmental effects was observed at 3- (valsartan) and 4- (amlodipine) fold the clinical exposure (based on AUC).

For the single compounds there was no evidence of mutagenicity, clastogenicity or carcinogenicity.

Amlodipine

<u>Reproductive toxicology</u>

Reproductive studies in rats and mice have shown delayed date of delivery, prolonged duration of labour and decreased pup survival at dosages approximately 50-fold greater than the maximum recommended dosage for humans based on mg/kg.

Fertility alterations

There was no effect on the fertility of rats treated with amlodipine (males for 64 days and females 14 days prior to mating) at doses up to 10 mg/kg/day (8-fold* the maximum recommended human dose of 10 mg on a mg/m^2 basis). In another rat study in which male rats were treated with amlodipine besylate for 30 days at a dose comparable with the human dose based on mg/kg, decreased plasma follicle-stimulating hormone and testosterone were found as well as decreases in sperm density and in the number of mature spermatids and Sertoli cells.

Carcinogenesis, mutagenesis

Rats and mice treated with amlodipine in the diet for two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 mg/kg/day showed no evidence of carcinogenicity. The highest dose (similar for mice and twice* the maximum recommended dose of 10 mg on a mg/m^2 basis for rats) was close to the maximum dose tolerated for mice but not for rats.

Mutagenicity studies did not reveal any drug-related effects neither at genetic level nor at chromosomal level.

* Based on patient weight of 50 kg

Valsartan

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

In rats, maternally toxic doses (600 mg/kg/day) during the last days of gestation and lactation led to lower survival, lower weight gain and delayed development (pinna detachment and ear-canal opening) in the offspring (see section 4.6). These doses in rats (600 mg/kg/day) are approximately 18 times the maximum recommended human dose on a mg/m^2 basis (calculations assume an oral dose of 320 mg/day and a 60-kg patient).

In non-clinical safety studies, high doses of valsartan (200 to 600 mg/kg body weight) caused in rats a reduction of red blood cell parameters (erythrocytes, haemoglobin, haematocrit) and evidence of changes in renal haemodynamic (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/m^2 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Microcrystalline cellulose

Crospovidone

Colloidal anhydrous silica

Magnesium stearate

Coating:

Opadry II white 85F18422 (contains: poly (vinyl alcohol), titanium dioxide (E-171), macrogol 4000, and talc).

Yellow iron oxide (E-172).

Red iron oxide (E-172).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

30 months.

6.4 Special precautions for storage

No special storage conditions are required.

6.5 Nature and contents of container

Aluminium/Aluminium-Polyamide-PVC blisters. Each blister contains 28 film-coated tablets.
Pack sizes: 28 film-coated tablets.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

LABORATORIOS NORMON, S.A.
Ronda de Valdecarrizo, 6. 28760 Tres Cantos, Madrid

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10. DATE OF REVISION OF THE TEXT

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