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1. NAME OF THE MEDICINAL PRODUCT

Vamloset® 5 mg/80 mg film-coated tablets
Vamloset® 5 mg/160 mg film-coated tablets
Vamloset® 10 mg/160 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Vamloset 5 mg/80 mg film-coated tablets
Each film-coated tablet contains 5 mg amlodipine (as amlodipine besilate) and 80 mg valsartan.
Vamloset 5 mg/160 mg film-coated tablets
Each film-coated tablet contains 5 mg amlodipine (as amlodipine besilate) and 160 mg valsartan.
Vamloset 10 mg/160 mg film-coated tablets
Each film-coated tablet contains 10 mg amlodipine (as amlodipine besilate) and 160 mg valsartan.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Vamloset 5 mg/80 mg film-coated tablets are brownish yellow, round, slightly biconvex, film-coated tablets with bevelled edges and with possible dark spots.
Vamloset 5 mg/160 mg film-coated tablets are brownish yellow, oval, biconvex, film-coated tablets with possible dark spots.
Vamloset 10 mg/160 mg film-coated tablets are brownish yellow, oval, biconvex, film-coated tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Arterial hypertension (in patients who require treatment with the combination).

4.2 Posology and method of administration

Posology

It is recommended to take Vamloset with some water. Vamloset can be used with or without food one tablet per day.

The recommended daily dose - 1 tablet of Vamloset consists of amlodipine/valsartan dose 5/80 mg, 5/160 mg, 10/160 mg, 5/320 mg or 10/320 mg.

The recommended starting dose of Vamloset is 5/80 mg once a day. The dose may be increased 1-2 weeks after initiation of therapy.

The maximum daily dose is 5/320 mg (based on valsartan), 10/160 mg (based on amlodipine) or 10/320 mg.

Additional information on special populations

In the elderly

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Normal dosage regimens are recommended in the elderly. In these patients, if necessary, it is possible to reduce the initial dose of Vamloset to the lowest dose of amlodipine.

Use in children and adolescents (under the age of 18 years)
Since no data on the safety and effectiveness is available in children and adolescents, this medicine is not recommended for use in these patients.

In patients with renal impairment
No dosage adjustment is required for patients with a creatinine clearance >30 ml/min (see sections 4.4 and 5.2)

In patients with hepatic impairment
Vamloset should be administered with caution (see 4.4 "Special warnings and precautions for use"). Valsartan is contraindicated in patients with severe hepatic impairment, biliary cirrhosis and in patients with cholestasis (see sections 4.3, 4.4 and 5.2). In patients with mild to moderate hepatic impairment without cholestasis, the dose of valsartan component should not exceed 80 mg (Vamloset in doses 5/160 mg, 5/320 mg, 10/150 mg and 10/320 mg is contraindicated).

4.3 Contraindications

- Hypersensitivity to the active substances, to dihydropyridine derivatives, or to any of the excipients listed in section 6.1.
- Hereditary angioedema or oedema in patients with previous therapy with sartans
- Severe hepatic impairment, biliary cirrhosis or cholestasis.
- Severe renal impairment (glomerular filtration rate (GFR) <30 ml/min/1.73 m^2) and patients undergoing dialysis.
- Pregnancy and lactation (see sections 4.4 and 4.6).
- Severe arterial hypotension, collapse or shock (including cardiogenic shock).
- Obstruction of the outflow tract of the left ventricle (e.g. hypertrophic obstructive cardiomyopathy and high grade aortic stenosis).
- Haemodynamically unstable heart failure after acute myocardial infarction.
- Primary hyperaldosteronism.
- The concomitant use of Vamloset with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2)
- Concomitant use with ACE inhibitors in patients with diabetic nephropathy.

Safety of the amlodipine/valsartan fixed combination in patients with unilateral or bilateral renal artery stenosis or stenosis of the renal artery after undergoing a kidney transplant, as well as in children and adolescents under 18 years of age has not been established.

4.4 Special warnings and precautions for use

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

Sodium- and/or volume-depleted patients

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

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If hypotension occurs with Vamloset, 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

Vamloset 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 fixed combination 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 Vamloset to patients with mild to moderate hepatic impairment or biliary obstructive disorders.

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

Renal impairment

No dosage adjustment of Vamloset 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.

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 angiotensin-converting enzyme (ACE) inhibitors. Vamloset 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

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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, ARBs 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, ARBs 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 ARBs should not be used concomitantly in patients with diabetic nephropathy.

Fixed combination 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 fixed combination 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.

Interactions linked to amlodipine

Concomitant use not recommended

Grapefruit or grapefruit juice

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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 pharmacokinetic variations may be more pronounced in the elderly. Clinical monitoring and dose adjustment may thus be required.

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

Upon co-administration 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*).

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 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.

Tacrolimus

There is a risk of increased tacrolimus blood levels when co-administered with amlodipine but the pharmacokinetic mechanism of this interaction is not fully understood. In order to avoid toxicity of tacrolimus, administration of amlodipine in a patient treated with tacrolimus requires monitoring of tacrolimus blood levels and dose adjustment of tacrolimus when appropriate.

Cyclosporine

No drug interaction studies have been conducted with cyclosporine and amlodipine in healthy volunteers or other populations with the exception of renal transplant patients, where variable trough concentration increases (average 0% - 40%) of cyclosporine were observed. Consideration should be given for monitoring cyclosporine levels in renal transplant patients on amlodipine, and cyclosporine dose reductions should be made as necessary.

Clarithromycin

Clarithromycin is an inhibitor of CYP3A4. There is an increased risk of hypotension in patients

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receiving clarithromycin with amlodipine. Close observation of patients is recommended when amlodipine is co administered with clarithromycin.

Mechanistic Target of Rapamycin (mTOR) Inhibitors

mTOR inhibitors such as sirolimus, temsirolimus, and everolimus are CYP3A substrates. Amlodipine is a weak CYP3A inhibitor. With concomitant use of mTOR inhibitors, amlodipine may increase exposure of mTOR inhibitors.

To be taken into account with concomitant use

Others

In clinical studies of amlodipine, there is no significant interaction with thiazide diuretics, alpha-adrenergic blocking agents, beta-blockers, ACE inhibitors, long-acting nitrates, nitroglycerin for sublingual use, digoxin, warfarin, atorvastatin, sildenafil, aluminum or magnesium antacids, simeticone, cimetidine, non-steroidal anti-inflammatory drugs (NSAIDs), antibiotics and hypoglycemic agents for oral administration.

The simultaneous administration of amlodipine and ethanol does not affect the pharmacokinetics of the latter.

Calcium preparations can reduce the effect of calcium channel blockers.

With the simultaneous use of calcium channel blockers and lithium preparations (data are not available for amlodipine), it is possible to increase the manifestation of their neurotoxicity (nausea, vomiting, diarrhea, ataxia, tremor, tinnitus).

Glucocorticosteroids
Decreased antihypertensive effect (fluid and sodium ion retention due to corticosteroids).

Interactions linked to valsartan

Concomitant use is contraindicated

The concomitant use of sartans, including valsartan, with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2)

Concomitant use not recommended

Lithium

Reversible increases in serum lithium concentrations and toxicity have been reported during concurrent use of ACE inhibitors. Despite the lack of experience with concomitant use of valsartan and lithium, this combination is not recommended. If the combination proves necessary, careful monitoring of serum lithium levels is recommended (see section 4.4).

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.

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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. This should be considered at the beginning or at the end of concurrent therapy.

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

Clinical trial data have shown that dual blockade of the RAAS through the combined use of ACE inhibitors, ARBs 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).

Others

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

4.6 Fertility, pregnancy and lactation

Pregnancy

The use of Vamloset is contraindicated during pregnancy.

Given the mechanism of action of angiotensin receptor antagonists II, we can eliminate the risk to the fetus when using the drug in the I trimester of pregnancy.

Whilst there is no controlled epidemiological data on the risk with 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 anti-hypertensive 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.

The use of AIIRAs is contraindicated during the second and third trimesters of pregnancy (see sections 4.3 and 4.4). Exposure to AIIRA therapy 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, hyperkalemia); see also section 5.3 “Preclinical safety data”. Infants whose mothers have taken AIIRAs should be closely observed for hypotension (see also sections 4.3 and 4.4).

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Breast-feeding

Do not use Vamloset during breastfeeding. If the use of Vamloset is unavoidable, breast-feeding should be discontinued.

Amlodipine is excreted in human milk. The median amlodipine concentration ratio of milk/plasma in 31 lactating women with pregnancy-induced hypertension was 0.85 following amlodipine administration at an initial dose of 5mg once daily which was adjusted as needed (mean daily dose and body weight adjusted daily dose: 6mg and 98.7 mcg/kg, respectively). The estimated daily dose of amlodipine in the infant via breast milk was 4.17 mcg/kg.

4.7 Effects on ability to drive and use machines

Patients taking Vamloset 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

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 to <1/10)
- Uncommon (≥1/1,000 to <1/100)
- Rare (≥1/10,000 to <1/1,000)
- Very rare (<1/10,000)
- Not known (cannot be estimated from the available data)

MedDRA System organ class	**Adverse reactions**	**Frequency**		
		Amlodipine/valsartan	**Amlodipine**	**Valsartan**
Infections and infestations	Nasopharyngitis	Common	-	-
	Influenza	Common	-	-
Blood and lymphatic system disorders	Decrease in haemoglobin and in haematocrit	-	-	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	Anorexia	Uncommon	-	-

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and nutrition disorders	Hypercalcaemia	Uncommon	-	-
	Hyperglycaemia	-	Very rare	-
	Hyperlipidaemia	Uncommon	-	-
	Hyperuricaemia	Uncommon	-	-
	Hypokalaemia	Common	-	-
	Hyponatraemia	Uncommon	-	-
Psychiatric disorders	Depression	-	Uncommon	-
	Anxiety	Rare	-	-
	Insomnia/sleep disturbances	-	Uncommon	-
	Mood swings	-	Uncommon	-
	Confusion	-	Rare	-
Nervous system disorders	Coordination abnormal	Uncommon	-	-
	Dizziness	Uncommon	Common	-
	Dizziness postural	Uncommon	-	-
	Dysgeusia	-	Uncommon	-
	Extrapyramidal syndrome	-	Not known	-
	Headache	Common	Common	-
	Hypertonia	-	Very rare	-
	Paraesthesia	Uncommon	Uncommon	-
	Peripheral neuropathy, neuropathy	-	Very rare	-
	Somnolence	Uncommon	Common	-
	Syncope	-	Uncommon	-
	Tremor	-	Uncommon	-
	Hypoesthesia	-	Uncommon	-
Eye disorders	Visual disturbance	Rare	Uncommon	-
	Visual 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	-	Very rare	-

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	tachycardia, and atrial fibrillation)			
	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
	Change of bowel habit	-	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	Hepatic enzyme elevation, including increase of serum bilirubin	-	Very rare*	Not known
	Hepatitis	-	Very rare	-
	Intrahepatic cholestasis, jaundice	-	Very rare	-
Skin and subcutaneous tissue disorders	Alopecia	-	Uncommon	-
	Angioedema	-	Very rare	Not known
	Erythema	Uncommon	-	-
	Erythema multiforme	-	Very rare	-
	Exanthema	Rare	Uncommon	-
	Hyperhidrosis	Rare	Uncommon	-

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	Photosensitivity reaction	-	Uncommon	-
	Pruritus	Rare	Uncommon	Not known
	Purpura	-	Uncommon	-
	Rash	Uncommon	Uncommon	Not known
	Skin discolouration	-	Uncommon	-
	Urticaria	-	Very rare	-
	Exfoliative dermatitis	-	Very rare	-
	Stevens-Johnson syndrome	-	Very rare	-
	Quincke oedema	-	Very rare	-
Musculoskeletal and connective tissue disorders	Arthralgia	Uncommon	Uncommon	-
	Back pain	Uncommon	Uncommon	-
	Joint swelling	Uncommon	-	-
	Muscle spasm	Rare	Uncommon	-
	Myalgia	-	Uncommon	Not known
	Ankle swelling	-	Common	-
	Sensation of heaviness	Rare	-	-
Renal and urinary disorders	Elevation of serum creatinine	-	-	Not known
	Micturition disorder	-	Uncommon	-
	Nocturia	-	Uncommon	-
	Pollakiuria	Rare	Uncommon	-
	Polyuria	Rare	-	-
	Renal failure and impairment	-	-	Not known
Reproductive system and breast disorders	Impotence	-	Uncommon	-
	Erectile dysfunction	Rare	-	-
	Gynaecomastia	-	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	-
	Oedema peripheral	Common	-	-

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	Pain	-	Uncommon	-
	Pitting oedema	Common	-	-
Investigations	Serum potassium increased	-	-	Not known
	Weight increase	-	Uncommon	-
	Weight decrease	-	Uncommon	-

* Mostly consistent with cholestasis

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 fixed combination 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.

4.9 Overdose

Symptoms

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There is no experience of overdose with fixed combination 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

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 overdose with amlodipine/valsartan 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: angiotensin II antagonists and calcium channel blockers, ATC code: C09DB01.

Vamloset 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 fixed combination 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

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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.

Fixed combination 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 mm Hg 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 fixed combination 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/m2, <30 kg/m2) did not influence the response to fixed combination amlodipine/valsartan.

Fixed combination 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 Vamloset 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.

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.

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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.

Valsartan

Valsartan is an orally active, potent and specific angiotensin II receptor antagonist. It acts selectively on the receptor subtype AT1, 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 receptor subtype AT2, 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.

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 does not 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 ARB.

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 ARBs.

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ACE inhibitors and ARBs 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 ARB 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 fixed combination 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 fixed combination 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 2–3 hours. Mean absolute bioavailability is 23%. Food decreases 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 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.

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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 population

Paediatric population (age below 18 years)

No pharmacokinetic data are available in the paediatric population.

Elderly (age 65 years or over)

The time to reach peak plasma concentrations of amlodipine is similar in elderly and younger subjects. In elderly patients, amlodipine clearance tends to decline, causing increases in the area under the curve (AUC) and elimination half-life. Systemic exposure in elderly patients was slightly more pronounced than in young patients, but this was not clinically significant. Normal dosage regimens are recommended in the elderly.

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.
No dosage adjustment is required for patients with mild to moderate renal impairment (creatinine clearance 30-50 ml/min)

Hepatic impairement
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).

5.3 Preclinical safety data

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Cellulose, microcrystalline
Mannitol
Magnesium stearate
Croscarmellose sodium
Povidone
Silica, colloidal anhydrous

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Sodium laurilsulfate

Film coating:
Opadry II White (Polyvinyl alcohol-part. Hydrolysed, Titanium dioxide (E171), Macrogol, Talc)
Iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

for 5 mg/80 mg, 5 mg/160 mg, 10 mg/160 mg tablets:
Blister (OPA/Al/PVC-foil, Al-foil): 30, 60, 90 or 100 tablets in a box (3, 6, 9 or 10 blister packs of 10 tablets).
for 5 mg/80 mg tablets
Blister (OPA/Al/PVC-foil, Al-foil): 14, 28, 56 or 98 tablets in a box (1, 2, 4 or 7 blister packs of 14 tablets).
for 5 mg/160 mg, 10 mg/160 mg tablets
Blister (OPA/Al/PVC-foil, Al-foil): 14, 28, 56 or 98 tablets in a box (2, 4, 8 or 14 blister packs of 7 tablets).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

KRKA-RUS LLC, 50 Moskovskaya str., Istra, Moscow region, 143500, Russia

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT