PROFESSIONAL INFORMATION FOR VALDUO 5/80, 5/160, 10/160, 5/320, 10/320

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

VALDUO 5/80 film coated tablet

VALDUO 5/160 film coated tablet

VALDUO 10/160 film coated tablet

VALDUO 5/320 film coated tablet

VALDUO 10/320 film coated tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

VALDUO 5/80: Each film coated tablet contains amlodipine besilate equivalent to 5 mg amlodipine base and 80 mg valsartan.

VALDUO 5/160: Each film coated tablet contains amlodipine besilate equivalent to 5 mg amlodipine base and 160 mg valsartan.

VALDUO 10/160: Each film coated tablet contains amlodipine besilate equivalent to 10 mg amlodipine base and 160 mg valsartan.

VALDUO 5/320: Each film coated tablet contains amlodipine besilate equivalent to 5 mg amlodipine and 320 mg valsartan.

VALDUO 10/320: Each film coated tablet contains amlodipine besilate equivalent to 10 mg amlodipine and 320 mg valsartan.

VALDUO is sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

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Film coated tablet.

VALDUO 5/80: Light yellow, round shaped, biconvex, film coated tablet, plain on both sides.

VALDUO 5/160: Dark yellow, oval shaped, biconvex, film coated tablet, debossed with ‘L298’ on one side and plain on the other side.

VALDUO 10/160: Light yellow, oval shaped, biconvex, film coated tablet, debossed with ‘L300’ on one side and plain on the other side.

VALDUO 5/320: Dark yellow, oval shaped, biconvex, film coated tablet, debossed with ‘L299’ on one side and plain on the other side.

VALDUO 10/320: Light yellow, oval shaped, biconvex, film coated tablet, debossed with ‘L301’ on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

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

Posology:

The recommended dose is one tablet daily.

The dose will be determined on an individual patient basis.

Special populations

Renal impairment:

No dosage adjustment is required for patients with mild to moderate renal

impairment. VALDUO is contraindicated for use in patients with severe renal impairment (see section 4.3).

Hepatic impairment:

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

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

Elderly:

No dosage adjustment is required for elderly patients.

The elimination half-life of amlodipine 5 mg oral dose is significantly prolonged, suggesting a decreased oral clearance or increased bioavailability. Therefore, VALDUO should be used with caution in elderly subjects.

Children and adolescents:

VALDUO is not recommended for use in children 18 years and younger (see section 4.4).

Method of administration:

Oral use.

It is recommended to take VALDUO with some water. VALDUO can be taken with or without food.

4.3 Contraindications

- Hypersensitivity to amlodipine, valsartan or to any of the excipients of VALDUO listed in section 6.1.
- A history of angioedema related to previous therapy with angiotensin-

PROFESSIONAL INFORMATION FOR VALDUO 5/80, 5/160, 10/160, 5/320, 10/320

converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs): These patients must never again be given these medicines.

- Hereditary or idiopathic angioedema.
- Hypertrophic obstructive cardiomyopathy (HOCM).
- Severe renal function impairment (creatinine clearance less than 30 mL/min).
- Severe hepatic impairment (Child-Pugh C), biliary cirrhosis or cholestasis
- Bilateral renal artery stenosis.
- Renal artery stenosis in patients with a single kidney.
- Aortic valve stenosis.
- Mitral valve stenosis
- Concomitant therapy with potassium-sparing diuretics such as spironolactone, triamterene, amiloride (see sections 4.4 and 4.5).
- Porphyria.
- Lithium therapy: Concomitant administration with VALDUO may lead to toxic blood concentrations of lithium (see section 4.5).
- Pregnancy and lactation (see section 4.6).
- Concomitant use of VALDUO with aliskiren-containing products in patients with diabetes mellitus or renal impairment (GFR < 60 mL/min/1.73 m^2) (see section 4.4).
- Severe hypotension.
- Shock (including cardiogenic shock).
- Haemodynamically unstable heart failure after acute myocardial infarction.
- Concomitant use of fluoroquinolones with ACE inhibitors/angiotensin receptor blockers is contraindicated in patients with moderate to severe renal impairment (creatinine clearance ≤ 30 mL/min) and in elderly patients.

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4.4 Special warnings and precautions for use

Pregnancy

Angiotensin II Receptor Antagonists (AIIRAs) should not be initiated during pregnancy. When pregnancy is diagnosed, treatment with VALDUO should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

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

There is evidence that the concomitant use of angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs) or renin inhibitors, such as aliskiren, may increase the risk of hypotension and hyperkalaemia, and decreases renal function (including acute renal failure). Dual blockade of RAAS through the combined use of VALDUO and renin inhibitors, such as aliskiren, is therefore contraindicated (see section 4.3). VALDUO should not be used concomitantly with renin inhibitors, such as aliskiren (see section 4.3).

Renal impairment

Amlodipine is extensively metabolised to inactive metabolites with 10 % excreted unchanged in the urine. Changes in amlodipine plasma concentrations are not correlated with mild renal impairment.

VALDUO may be used in such patients at normal doses. In patients with moderate renal impairment, VALDUO containing reduced amlodipine dosages (5 mg) may need to be administered in these patients. Amlodipine is not dialysable.

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

Concomitant use with fluoroquinolones

Concomitant use of fluoroquinolones and ACE inhibitors/angiotensin receptor

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

Hepatic impairment

Valsartan is mostly eliminated unchanged via the bile whereas amlodipine is extensively metabolised by the liver. Amlodipine half-life is prolonged in patients impaired hepatic function. Caution is advised when administering VALDUO 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.
VALDUO containing lower amlodipine dosages (5 mg) should be administered in patients with impaired hepatic function.

VALDUO is contraindicated in severe hepatic impairment, biliary cirrhosis or cholestasis (see section 4.3)

Sodium- and/or volume-depleted patients

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 (ARBs), symptomatic hypotension may occur. Correction of this condition prior to administration of VALDUO or close medical supervision at the start of treatment is recommended. If hypotension occurs with VALDUO, the patient should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline. Treatment with VALDUO can be continued once the blood pressure has been stabilised.

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Hyperkalaemia

Concomitant use of VALDUO with potassium supplements, potassium-sparing diuretics, salt substitutes containing potassium or other medicines that may increase potassium levels, such as heparin, should be used with caution and with frequent monitoring of potassium levels (see section 4.3).

Renal artery stenosis

See section 4.3.

Kidney transplantation

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

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. VALDUO 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 uraemia and 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 nonischaemic 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.

Acute myocardial infarction

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

Aortic and mitral valve stenosis

See section 4.3.

Children

Safety and effectiveness of VALDUO in children 18 years and younger has not been established (see section 4.2).

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4.5 Interaction with other medicines and other forms of interaction

Interactions common to the combination

No drug-drug interaction studies have been performed with VALDUO and other medicines.

To be taken into account with concomitant use

Other antihypertensive medicines

Commonly used antihypertensive medicines (e.g. alpha blockers, diuretics) and other medicines 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:

Grapefruit or grapefruit juice:

Administration of amlodipine (as contained in VALDUO) with grapefruit or grapefruit juice is not recommended as the bioavailability may be increased in some patients, increasing the antihypertensive effect.

CYP3A4 inhibitors:

Concomitant use of amlodipine (as contained in VALDUO) with strong or moderate CYP3A4 inhibitors (protease inhibitors, azole antifungals, macrolides like erythromycin or clarithromycin, verapamil or diltiazem) may give rise to a 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.

There is an increased risk of hypotension in patients receiving clarithromycin with amlodipine. Close observation of patients is recommended when amlodipine is co-administered with clarithromycin.

CYP3A4 inducers (anticonvulsant medicines [e.g. carbamazepine, phenobarbitone, 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, as contained in VALDUO.

Dantrolene (infusion):

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 (as contained in in VALDUO) be avoided in patients susceptible to malignant hypertherima and in the management of malignant hyperthermia.

Tacrolimus

There is a risk of increased tacrolimus blood levels when co administered with amlodipine. 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.

Others:

In monotherapy, amlodipine has been safely administered with hydrochorothiazides beta-blockers, angiotensin-converting enzyme inhibitors, long-acting nitrates, sublingual nitro-glycerine, digoxin, warfarin, atorvastatin, sildenafil, aluminium hydroxide gel, magnesium hydroxide, simethicone, cimetidine, nonsteroidal anti-inflammatory medicine, antibiotics and oral hypoglycaemic medicines.

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

In vitro data from studies with human plasma indicate that monotherapy amlodipine has no effect on protein binding of the medicines tested (digoxin, phenytoin, warfarin or indomethacin). Monotherapy amlodipine does not significantly alter the effect of warfarin on prothrombin response time or the pharmacokinetics of ciclosporin.

Interactions linked to valsartan:

Lithium therapy:

Concomitant administration of valsartan (as contained in VALDUO) with lithium may lead to toxic blood concentrations of lithium (see section 4.3). Careful monitoring of serum lithium levels is advised during concomitant use. If a diurectic is also used, the risk of lithium toxicity may presumably be increased further with VALDUO.

Dual blockade of the renin-angiotensin-aldosterone system (RAAS) with angiotensin receptor blockers (ARBs), angiotensin- converting enzyme (ACE) inhibitors or renin inhibitors:

Clinical trial data have shown that dual blockade of the renin-angiotensin-aldosterone system (RAAS) through the combined use of angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs) or renin inhibitors

is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (see sections 4.3 and 4.4).

Nonsteroidal anti-inflammatory drugs (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 or efflux transporter:

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

Others:

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

Potassium

Concomitant use with potassium supplements, potassium-sparing diuretics (see section 4.3), salt substitutes containing potassium or other medicines that may increase potassium levels, such as heparin, are contraindicated (see section 4.3).

Concomitant use of fluoroquinolones and ACE inhibitors/Angiotensin receptor

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

4.6 Fertility, pregnancy and lactation

Should a woman become pregnant while receiving VALDUO, the treatment should be stopped promptly and switched to a different class of antihypertensive medicine (see section 4.3).

Women of childbearing potential/Contraception in males and females

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

Women of childbearing age should ensure effective contraception.

Pregnancy

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

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

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

Breastfeeding

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

Fertility

There are no clinical studies on fertility with amlodipine/valsartan (e.g., VALDUO).

4.7 Effects on ability to drive and use machines:

VALDUO may cause side effects, such as dizziness, drowsiness and visual disturbances and can affect the ability to drive a vehicle and use machines (see section 4.8). Caution is advised before driving a vehicle or operating machinery until the effects of VALDUO are known.

4.8 Undesirable effects

System Organ Class	**Adverse reaction**	**Frequency**		
		Amlodipine/ valsartan - VALDUO	**Amlodipine**	**Valsartan**
Infections and infestations	Nasopharyngitis	Frequent	--	--
	Influenza	Frequent	--	--

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Blood and lymphatic system disorders	Decrease in haemoglobin and in haematocrit	--	--	Unknown
	Leukopenia	--	Less frequent	--
	Neutropenia	--	--	Unknown
	Thrombocytopenia sometimes with purpura	--	Less frequent	Unknown
Immune system disorders	Hypersensitivity	Less frequent	Less frequent	Unknown
Metabolism and nutrition disorders	Anorexia	Less frequent	--	--
	Hypercalcaemia	Less frequent	--	--
	Hyperglycaemia	--	Less frequent	--
	Hyperlipidaemia	Less frequent	--	--
	Hyperuricaemia	Less frequent	--	--
	Hypokalaemia	Frequent	--	--
	Hyponatraemia	Less frequent	--	--
Psychiatric disorders	Depression	--	Less frequent	--
	Anxiety	Less frequent	--	--
	Insomnia/sleep disturbances	--	Less frequent	--
	Mood swings	--	Less frequent	--
	Confusion	--	Less frequent	--
Nervous system disorders	Coordination abnormal	Less frequent	--	--
	Dizziness	Less frequent	Frequent	--
	Dizziness postural	Less frequent	--	--
	Dysgeusia	--	Less frequent	--
	Extrapyramidal syndrome	--	Unknown	--
	Headache	Frequent	Frequent	--
	Hypertonia	--	Less frequent	--
	Paraesthesia	Less frequent	Less frequent	--
	Peripheral neuropathy,	--	Less frequent	--

	neuropathy			
	Somnolence	Less frequent	Frequent	--
	Tremor	--	Less frequent	--
	Hypoesthesia	--	Less frequent	--
Eye disorders	Visual disturbance	Less frequent	Less frequent	--
	Visual impairment	Less frequent	Less frequent	--
Ear and labyrinth disorders	Tinnitus	Less frequent	Less frequent	--
	Vertigo	Less frequent	--	Less frequent
Cardiac disorders	Palpitations	Less frequent	Frequent	--
	Syncope	Less frequent	Less frequent	--
	Tachycardia	Less frequent	--	--
	Dysrhythmias (including bradycardia, ventricular tachycardia, and atrial fibrillation)	--	Less frequent	--
	Myocardial infarction	--	Less frequent	--
Vascular disorders	Flushing	--	Frequent	--
	Hypotension	Less frequent	Less frequent	--
	Orthostatic hypotension	Less frequent	--	--
	Vasculitis	--	Less frequent	Unknown
Respiratory, thoracic and mediastinal disorders	Cough	Less frequent	Less frequent	Less frequent
	Dyspnoea	--	Less frequent	--
	Pharyngolaryngeal pain	Less frequent	--	--
	Rhinitis	--	Less frequent	--
	Abdominal discomfort, abdominal pain upper	Less frequent	Frequent	Less frequent

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Gastrointestinal disorders	Change of bowel habit	--	Less frequent	--
	Constipation	Less frequent	Less frequent	--
	Diarrhoea	Less frequent	Less frequent	--
	Dry mouth	Less frequent	Less frequent	--
	Dyspepsia	--	Less frequent	--
	Gastritis	--	Less frequent	--
	Gingival hyperplasia	--	Less frequent	--
	Nausea	Less frequent	Frequent	--
	Pancreatitis	--	Less frequent	--
	Vomiting	--	Less frequent	--
Hepato-biliary disorders	Liver function test abnormal, including blood bilirubin increase	--	Less frequent*	Unknown
	Hepatitis	--	Less frequent	--
	Intrahepatic cholestasis, jaundice	--	Less frequent	--
Skin and Subcutaneous tissue disorders	Angioedema	--	Less frequent	Unknown
	Alopecia	--	Less frequent	--
	Dermatitis bullous	--	--	Unknown
	Erythema	Less frequent	--	--
	Erythema multiforme	--	Less frequent	--
	Exanthema	Less frequent	Less frequent	--
	Hyperhidrosis	Less frequent	Less frequent	--
	Photosensitivity reaction	--	Less frequent	--
	Pruritus	Less frequent	Less frequent	Unknown
	Purpura	--	Less frequent	--
	Rash	Less frequent	Less frequent	Unknown
	Skin	--	Less frequent	--

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	discolouration			
	Urticaria and other forms of rash	--	Less frequent	--
	Exfoliative dermatitis	--	Less frequent	--
	Stevens-Johnson syndrome	--	Less frequent	--
	Quincke oedema	--	Less frequent	--
	Toxic Epidermal Necrolysis	--	Unknown	--
Musculo-skeletal and connective tissue disorders	Arthralgia	Less frequent	Less frequent	--
	Back pain	Less frequent	Less frequent	--
	Joint swelling	Less frequent	--	--
	Muscle spasm	Less frequent	Less frequent	--
	Myalgia	--	Less frequent	Unknown
	Ankle swelling	--	Frequent	--
	Sensation of heaviness	Less frequent	--	--
Renal and urinary disorders	Increased blood creatinine	--	--	Unknown
	Micturition disorder	--	Less frequent	--
	Nocturia	--	Less frequent	--
	Pollakiuria	Less frequent	Less frequent	--
	Polyuria	Less frequent	--	--
	Renal failure and impairment	--	--	Unknown
Reproductive system and breast disorders	Impotence	--	Less frequent	--
	Erectile dysfunction	Less frequent	--	--
	Gynaecomastia	--	Less frequent	--
General disorders and	Discomfort, malaise	--	Less frequent	--

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Administration site conditions	Asthenia	Frequent	Less frequent	--
	Fatigue	Frequent	Frequent	Less frequent
	Facial oedema	Frequent	--	--
	Flushing, hot flush	Frequent	--	--
	Non cardiac chest pain	--	Less frequent	--
	Oedema	Frequent	Frequent	--
	Oedema peripheral	Frequent	--	--
	Pain	--	Less frequent	--
	Pitting oedema	Frequent	--	--
	Increased serum potassium	--	--	Unknown
Investigations	Increased weight	--	Less frequent	--
	Decreased weight	--	Less frequent	--

* mostly consistent with cholestasis

Reporting of suspected adverse reactions

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

4.9 Overdose

Symptoms:

There is no experience of overdose with amlodipine/valsartan.

Amlodipine:

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Overdose with amlodipine may result in:

- Excessive peripheral vasodilatation.
- Possibly reflex tachycardia.
- Bradycardia.
- Marked and potentially prolonged systemic hypotension up to and including shock with fatal outcome.
- Non-cardiogenic pulmonary oedema has 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.

Valsartan:

Overdose with valsartan may result in:

- Pronounced hypotension.
- Dizziness

Treatment:

If ingestion is recent, induction of vomiting may be considered.
Administration of activated charcoal immediately or up to two hours after ingestion of amlodipine, has been shown to significantly decrease amlodipine absorption.
Active cardiovascular support, in clinical significant hypotension, including frequent monitoring of cardiac and respiratory function, elevation of extremities, 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 a calcium channel blocker.
Both valsartan and amlodipine are unlikely to be removed by haemodialysis.

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5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

A 7.1.3 Vascular medicine – other hypotensives

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

ATC code: C09DB01.

Mechanism of action

Amlodipine:

Amlodipine belongs to the calcium antagonist class. Amlodipine 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 relaxing effect on vascular smooth muscle, causing a reduction in peripheral vascular resistance and a reduction in blood pressure. 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.

In hypertensive patients, therapeutic doses of amlodipine produce vasodilatation resulting in a reduction of supine and standing blood pressures. These decreases in blood pressure are not accompanied by a significant change in heart rate or plasma catecholamine levels with chronic dosing. Plasma concentrations correlate with effect in both young and elderly patients.

In hypertensive patients with normal renal function, therapeutic doses of amlodipine resulted in a decrease in renal vascular resistance and an increase in glomerular filtration rate and effective renal plasma flow without change in filtration fraction or proteinuria.

Haemodynamic measurements of cardiac function at rest and during exercise (or

pacing) in patients with normal ventricular function treated with amlodipine have generally demonstrated a small increase in cardiac index without significant influence on dP/dt or on left ventricular end diastolic pressure or volume.
Following administration of doses within the therapeutic dose range, amlodipine has not been associated with a negative inotropic effect. Amlodipine has minimal effect on sinoatrial nodal function or atrioventricular conduction.

Valsartan:

Valsartan is an orally active and specific angiotensin II receptor antagonist. It acts selectively on the 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 AT2 receptor, which appears to counterbalance the effect of the AT_1 receptor.
Valsartan does not exhibit any partial agonist activity at the AT_1 receptor and has much (about 20 000 fold) greater affinity for the AT_1 receptor than for the AT_2 receptor. Patients with hypertension, receiving valsartan, show a reduction of blood pressure with no effect on the pulse rate.
Onset of antihypertensive activity occurs within 2 hours after administration of a single oral dose and the peak reduction of blood pressure is achieved within 4-6 hours. The antihypertensive effect persists over 24 hours. The maximum reduction in blood pressure with any dose, during repeated administration, is generally attained within 2-4 weeks and is sustained during long-term therapy.
Rebound hypertension or other adverse clinical events have not been associated with abrupt withdrawal of valsartan. Valsartan significantly reduces hospitalisation in patients with chronic heart failure (NYHA class II-IV). The benefits were greatest in patients not receiving either an angiotensin-converting enzyme (ACE) inhibitor or a beta-blocker. Valsartan reduces cardiovascular mortality in clinically stable patients with left ventricular failure or left ventricular dysfunction following myocardial infarction.

Amlodipine/valsartan:

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

Age, gender and race did not influence the antihypertensive response.

5.2. Pharmacokinetic properties

Linearity:

Amlodipine and valsartan exhibit linear pharmacokinetics.

Amlodipine:

Absorption:

After oral administration of therapeutic doses of amlodipine alone, peak plasma concentrations are reached within 6-12 hours. Absolute bioavailability is between 64 % and 80 %. Amlodipine bioavailability is not affected by food ingestion (see section 5.2).

Distribution:

Volume of distribution is approximately 21 L/kg. Approximately 97,5 % of the circulating compound is bound to plasma proteins in hypertensive patients.

Biotransformation:

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

Elimination:

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

PROFESSIONAL INFORMATION FOR VALDUO 5/80, 5/160, 10/160, 5/320, 10/320

Valsartan:

Absorption:

Following oral administration of valsartan alone, peak plasma concentrations are reached within 2–4 hours. Mean absolute bioavailability is 23 %. Valsartan shows multi-exponential decay kinetics (t½ α < 1 hour and t½ β about 9 hours). Food decreases the exposure (as measured by AUC) to valsartan by about 40 % and peak plasma concentration (Cmax) by about 50 %, although from about 8 hours post dosing plasma valsartan concentrations are similar for the fed and fasted group. This reduction in AUC, however, is not accompanied by a clinically significant reduction in the therapeutic effect. Valsartan can be given either with or without food (see section 5.2).

Distribution:

Valsartan is highly bound to serum proteins (94 - 97 %), mainly serum albumin, and does not distribute extensively into tissue.

Biotransformation:

Valsartan is not transformed to a high extent as only about 20 % of the 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 is primarily eliminated unchanged in faeces (about 83 % of the dose) and urine (about 13 % of the dose), mainly as the unchanged compound. Following intravenous administration, plasma clearance of valsartan is about 2 L/h and its renal clearance is 0,02 L/h (about 30 % of total clearance). The half-life of valsartan is 6 hours.

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Amlodipine/valsartan:

Following oral administration of the amlodipine/valsartan combination, peak plasma concentrations of amlodipine and valsartan are reached in 6 - 8 and 3 hours, respectively. The rate and extent of absorption of the amlodipine/valsartan combination are equivalent to the bioavailability of amlodipine and valsartan when administered alone (see section 5.2).

Special populations:

Paediatric:

No pharmacokinetic data are available in the paediatric population.

Elderly:

Systemic exposure to valsartan is slightly elevated in the elderly as compared to the young, but this has not been shown to have any clinical significance. Since the two components are equally well tolerated in younger and elderly patients, normal dose regimens are recommended (see section 4.2)

Renal impairment:

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

Hepatic impairment:

Patients with hepatic insufficiency have decreased clearance of amlodipine with resulting increase in AUC of approximately 40-60 %. On average, in patients with mild to moderate chronic hepatic disease, exposure (measured by AUC values) to

valsartan is twice that found in healthy volunteers (matched by age, sex and weight). Caution is advised in patients with hepatic disease (see section 4.2 and 4.4).

5.3. Preclinical safety data

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal anhydrous silica

Crospovidone

Magnesium stearate

Microcrystalline cellulose

Opadry Yellow (hypromellose, iron oxide yellow (colourant), macrogol, talc, titanium dioxide (colourant))

VALDUO 5/160, and 5/320 also contain iron oxide red (colourant).

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 30 °C.

Keep the blister strips in the outer carton until required for use.

Protect from moisture.

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6.5 Nature and contents of container

Silver aluminium/aluminium blister strips containing 10 tablets per blister strip.

Blister strips are packed into a cardboard carton.

Pack size: 30 film coated tablets.

6.6 Special precautions for disposal and other handling

No specific requirements for disposal

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

Forrester Pharma (Pty) Ltd

2 Waterford Mews

Waterford Place

Century City

7441

Cape Town

South Africa

8. REGISTRATION NUMBERS

VALDUO 5/80: 51/7.1.3/0067

VALDUO 5/160: 51/7.1.3/0068

VALDUO 10/160: 51/7.1.3/0069

VALDUO 5/320: 53/7.1.3/0179

VALDUO 10/320: 53/7.1.3/0180

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

VALDUO 5/80, VALDUO 5/160 and VALDUO 10/160: 25 September 2018

VALDUO 5/320 and VALDUO 10/320: 09 December 2019

10. DATE OF REVISION OF THE TEXT

PROFESSIONAL INFORMATION FOR VALDUO 5/80, 5/160, 10/160, 5/320, 10/320

22 July 2025