PACKAGE INSERT FOR VALDUO 5/80, 5/160 and 10/160

SCHEDULING STATUS
S3

PROPRIETARY NAME AND DOSAGE FORM
VALDUO 5/80 film coated tablet
VALDUO 5/160 film coated tablet
VALDUO 10/160 film coated tablet

COMPOSITION
Active ingredients
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.

Inactive ingredients
Colloidal anhydrous silica, crospovidone, magnesium stearate, microcrystalline cellulose, Opadry Yellow (hypromellose, iron oxide yellow (colourant), macrogol, talc, titanium dioxide (colourant)).
VALDUO 5/160 also contains iron oxide red (colourant).
VALDUO (5/80, 5/160, 10/160) is sugar free.

PHARMACOLOGICAL CLASSIFICATION
A 7.1.3 Vascular medicine - other hypotensives

PHARMACOLOGICAL ACTION
Pharmacodynamic properties
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 nondihydropyridine binding sites. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels.
In hypertensive patients, therapeutic doses of amlodipine produces vasodilatation resulting in a reduction of supine and standing blood pressures. These decreases in blood pressure are not accompanied by a significant change in heart rate or plasma catecholamine levels with chronic dosing. Plasma concentrations correlate with effect in both young and elderly patients.
In hypertensive patients with normal renal function, therapeutic doses of amlodipine resulted in a decrease in renal vascular resistance and an increase in glomerular filtration rate and effective renal plasma flow without change in filtration fraction or proteinuria.
Haemodynamic measurements of cardiac function at rest and during exercise (or pacing) in patients with normal ventricular function treated with amlodipine have generally demonstrated a small increase in cardiac index without significant influence on dP/dt or on left ventricular end diastolic pressure or volume. 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 AT_2 receptor, which appears to counterbalance the effect of the AT_1 receptor. Valsartan does not exhibit any partial agonist activity at the AT_1 receptor and has much (about 20 000-fold) greater affinity for the AT_1 receptor than for the AT_2 receptor. 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 - 5 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 hospitalisations 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.

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 5 - 12 hours. Absolute bioavailability is between 64 % and 80 %. Amlodipine bioavailability is not affected by food ingestion (see **Pharmacokinetic properties, *Amlodipine/Valsartan***).

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 %) metabolised in the liver to inactive metabolites.

Excretion
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.

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 ($t_{½}$ α < 1 hour and $t_{½}$ β about 9 hours). Food decreases the exposure (as measured by AUC) to valsartan by about 40 % and peak plasma concentration (C_{max}) by about 50 %, although from about 8 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 **Pharmacokinetic properties, *Amlodipine/Valsartan***).

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.

Excretion
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.

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 **Amlodipine,** *Absorption* and **Valsartan,** *Absorption*).

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 **DOSAGE AND DIRECTIONS FOR USE**).

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 **DOSAGE AND DIRECTIONS FOR USE** and **WARNINGS AND SPECIAL PRECAUTIONS**).

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 liver 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 liver disease (see **DOSAGE AND DIRECTIONS FOR USE** and **WARNINGS AND SPECIAL PRECAUTIONS**).

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

CONTRAINDICATIONS
- Hypersensitivity to amlodipine, valsartan or to any of the inactive ingredients of **VALDUO** (see **COMPOSITION**).
- A history of angioedema related to previous therapy with angiotensin-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).
- Bilateral renal artery stenosis.
- Renal artery stenosis in patients with a single kidney.
- Aortic stenosis.
- Concomitant therapy with potassium-sparing diuretics such as spironolactone, triamterene, amiloride (see **WARNINGS AND SPECIAL PRECAUTIONS** and **INTERACTIONS**).
- Porphyria.
- Lithium therapy: Concomitant administration with **VALDUO** may lead to toxic blood concentrations of lithium (see **INTERACTIONS**).
- Pregnancy and lactation (see **PREGNANCY AND LACTATION**).
- Concomitant use of **VALDUO** with renin inhibitors such as aliskiren-containing medicines (see **WARNINGS AND SPECIAL PRECAUTIONS** and **INTERACTIONS**).
- Severe hypotension.
- Shock (including cardiogenic shock).
- Haemodynamically unstable heart failure after acute myocardial infarction.

WARNINGS AND SPECIAL PRECAUTIONS

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

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 **CONTRAINDICATIONS**).
VALDUO should not be used concomitantly with renin inhibitors, such as aliskiren (see **CONTRAINDICATIONS**).

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. No dosage adjustment of **VALDUO** is required for patients with mild to moderate renal impairment. However, no data is available for severe cases of renal impairment (creatinine clearance < 10 ml/min) and caution is advised in patients with severe renal impairment. **VALDUO** containing reduced amlodipine dosages (5 mg) may need to be administered in patients with severe renal impairment. Amlodipine is not dialysable.

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 with impaired liver function.
Caution is advised when administering **VALDUO** to patients with hepatic impairment or biliary obstructive disorders.
VALDUO containing lower amlodipine dosages (5 mg) should be administered in patients with impaired liver function.

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.

Hyperkalaemia
Concomitant use of **VALDUO** with potassium supplements, potassium-sparing diuretics (see **CONTRAINDICATIONS**), 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.

Children
Safety and effectiveness of **VALDUO** in children has not been established (see **DOSAGE AND DIRECTIONS FOR USE**).

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 **SIDE EFFECTS**). Caution is advised before driving a vehicle or operating machinery until the effects of **VALDUO** are known.

INTERACTIONS
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 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 medicines [e.g. carbamazepine, phenobarbital, phenytoin, fosphenytoin, primidone], rifampicin, *Hypericum perforatum*)
There are no data available regarding the effect of CYP3A4 inducers on amlodipine (as contained in **VALDUO**). The concomitant use of CYP3A4 inducers (e.g. rifampicin, *Hypericum perforatum*) may give a lower plasma concentration of amlodipine. Amlodipine should be used with caution concomitantly with CYP3A4 inducers.

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 **VALDUO**) be avoided in patients susceptible to malignant hyperthermia and in the management of malignant hyperthermia.

Others
In monotherapy, amlodipine has been safely administered with hydrochlorothiazides, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, long-acting nitrates, sublingual nitroglycerin, 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.

Valsartan
Lithium therapy
Concomitant administration of valsartan (as contained in **VALDUO**) with lithium may lead to toxic blood concentrations of lithium (see **CONTRAINDICATIONS**). Careful monitoring of serum lithium levels is advised during concomitant use.

Dual blockade of the renin-angiotensin-aldosterone system (RAAS) with angiotensin receptor blockers (ARBs), angiotensin-converting enzyme (ACE) inhibitors or aliskiren
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 **CONTRAINDICATIONS** and **WARNINGS AND SPECIAL PRECAUTIONS**).

Nonsteroidal 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 (as contained in **VALDUO**).

Others
In monotherapy with valsartan, no interactions of clinical significance have been found with the following medicines: cimetidine, warfarin, furosemide, digoxin, atenolol, indometacin, hydrochlorothiazide, amlodipine, glibenclamide.
Concomitant use with potassium supplements, potassium-sparing diuretics (see **CONTRAINDICATIONS**), 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.

PREGNANCY AND LACTATION
Pregnancy
Safety in pregnancy has not been established (see **CONTRAINDICATIONS**). When pregnancy is planned or confirmed, treatment with **VALDUO** should be discontinued. Medicines affecting the renin-angiotensin system, such as **VALDUO**, can cause embryonal toxicity, foetal and neonatal morbidity and mortality when administered to pregnant women.

Women of childbearing potential
Women of childbearing age should ensure effective contraception.

Lactation
Safety in lactation has not been established (see **CONTRAINDICATIONS**).

DOSAGE AND DIRECTIONS FOR USE
Patients receiving amlodipine and valsartan from separate tablets may be switched to **VALDUO** containing the same component doses.

Adults
The recommended dose is one tablet daily, with some water.
VALDUO can be taken with or without food.
The dose will be determined on an individual patient basis.

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 **CONTRAINDICATIONS**).

Hepatic impairment
Caution should be exercised when administering **VALDUO** to patients with hepatic impairment or biliary obstructive disorders (see **WARNINGS AND SPECIAL PRECAUTIONS**).

Elderly
No dosage adjustment is required for elderly patients.

Children and adolescents
VALDUO is not recommended for use in children 18 years and younger (see **WARNINGS AND SPECIAL PRECAUTIONS**).

SIDE EFFECTS
Amlodipine/valsartan (VALDUO)
Immune system disorders:
Less frequent: Hypersensitivity.

Metabolism and nutrition disorders:
Frequent: Hypokalaemia.
Less frequent: Anorexia, hypercalcaemia, hyperglycaemia, hyperlipidaemia, hyperuricaemia, hyponatraemia.

Psychiatric disorders:
Less frequent: Anxiety.

Nervous system disorders:
Frequent: Headache.
Less frequent: Dizziness, somnolence, postural dizziness, paraesthesia.

Eye disorders:
Less frequent: Visual disturbance.

Ear and labyrinth disorders:
Less frequent: Vertigo, tinnitus.

Cardiac disorders:
Less frequent: Tachycardia, palpitations.

Vascular disorders:
Frequent: Hot flushes, flushing.
Less frequent: Orthostatic hypotension, hypotension, syncope.

Respiratory, thoracic and mediastinal disorders:
Frequent: Nasopharyngitis, influenza.
Less frequent: Cough, pharyngolaryngeal pain.

Gastrointestinal disorders:
Less frequent: Diarrhoea, nausea, vomiting, abdominal pain, constipation, dry mouth.

Skin and subcutaneous tissue disorders:
Less frequent: Rash, erythema, exanthema, pruritus, hyperhidrosis.

Musculoskeletal, connective tissue and bone disorders:
Less frequent: Joint swelling, back pain, arthralgia, muscle spasm, sensation of heaviness.

Renal and urinary disorders:
Less frequent: Pollakiuria, polyuria.

Reproductive system and breast disorders:
Less frequent: Erectile dysfunction.

General disorders and administration site conditions:
Frequent: Fatigue, asthenia, oedema (pitting, facial and peripheral).

Amlodipine
Blood and the lymphatic system disorders:
Less frequent: Leucopenia, thrombocytopenia.

Immune system disorders:
Less frequent: Angioedema, erythema multiforme.

Metabolism and nutrition disorders:
Less frequent: Hyperglycaemia.

Psychiatric disorders:
Less frequent: Depression, mood changes.

Nervous system disorders:
Frequent: Headache, somnolence, dizziness, migraine.
Less frequent: Peripheral neuropathy, tremor.

Eye disorders:
Less frequent: Visual disturbances, eye pain.

Ear and labyrinth disorders:
Less frequent: Vertigo.

Cardiac disorders:
Frequent: Palpitations, tachycardia.
Less frequent: Angina, bradycardia.

Vascular disorders:
Frequent: Flushing.
Less frequent: Vasculitis, syncope, hypotension, orthostatic hypotension.

Respiratory, thoracic and mediastinal disorders:
Less frequent: Dyspnoea, rhinitis.

Gastrointestinal disorders:
Frequent: Nausea, vomiting, abdominal pain.
Less frequent: Altered bowel habits, dyspepsia, gastritis, gingival hyperplasia, dry mouth, constipation.

Hepato-biliary disorders:
Less frequent: Pancreatitis, hepatitis, jaundice.

Skin and subcutaneous tissue disorders:
Less frequent: Alopecia, pruritus, rash.

Musculoskeletal, connective tissue and bone disorders:
Less frequent: Myalgia, arthralgia, back pain, muscle cramps.

Renal and urinary disorders:
Less frequent: Increased urinary frequency, micturition.

Reproductive system and breast disorders:
Less frequent: Gynaecomastia, impotence.

General disorders and administration site conditions:
Frequent: Fatigue, oedema.
Less frequent: Increased sweating, malaise, asthenia.

Valsartan
Infections and infestations:
Frequent: Viral infections.

Blood and the lymphatic system disorders:
Frequent: Neutropenia.
Less frequent: Thrombocytopenia.

Immune system disorders:
Less frequent: Hypersensitivity including serum sickness, angioedema.

Metabolism and nutrition disorders:
Less frequent: Hyperkalaemia.

Psychiatric disorders:
Less frequent: Insomnia.

Nervous system disorders:
Frequent: Postural dizziness.
Less frequent: Dizziness, headache.

Eye disorders:
Less frequent: Blurred vision.

Ear and labyrinth disorders:
Less frequent: Vertigo.

Cardiac disorders:
Less frequent: Cardiac failure.

Vascular disorders:
Frequent: Orthostatic hypotension.
Less frequent: Hypotension, vasculitis, syncope.

Respiratory, thoracic and mediastinal disorders:
Less frequent: Upper respiratory tract infection, pharyngitis, sinusitis, rhinitis, cough.

Gastrointestinal disorders:
Less frequent: Diarrhoea, abdominal pain, nausea.

Hepato-biliary disorders:
Frequency unknown: Hepatitis.

Skin and subcutaneous tissue disorders:
Less frequent: Rash, pruritus, alopecia, urticaria.

Musculoskeletal, connective tissue and bone disorders:
Less frequent: Back pain, arthralgia, myalgia, rhabdomyolysis.

Renal and urinary disorders:
Less frequent: Renal impairment, acute renal failure, renal insufficiency.

Reproductive system and breast disorders:
Less frequent: Decrease libido.

General disorders and administration site conditions:
Less frequent: Fatigue, asthenia, oedema.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT
Symptoms
Amlodipine
Overdose with amlodipine may result in:
- Excessive peripheral vasodilatation.
- Possibly reflex tachycardia.
- Bradycardia.
- Potentially prolonged systemic hypotension up to and including shock with fatal outcome.

Valsartan
Overdose with valsartan may result in:
- Pronounced hypotension.
- Dizziness.
- Tachycardia.
- Bradycardia.

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

IDENTIFICATION
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.

PRESENTATION
Silver aluminium/aluminium blister strip containing 10 tablets per blister strip. Blister strips are packed into a cardboard carton.
Pack size: 30 film coated tablets.

STORAGE INSTRUCTIONS
Store at or below 30 °C.
Keep the blister strips in the outer carton until required for use.
Protect from moisture.
KEEP OUT OF REACH OF CHILDREN.

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

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION
Forrester Pharma (Pty) Ltd
13 Pasita Street
Rosen Heights
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PATIENT INFORMATION LEAFLET FOR VALDUO 5/80, 5/160 and 10/160

SCHEDULING STATUS
Schedule 3

PROPRIETARY NAME, STRENGTH AND PHARMACEUTICAL FORM
VALDUO 5/80 film coated tablet
VALDUO 5/160 film coated tablet
VALDUO 10/160 film coated tablet

Read all of this leaflet carefully before you start taking VALDUO.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- **VALDUO** has been prescribed for you personally and you should not share your medicine with other people. It may harm them, even if their symptoms are the same as yours.

1. WHAT VALDUO CONTAINS
VALDUO 5/80: The active substances per film coated tablet are amlodipine besilate equivalent to 5 mg amlodipine base and 80 mg valsartan.
VALDUO 5/160: The active substances per film coated tablet are amlodipine besilate equivalent to 5 mg amlodipine base and 160 mg valsartan.
VALDUO 10/160: The active substances per film coated tablet are amlodipine besilate equivalent to 10 mg amlodipine base and 160 mg valsartan.
The other ingredients are colloidal anhydrous silica, crospovidone, magnesium stearate, microcrystalline cellulose, Opadry Yellow (hypromellose, iron oxide yellow (colourant), macrogol, talc, titanium dioxide (colourant)).
VALDUO 5/160 also contains iron oxide red (colourant).
VALDUO (5/80, 5/160, 10/160) is sugar free.

2. WHAT VALDUO IS USED FOR
VALDUO contains two active substances called amlodipine and valsartan. Both substances are used to treat high blood pressure.
- Amlodipine belongs to a group of substances called calcium channel blockers.
- Valsartan belongs to a group of substances called angiotensin receptor blockers (ARBs).

VALDUO is used to treat high blood pressure in adult patients whose blood pressure is not controlled with either amlodipine or valsartan on its own.

3. BEFORE YOU TAKE VALDUO
Do not take VALDUO
- If you are hypersensitive (allergic) to amlodipine besilate, valsartan or any of the other ingredients of **VALDUO** (see **WHAT VALDUO CONTAINS**).
- If you have experienced swelling of the face and throat while taking other medicines (including angiotensin receptor blockers (ARBs)). If you get these symptoms, stop taking **VALDUO** and contact your doctor immediately.
  You should never take **VALDUO** again.
- If your doctor has told you that the thickness of your heart muscle is abnormally increased (hypertrophic obstructive cardiomyopathy (HOCM)) or that you have a narrowing of the valves in your heart (aortic stenosis).
- If you have had a kidney transplant or if you have been told that you have a narrowing of your kidney arteries or if you have severe kidney problems.
- If you have porphyria (a rare hereditary disease in which there is an abnormal metabolism of the blood pigment haemoglobin in your blood).
- If you are pregnant or breastfeeding (see **Pregnancy and breastfeeding**).
- If you have severe low blood pressure (hypotension).
- If you suffer from a condition where your heart is unable to supply enough blood to the body (cardiogenic shock).
- If you suffer from heart failure after a heart attack.
- If you are using any of the following medicine (see **Taking other medicines with VALDUO**):
  - Renin inhibitors such as aliskiren (used to treat high blood pressure).
  - Lithium (used to treat some types of depression).
  - Potassium-sparing diuretics such as spironolactone, triamterene, amiloride (water tablets).

Take special care with VALDUO

If you become pregnant, stop taking VALDUO and call your doctor right away. VALDUO can harm an unborn baby causing injury and even death. If you plan to become pregnant, talk to your doctor about other treatment options to lower your blood pressure before taking VALDUO (see Do not take VALDUO).

- If you have kidney problems.
- If you have liver problems.
- If you have low blood pressure.
- If you have been sick (vomiting or diarrhoea).
- If you are 18 years of age or younger.

Taking VALDUO with food and drink
VALDUO can be taken with or without food. Take **VALDUO** with some water. Do not eat grapefruit or drink grapefruit juice while taking **VALDUO**. Grapefruit or grapefruit juice can increase the blood pressure lowering effect of **VALDUO**.

Pregnancy and breastfeeding
If you are pregnant or breastfeeding your baby, please consult your doctor, pharmacist or other healthcare professional for advice before taking **VALDUO**. Do not take **VALDUO** if you are pregnant or breastfeeding.

Driving and using machinery
VALDUO may cause side effects, such as dizziness, drowsiness and visual disturbances and can affect your ability to drive a vehicle and use machines (see **POSSIBLE SIDE EFFECTS**). Do not drive a vehicle, operate machinery, or do anything else that requires your attention until you know how **VALDUO** affects you.

Taking other medicines with VALDUO
Always tell your healthcare professional if you are taking any other medicine. (This includes complementary or traditional medicines.)
Tell your doctor or pharmacist if you are currently using (see **Do not take VALDUO**):
- Angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs) or renin inhibitors, such as aliskiren (used to treat high blood pressure).
- Lithium (used to treat some types of depression).
- Potassium-sparing diuretics such as spironolactone, triamterene, amiloride (used to remove excess fluid from your body).
- Potassium supplements, salt substitutes containing potassium and other substances that may increase potassium levels.
- Certain types of painkillers called nonsteroidal anti-inflammatory medicines (NSAIDs, such as aspirin, diclofenac, ibuprofen) or selective cyclooxygenase-2 inhibitors (COX-2 inhibitors, such as rofecoxib, celecoxib).
- Anticonvulsant medicines (such as carbamazepine, phenobarbital, phenytoin, fosphenytoin, primidone).
- St. John's wort (a herbal medicine used to treat depression).
- Medicines used for HIV/AIDS (such as ritonavir, indinavir, nelfinavir).
- Medicines used to treat fungal infections (such as ketoconazole, itraconazole).
- Medicines used to treat bacterial infections (such as rifampicin, erythromycin, clarithromycin, telithromycin).
- Verapamil, diltiazem (heart medicines).
- Simvastatin (a medicine used to control high cholesterol levels).
- Dantrolene (infusion to treat severe body temperature abnormalities).
- Medicines used to protect against transplant rejection (ciclosporin).

4. HOW TO TAKE VALDUO
Do not share medicines prescribed for you with any other person.
Always take **VALDUO** exactly as your doctor has instructed you. You should check with your doctor or pharmacist if you are unsure.

Adults
The usual dose is one tablet daily, at the same time each day. Take the tablet with some water. If you have the impression that the effect of **VALDUO** is too strong or too weak, tell your doctor or pharmacist.

If you take more VALDUO than you should
In the event of overdosage, consult your doctor or pharmacist. If neither is available, contact the nearest hospital or poison centre.
Take this leaflet and the rest of the remaining **VALDUO** with you so the doctor will know what you have taken.

If you forget to take VALDUO
If you have missed your dose by only a few hours, take the missed dose as soon as you remember. If it is almost time for your next dose, skip the missed dose and take **VALDUO** at the next regularly scheduled time. Do not take a double dose to make up for the forgotten individual dose.

Effects when treatment with VALDUO is stopped
Your doctor will tell you how long to take **VALDUO**. Your condition may return if you stop taking **VALDUO** before you are advised.

5. POSSIBLE SIDE EFFECTS
VALDUO can have side effects.
Not all side effects reported for **VALDUO** are included in this leaflet. Should your general health worsen or if you experience any untoward effects while taking **VALDUO**, please consult your doctor, pharmacist or other healthcare professional for advice.

If any of the following happens, stop taking **VALDUO** and tell your doctor immediately or go to the casualty department at your nearest hospital:
- Swelling of your hands, feet, ankles, face, lips, mouth or throat, which may cause difficulty in swallowing or breathing.
- Rash or itching.
- Fainting.

These are all very serious side effects. If you have them, you may have had a serious allergic reaction to **VALDUO**. You may need urgent medical attention or hospitalisation.

Tell your doctor immediately or go to the casualty department at your nearest hospital if you notice any of the following:
Frequent:
- Frequent infections such as fever, severe chills, sore throat or mouth ulcers.
- Changes in the way your heart beats (beating faster or skipping beats).

Less frequent:
- Bleeding or bruising more easily than normal.
- High potassium levels in your blood (abdominal pain, confusion, irregular heartbeat, nausea (feeling sick) and vomiting (being sick), nervousness, numbness or tingling in your hands, feet or lips, shortness of breath, difficulty breathing, weakness or heaviness in your legs).
- Peripheral neuropathy (tingling or numbness in your hands or feet, dropping things from your hands regularly, feeling of weakness or heaviness in your arms and legs, sharp stabbing pains).
- Heart failure (shortness of breath, tiredness and weakness, swelling of your legs, ankles and feet, rapid or irregular heartbeat, persistent cough with white or pink phlegm).
- Changes in the way your heart beats (beating slower than normal), chest pain.
- Vasculitis (fever, headache, fatigue, weight loss, general aches and pains, night sweats, nerve problems such as numbness or weakness).
- Gastritis (pain, nausea, vomiting, vomiting blood, blood in the stool).
- Pancreatitis (nausea, vomiting, fever, pain in your stomach area radiating to your back).
- Yellowing of the skin and eyes, also called jaundice.
- Erythema multiforme (red, often itchy spots, similar to the rash of measles which starts on your limbs and sometimes on the face and the rest of your body, the spots may blister or may progress to form raised, red, pale-centred marks, other symptoms include fever, sore throat, headache and/or diarrhoea).
- High sugar (glucose) levels in your blood (passing large amounts or urine, excessive thirst, dry mouth and skin).
- Renal failure (drowsiness, shortness of breath, tiredness, confusion, nausea, fits, passing less urine than is normal for you).
- Passing more urine than is normal for you, increased urine frequency, especially in the daytime.

These are all serious side effects. You may need urgent medical attention.

Tell your doctor as soon as possible if you notice any of the following:
Frequent:
- Headache and severe headaches (migraine).
- Light-headedness when getting up from a lying or sitting position.
- Dizziness, drowsiness.
- Influenza or viral infections (fever, cough, general feeling of discomfort or illness, headache, joint pain, muscle aches and pains, loss of appetite, sweating).
- Nasopharyngitis (sore throat, runny or blocked nose, sneezing, muscle pains, headache).
- Nausea, vomiting, stomach pain.
- Skin and face becomes red and hot.
- Unusual tiredness or weakness.

Less frequent:
- Feeling anxious and/or depressed, having mood changes, inability to sleep.
- Decreased appetite.
- Abnormal blood test results showing high levels of fat in your blood (hyperlipidaemia), high blood sugar levels (hyperglycaemia) or low blood sugar levels (hypoglycaemia).
- Blood test results showing abnormal levels of sodium, potassium, calcium or urea in your blood.
- Tingling or numbness of your hands and feet (pins and needles).
- Tremors (involuntary trembling or shaking of your hands and feet).
- Visual disturbances, pain in the eye(s), blurred vision.
- Vertigo (spinning sensation), ringing in the ears.
- Low blood pressure.
- Upper respiratory tract infection (cough, fever, sore throat, sneezing).
- Rhinitis (runny nose or blocked nose, sneezing), sore throat, coughing.
- Sinusitis (pain and tenderness around your eyes and cheekbones, fever, stuffy or runny nose, headache, cough).
- Diarrhoea, constipation, dry mouth, indigestion.
- Gingival hyperplasia (increase in the size of your gum tissue).
- Changes in your bowel habits (shift in your stool frequency and consistency).
- Redness of your skin and mucous membranes, itchy rash.
- Hair loss (temporary).
- Painful swollen joints, muscle cramps and pain, back pain, feeling of heaviness.
- Temporary paralysis or weakness of muscles.
- Breast enlargement in men.
- Erectile dysfunction (the inability to develop or maintain an erection).
- Increased sweating.
- Abnormal physical weakness or lack of energy, generally feeling unwell.
- Loss of sex drive.

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

6. STORING AND DISPOSING OF VALDUO
- Store at or below 30 °C.
- Keep the blister strips in the outer carton until required for use.
- Protect from moisture.
- **STORE ALL MEDICINES OUT OF REACH OF CHILDREN.**
- Do not use after the expiry date printed on the carton.
- Return all unused medicine to your pharmacist.
- Do not dispose of unused medicine in drains and sewerage systems (e.g. toilets).

7. PRESENTATION OF VALDUO
Silver aluminium/aluminium blister strip containing 10 tablets per blister strip. Blister strips are packed into a cardboard carton.
Pack size: 30 film coated tablets.

8. IDENTIFICATION OF VALDUO
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.

9. 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

10. NAME AND ADDRESS OF REGISTRATION HOLDER
Forrester Pharma (Pty) Ltd
13 Pasita Street
Rosen Heights
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11. DATE OF PUBLICATION
October 2018

LI0191/18A

VOUBILJET VIR VALDUO 5/80, 5/160 EN 10/160

SKEDULERINGSTATUS
S3

EIENDOMSNAAM EN DOSEERVORM
VALDUO 5/80 filmbedekte tablet
VALDUO 5/160 filmbedekte tablet
VALDUO 10/160 filmbedekte tablet

SAMESTELLING
Aktiewe bestanddele
VALDUO 5/80: Elke filmbedekte tablet bevat amlodipienbesilaat gelykstaande aan 5 mg amlodipien basis en 80 mg valsartaan.
VALDUO 5/160: Elke filmbedekte tablet bevat amlodipienbesilaat gelykstaande aan 5 mg amlodipien basis en 160 mg valsartaan.
VALDUO 10/160: Elke filmbedekte tablet bevat amlodipienbesilaat gelykstaande aan 10 mg amlodipien basis en 160 mg valsartaan.

Onaktiewe bestanddele
Kolloïdale anhidriese silika, krospovidoon, magnesiumstearaat, mikrokristallyne sellulose, Opadry geel (hipromellose, geel ysteroksied (kleurmiddel), makrogol, talk, titaandioksied (kleurmiddel)).
VALDUO 5/160 bevat ook rooi ysteroksied (kleurmiddel).
VALDUO (5/80, 5/160, 10/160) is suikervry.

FARMAKOLOGIESE KLASSIFIKASIE
A 7.1.3 Vaskulêre medisyne - ander hipotensiewe

FARMAKOLOGIESE WERKING
Farmakodinamiese eienskappe
Amlodipien
Amlodipien behoort aan die klas van kalsiumantagoniste. Amlodipien inhibeer die transmembraan-influks van kalsiumione in die hartspier en vaskulêre gladdespier. Die meganisme van die antihipertensiewe werking van amlodipien is weens 'n direkte ontspannende effek op die vaskulêre gladdespier, wat die perifere vaskulêre weerstand verminder en verlaging in bloeddruk veroorsaak. Amlodipien bind aan beide dihidropiridien- en nie-dihidropiridien-bindingsetels. Die kontraktiele prosesse van hartspier en vaskulêre gladdespiere is afhanklik van die beweging van ekstrasellulêre kalsiumione in hierdie selle in deur spesifieke ioonkanale.
In hipertensiewe pasiënte veroorsaak terapeutiese dosisse van amlodipien vasodilatasie, wat 'n verlaging in rugliggende en staande bloeddrukke tot gevolg het. Met chroniese dosering gaan hierdie afnames in bloeddruk nie gepaard met 'n beduidende verandering in hartklop of plasma katesjolamienvlakke nie. Plasmakonsentrasies korreleer met effek by sowel jong as bejaarde pasiënte.
By hipertensiewe pasiënte met normale nierfunksie veroorsaak terapeutiese dosisse van amlodipien 'n afname in renale vaskulêre weerstand en 'n verhoging in die glomerulêre filtrasietempo en effektiewe plasmavloei in die nier sonder 'n verandering in filtrasiefraksie of proteïnurie.
Hemodinamiese metings van hartfunksie tydens rus en tydens oefening (of stap) by pasiënte met normale ventrikulêre funksie wat behandel is met amlodipien, het oor die algemeen 'n klein toename in die hartindeks sonder 'n beduidende invloed op dP/dt of op die linkerventrikulêre eind-diastoliese druk of volume getoon. Na toediening van dosisse binne die terapeutiese dosisreikwydte, is amlodipien nie met 'n negatiewe inotropiese effek geassosieer nie. Amlodipien het minimale effek op sinoatriale nodale funksie of atrioventrikulêre geleiding.

Valsartaan
Valsartaan is 'n orale aktiewe en spesifieke angiotensien II-reseptor antagonis. Dit werk selektief op die reseptor subtipe (AT_1), wat vir die bekende aksies van angiotensien II verantwoordelik is. Die verhoogde plasmavlakke van angiotensien II na aanleiding van AT_1-reseptor blokkade met valsartaan kan die ongeblokkeerde AT_2-reseptor stimuleer, wat die effek van die AT_1-reseptor voorkom. Valsartaan vertoon nie enige gedeeltelike agonistiese aktiwiteit by die AT_1-reseptor nie en het baie (ongeveer 20 000-voudig) groter affiniteit vir die AT_1-reseptor as vir die AT_2-reseptor. Pasiënte met hipertensie, wat valsartaan ontvang, toon 'n vermindering van bloeddruk met geen effek op die polsslag nie.
By meeste pasiënte vind antihipertensiewe aktiwiteit binne 2 uur na toediening van 'n enkele orale dosis plaas en die piekverlaging van bloeddruk word binne 4 - 5 uur behaal. Die antihipertensiewe effek duur meer as 24 uur. Met herhaalde toediening word die maksimum verlaging in bloeddruk met enige dosis gewoonlik binne 2 - 4 weke behaal en word gedurende langtermynterapie onderhou.
Terugslag van hipertensie of ander nadelige kliniese gebeure word nie geassosieer met die skielike onttrekking van valsartaan nie.
Valsartaan verminder hospitaalopnames aansienlik in pasiënte met chroniese hartversaking (NYHA klas II-IV). Die voordele was die grootste in pasiënte wat nie 'n angiotensienomsettingsensiem (ACE) inhibeerder of 'n beta-blokker ontvang het nie. Valsartaan verminder kardiovaskulêre mortaliteit in klinies stabiele pasiënte met linkerventrikulêre versaking of linkerventrikulêre disfunksie na afloop van miokardiale infarksie.

Amlodipien/valsartaan
Die antihipertensiewe effek van 'n enkel dosis duur vir 24 uur. Ouderdom, geslag en ras het geen invloed op die antihipertensiewe reaksie gehad nie.

Farmakokinetiese eienskappe
Lineariteit
Amlodipien en valsartaan toon lineêre farmakokinetika.

Amlodipien
Absorpsie
Na orale toediening van terapeutiese dosisse amlodipien alleen, word piek plasmakonsentrasies binne 5 - 12 uur bereik. Absolute biobeskikbaarheid is tussen 64 % en 80 %. Amlodipien biobeskikbaarheid word nie beïnvloed deur voedsel inname nie (sien **Farmakokinetiese eienskappe, Amlodipien / Valsartaan**).

Verspreiding
Volume van verspreiding is ongeveer 21 L/kg. By hipertensiewe pasiënte is ongeveer 97,5 % van die sirkulerende verbinding aan plasmaproteïene gebind.

Biotransformasie
Amlodipien word in die lewer breedvoerig (ongeveer 90 %) na die onaktiewe metaboliete gemetaboliseer.

Uitskeiding
Uitskeiding van amlodipien uit plasma vind in twee fases plaas, met 'n terminale uitskeidingshalflewe van ongeveer 30 tot 50 uur. Bestendigetaat-plasmavlakke word na deurlopende toediening van 7 - 8 dae bereik. Tien persent van die oorspronklike amlodipien en 60 % van amlodipienmetaboliete word in die urine uitgeskei.

Valsartaan
Absorpsie
Na orale toediening van valsartaan alleen, word piek plasmakonsentrasies bereik binne 2 - 4 ure.

Die gemiddelde absolute biobeskikbaarheid is 23 %. Valsartaan toon multi-eksponensiële vervalkinetika ($t_{½}$ α <1 uur en $t_{½}$ β ongeveer 9 uur). Voedsel verlaag die blootstelling (soos gemeet aan AOK) aan valsartaan met ongeveer 40 % en piek plasmakonsentrasie (K_{maks}) met ongeveer 50 %, alhoewel die plasmakonsentrasies van valsartaan vanaf ongeveer 8 uur na dosering vir die gevoede en vastende groepe soortgelyk is. Hierdie verlaging in AOK word egter nie vergesel deur 'n klinies beduidende verlaging in die terapeutiese effek nie. Valsartaan kan met of sonder voedsel gegee word (sien **Farmakokinetiese eienskappe, *Amlodipien/ Valsartaan***).

Verspreiding
Valsartaan is sterk gebind aan serumproteïene (94 - 97 %), hoofsaaklik serumalbumien, en versprei nie breedvoerig in die weefsel nie.

Biotransformasie
Valsartaan word nie tot 'n groot mate omgeskakel nie, aangesien slegs ongeveer 20 % van die dosis as metaboliete herwin word. 'n Hidroksi-metaboliet is teen lae konsentrasies in die plasma geïdentifiseer (minder as 10 % van die valsartaan AOK). Hierdie metaboliet is farmakologies onaktief.

Uitskeiding
Valsartaan word hoofsaaklik onveranderd in feses (ongeveer 83 % van die dosis) en urine (ongeveer 13 % van die dosis) uitgeskei, hoofsaaklik as onveranderde verbinding. Na intraveneuse toediening is plasma-opruiming van valsartaan ongeveer 2 L/h en die renale opruiming is 0,02 L/h (ongeveer 30 % van die totale opruiming). Die halfleeftyd van valsartaan is 6 uur.

Amlodipien/valsartaan
Na orale toediening van die amlodipien/valsartaan-kombinasie word piek plasmakonsentrasies van amlodipien en valsartaan in onderskeidelik 6 - 8 en 3 uur bereik.

Die tempo en mate van absorpsie van die amlodipien/valsartaan-kombinasie is gelykstaande aan die biobeskikbaarheid van amlodipien en valsartaan wanneer dit alleen toegedien word (sien ***Amlodipien**, Absorpsie* en ***Valsartaan**, Absorpsie*).

Spesiale populasies
Pediatriese pasiënte
Daar is geen farmakokinetiese data beskikbaar in die pediatriese populasie nie.

Bejaarde pasiënte
Sistemiese blootstelling aan valsartaan is effens verhoog by bejaarde pasiënte in vergelyking met jonger pasiënte, maar dit is nie bewys dat dit kliniese betekenis het nie. Aangesien die twee komponente ewe goed verdra word by jonger en ouer pasiënte, word normale dosis regimes aanbeveel (sien **DOSIS EN GEBRUIKSAANWYSINGS**).

Renale belemmering
Renale belemmering het nie 'n beduidende invloed op die farmakokinetika van amlodipien nie. Daar is geen korrelasie tussen nierfunksie (bepaal deur kreatinienopruiming) en blootstelling (gemeet as AOK) aan valsartaan by pasiënte met verskillende grade van renale belemmering nie. Pasiënte met geringe tot matige renale belemmering mag die gewone aanvanklike dosis ontvang (sien **DOSIS EN GEBRUIKSAANWYSINGS** en **WAARSKUWINGS EN SPESIALE VOORSORGMAATREËLS**).

Hepatiese belemmering
Pasiënte met hepatiese ontoereikendheid het verlaagde opruiming van amlodipien met 'n gevolglike toename in die AOK van ongeveer 40 - 60 %. By pasiënte met geringe tot matige chroniese lewersiekte is blootstelling (soos bepaal met AOK-waardes) aan valsartaan gemiddeld dubbel dit wat by gesonde vrywilligers (met ooreenstemmende ouderdom, geslag en gewig) gevind word. Omsigtigheid word aangeraai by pasiënte met lewersiekte (sien **DOSIS EN GEBRUIKSAANWYSINGS** en **WAARSKUWINGS EN SPESIALE VOORSORGMAATREËLS**).

INDIKASIES
Behandeling van ligte tot matige hipertensie by pasiënte wie se bloeddruk genormaliseer word met die individuele komponente in dieselfde dosisse as die voorgestelde vaste-dosis kombinasie van **VALDUO**.

KONTRA-INDIKASIES
- Hipersensitiwiteit vir amlodipien, valsartaan of enige van die onaktiewe bestanddele van **VALDUO** (sien **SAMESTELLING**).
- 'n Geskiedenis van angio-edeem verwant aan vorige terapie met angiotensienomskakelingsensiem (ACE) inhibeerders of angiotensien-reseptorblokkers (ARB's):

Hierdie pasiënte moet nooit weer hierdie medisynes ontvang nie.
- Oorerflike of idiopatiese angio-edeem.
- Hipertrofiese obstruktiewe kardiomiopatie (HOCM).
- Erg belemmerde nierfunksie (kreatinienopruiming minder as 30 ml/min).
- Bilaterale renale arteriestenose.
- Renale arteriestenose by pasiënte met net een nier.
- Aortiese stenose.
- Gelyktydige terapie met kaliumbesparende diuretikas soos spironolaktoon, triamtereen, amiloried (sien **WAARSKUWINGS EN SPESIALE VOORSORGMAATREËLS** en **INTERAKSIES**).
- Porfirie
- Litiumterapie: Gelyktydige toediening met **VALDUO** mag lei tot toksiese bloedkonsentrasies van litium (sien **INTERAKSIES**).
- Swangerskap en borsvoeding (sien **SWANGERSKAP EN BORSVOEDING**).
- Gelyktydige gebruik van **VALDUO** met renien-inhibeerders soos aliskiren-bevattende medisyne (sien **WAARSKUWINGS EN SPESIALE VOORSORGMAATREËLS** en **INTERAKSIES**).
- Erge hipotensie.
- Skok (insluitend kardiogeniese skok).
- Hemodinamiese onstabiele hartversaking na akute miokardiale infarksie.

WAARSKUWINGS EN SPESIALE VOORSORGMAATREËLS

Indien 'n vrou swanger sou raak terwyl sy VALDUO neem, moet die behandeling onmiddellik gestaak word en moet na 'n ander klas anti-hipertensiewe medisyne oorgeskakel word (sien KONTRA-INDIKASIES en SWANGERSKAP EN BORSVOEDING).

Dubbele blokkade van die renien-angiotensien-aldosteroonstelsel (RAAS)
Daar is bewyse dat die gelyktydige gebruik van ACE-inhibeerders, angiotensien II reseptorblokkers (ARB's) of renieninhibeerders, soos aliskiren, die risiko vir hipotensie, hiperkalemie mag verhoog en nierfunksie verminder (insluitende akute nierversaking). Dubbele blokkade van RAAS deur die gesamentlike gebruik van **VALDUO** en renien-inhibeerders, soos aliskiren, is gevolglik teenaangedui (sien **KONTRA-INDIKASIES**).

VALDUO moet nie saam met renien-inhibeerders, soos aliskiren, gebruik word nie (sien **KONTRA-INDIKASIES**)

Renale belemmering
Amlodipien word omvattend na onaktiewe metaboliete gemetaboliseer, met 10 % wat onveranderd in die urine uitgeskei word. Veranderinge in amlodipien plasmakonsentrasies korreleer nie met geringe renale belemmering nie. Dit is nie nodig om die dosis van **VALDUO** aan te pas vir pasiënte met geringe tot matige renale belemmering nie. Geen data is egter beskikbaar vir pasiënte met ernstige renale belemmering (kreatinienopruiming < 10 ml/min) nie en hierdie pasiënte moet **VALDUO** versigtig gebruik. **VALDUO** wat kleiner amlodipien dosisse bevat (5 mg), moet moontlik toegedien word aan pasiënte met ernstige renale belemmering. Amlodipien is nie dialiseerbaar nie.

Hepatiese belemmering
Valsartaan word grootliks onveranderd deur die gal uitgeskei, terwyl amlodipien breedvoerig deur die lewer gemetaboliseer word. Die halfleeftyd van amlodipien is verleng by pasiënte met belemmerde lewerfunksie.
Omsigtigheid word aanbeveel wanneer **VALDUO** aan pasiënte met hepatiese belemmering of biliêre obstruktiewe versteurings toegedien word.
VALDUO wat kleiner amlodipien dosisse bevat (5 mg) moet aan pasiënte met belemmerde lewerfunksie toegedien word.

Pasiënte met natrium- en/of volume-uitputting
By pasiënte met 'n geaktiveerde renien-angiotensienstelsel (soos pasiënte met volume- en/of soutuitputting wat hoë dosisse diuretika ontvang) wat angiotensienreseptorblokkers (ARB's) ontvang, mag simptomatiese hipotensie voorkom. Regstelling van hierdie toestand vóór toediening van **VALDUO** óf mediese toesig by die aanvang van behandeling word aanbeveel. Indien hipotensie tydens **VALDUO** behandeling voorkom, moet die pasiënt in die rugliggende posisie geplaas word en, indien nodig, moet 'n intraveneuse infusie van fisiologiese soutoplossing gegee word. Behandeling met **VALDUO** kan voortgesit word sodra die bloeddruk gestabiliseer is.

Hiperkalemie
Gelyktydige gebruik van **VALDUO** met kaliumaanvullings, kaliumbesparende diuretika (sien **KONTRA-INDIKASIES**), soutvervangers wat kalium bevat of ander middels wat kaliumvlakke kan verhoog, soos heparien, moet versigtig gebruik word en kaliumvlakke moet gereeld gemonitor word.

Kinders
Veiligheid en effektiwiteit van **VALDUO** by kinders is nie vasgestel nie (sien **DOSIS EN GEBRUIKSAANWYSINGS**).

Effekte op die vermoë om 'n voertuig te bestuur en masjiene te gebruik:
VALDUO kan newe-effekte soos duiseligheid, slaperigheid en visuele steurnisse veroorsaak en kan die vermoë om 'n voertuig te bestuur en masjiene te gebruik, beïnvloed (sien **NEWE-EFFEKTE**). Voordat 'n voertuig bestuur of masjinerie hanteer word moet die uitwerking van **VALDUO** bekend wees.

INTERAKSIES
Amlodipien
Pomelo of pomelosap
Gepaardgaande toediening van amlodipien (soos bevat in **VALDUO**) met pomelo of pomelosap word nie aanbeveel nie, aangesien die biobeskikbaarheid by sommige pasiënte verhoog kan word, wat die antihipertensiewe effek verhoog.

CYP3A4-inhibeerders
Gelyktydige gebruik van amlodipien (soos bevat in **VALDUO**) met sterk of matige CYP3A4-inhibeerders (protease-inhibeerders, asool-antiswammiddels, makroliede soos eritromisien of klaritromisien, verapamiel of diltiasem) mag lei tot 'n beduidende toename in amlodipienblootstelling. Die kliniese transformasie van hierdie farmakokinetiese variasies kan meer merkbaar wees by bejaarde pasiënte. Kliniese monitering en dosisaanpassing kan dus vereis word.

CYP3A4-induseerders (antikonvulsantmedisynes [bv. karbamasepien, fenobarbitaal, fenitoïen, fosfenitoïen, primidoon], rifampisien, *Hypericum perforatum*)
Daar is geen inligting beskikbaar oor die effek van CYP3A4-induseerders op amlodipien (soos bevat in **VALDUO**) nie. Die gepaardgaande gebruik van CYP3A4-induseerders (bv. rifampisien, *Hypericum perforatum*) kan tot 'n laer plasmakonsentrasie van amlodipien lei. Amlodipien moet versigtig saam met CYP3A4-induseerders gebruik word.

Simvastatien
Gelyktydige toediening van veelvoudige dosisse van 10 mg amlodipien met 80 mg simvastatien het gelei tot 'n 77 % toename in die blootstelling aan simvastatien in vergelyking met simvastatien alleen. Dit word aanbeveel om die dosis simvastatien tot 20 mg daagliks te beperk in pasiënte wat amlodipien gebruik, soos bevat in **VALDUO**.

Dantroleen (infusie)
Dodelike ventrikulêre fibrillasie en kardiovaskulêre ineenstorting word waargeneem in assosiasie met hiperkalemie na toediening van verapamiel en intraveneuse dantroleen. As gevolg van die risiko van hiperkalemie, word dit aanbeveel dat die kombinasie van kalsiumkanaalblokkers soos amlodipien (soos bevat in **VALDUO**) vermy word by pasiënte wat vatbaar is vir kwaadaardige hipertermie en in die behandeling van kwaadaardige hipertermie.

Ander
In monoterapie is amlodipien veilig toegedien saam met hidrochloortiasiede, beta-blokkers, angiotensienomskakelingsensiem-inhibeerders, langwerkende nitrate, ondertongse nitrogliserien, digoksien, warfarien, atorvastatien, sildenafiel, aluminiumhidroksiedgel, magnesiumhidroksied, simetikoon, simetidien, niesteroïdale anti-inflammatoriese medisyne, antibiotika en mondelikse hipoglukemiese medisynes.
Gesamentlike toediening van monoterapie amlodipien met digoksien het nie die serum digoksienvlakke of die renale opruiming van digoksien by normale vrywilligers verander nie en gesamentlike toediening van simetidien het nie die farmakokinetika van amlodipien gewysig nie.
In vitro data uit studies met menslike plasma dui aan dat monoterapie amlodipien geen uitwerking het op die proteïenbinding van die medisynes wat getoets is nie (digoksien, fenitoïen, warfarien of indometasien).
Monoterapie amlodipien toon nie 'n aansienlike verandering op die effek van warfarien op protrombien reaksietyd of die farmakokinetika van siklosporien nie.

Valsartaan
Litiumterapie
Gelyktydige toediening van valsartaan (soos bevat in **VALDUO**) met litium kan lei tot toksiese bloedkonsentrasies van litium (sien **KONTRA-INDIKASIES**). Noukeurige monitering van serum litiumvlakke word aanbeveel tydens gelyktydige gebruik van **VALDUO** en litium.

Dubbele blokkade van die renien-angiotensien-aldosteroonstelsel (RAAS) met angiotensien-reseptorblokkers (ARB's), angiotensienomskakelingsensiem (ACE) inhibeerders of aliskiren
Data van kliniese proewe het getoon dat dubbele blokkade van die renien-angiotensien-aldosteroonstelsel (RAAS) deur die gesamentlike gebruik van angiotensienomskakelingsensiem (ACE) inhibeerders, angiotensien II-reseptorblokkers (ARB's) of renieninhibeerders geassosieer word met 'n hoër frekwensie van ongunstige voorvalle soos hipotensie, hiperkalemie en verminderde nierfunksie (sien **KONTRA-INDIKASIES** en **WAARSKUWINGS EN SPESIALE VOORSORGMAATREËLS**).

Nie-steroïdale anti-inflammatoriese medisyne (NSAID's), insluitend selektiewe COX-2 inhibeerders, asetielsalisielsuur (> 3 g/dag) en nie-selektiewe NSAID's
Wanneer angiotensien II-antagoniste gelyktydig met NSAID's toegedien word, kan versterking van die hipertensiewe effek voorkom. Verder kan die gelyktydige gebruik van angiotensien II-antagoniste en NSAID's lei tot 'n verhoogde risiko van verergering van die nierfunksie en 'n toename in serum kalium. Daarom word dit aanbeveel om aan die begin van die behandeling die pasiënt se nierfunksie te monitor, sowel as voldoende hidrasie van die pasiënt.

Inhibeerders van die opnametransporteerder (rifampisien, siklosporien) of uitvloeitransporteerder (ritonavir)
Die resultate van 'n *in vitro* studie met menslike lewerweefsel dui daarop dat valsartaan 'n substraat van die hepatiese opnametransporteerder OATP1B1 en van die hepatiese uitvloeitransporteerder MRP2 is. Gelyktydige toediening van inhibeerders van die opnametransporteerder (rifampisien, siklosporien) of uitvloeitransporteerder (ritonavir) kan die sistemiese blootstelling aan valsartaan (soos bevat in **VALDUO**) verhoog.

Ander
In monoterapie met valsartaan is geen interaksies van kliniese belang gevind met die volgende medisyne nie: simetidien, warfarien, furosemied, digoksien, atenolol, indometasien, hidrochloortiasied, amlodipien, glibenklamied.
Gelyktydige gebruik met kaliumaanvullings, kaliumbesparende diuretikas (sien **KONTRA-INDIKASIES**), soutvervangers wat kalium bevat of ander medisyne wat kaliumvlakke kan verhoog, soos heparien, moet versigtig gedoen word en kaliumvlakke moet gereeld gemonitor word.

SWANGERSKAP EN BORSVOEDING
Swangerskap
Veiligheid tydens swangerskap is nie vasgestel nie (sien **KONTRA-INDIKASIES**).
Wanneer swangerskap beplan of bevestig word, moet die behandeling met **VALDUO** gestaak word.

Medisyne wat die renien-angiotensiensisteem beïnvloed, soos **VALDUO**, kan embrionale toksisiteit, fetale en neonatale morbiditeit en mortaliteit veroorsaak wanneer dit aan swanger vroue toegedien word.

Vroue van vrugbare potensiaal
Vroue van vrugbare ouderdom moet effektiewe voorbehoeding verseker.

Borsvoeding
Veiligheid in borsvoeding is nie vasgestel nie (sien **KONTRA-INDIKASIES**).

DOSIS EN GEBRUIKSAANWYSINGS
Pasiënte wat amlodipien en valsartaan van aparte tablette ontvang, kan oorskakel na **VALDUO** wat dieselfde dosisse bevat.

Volwassenes
Die aanbevole dosis is een tablet daagliks, met water.
VALDUO kan met of sonder kos geneem word.
Die dosis sal op 'n individuele pasiënt basis bepaal word.

Renale belemmering
Geen dosisaanpassing word benodig vir pasiënte met geringe tot matige renale belemmering nie. By pasiënte met ernstige renale belemmering is **VALDUO** teenaangedui (sien **KONTRA-INDIKASIES**).

Hepatiese belemmering
Wees versigtig wanneer **VALDUO** aan pasiënte met hepatiese belemmering of obstruktiewe galblaasversteurings toegedien word (sien **WAARSKUWINGS EN SPESIALE VOORSORGMAATREËLS**).

Bejaarde pasiënte
Geen dosisaanpassing word vereis vir bejaarde pasiënte nie.

Kinders en adolessente (tieners)
VALDUO word nie aanbeveel vir kinders 18 jaar en jonger nie (sien **WAARSKUWINGS EN SPESIALE VOORSORGMAATREËLS).**

NEWE-EFFEKTE
Amlodipien/valsartaan (VALDUO)
Immuunstelselversteurings:
Minder dikwels: Hipersensitiwiteit.

Metabolisme- en voedingsteurings:
Dikwels: Hipokalemie.
Minder dikwels: Anoreksie, hiperkalsemie, hiperglukemie, hiperlipidemie, hiperurisemie, hiponatremie.

Psigiatriese versteurings:
Minder dikwels: Angstigheid.

Senuweestelselversteurings:
Dikwels: Hoofpyn.
Minder dikwels: Duiseligheid, slaperigheid, posturale duiseligheid, parestesie

Oogversteurings:
Minder dikwels: Visuele versteuring.

Oor- en labirintversteurings:
Minder dikwels: Vertigo, tinnitus.

Kardiale versteurings:
Minder dikwels: Tagikardie, hartkloppings.

Vaskulêre versteurings:
Dikwels: Warm gloede, blosing.
Minder dikwels: Ortostatiese hipotensie, hipotensie, sinkopee.

Respiratoriese, torakale en mediastinale versteurings:
Dikwels: Nasofaringitis, griep.
Minder dikwels: Hoes, faringolaringeale pyn.

Gastro-intestinale versteurings:
Minder dikwels: Diarree, naarheid, braking, buikpyn, hardlywigheid, droë mond.

Vel- en subkutaneweefselversteurings:
Minder dikwels: Uitslag, eriteem, eksanteem, pruritus, hiperhidrose.

Spier-, bindweefsel- en beenversteurings:
Minder dikwels: Geswelde gewrigte, rugpyn, artralgie, spierspasma, swaar gevoel.

Nier- en urienwegversteurings:
Minder dikwels: Pollakurie, poliurie.

Voortplantingstelsel- en borsversteurings:
Minder dikwels: Erektiele disfunksie.

Algemene versteurings en toestande by plek van toediening:
Dikwels: Moegheid, astenie, edeem (vorming van holtetjies, in gesig en perifeer).

Amlodipien
Bloed- en limfstelselversteurings:
Minder dikwels: Leukopenie, trombositopenie.

Immuunstelselversteurings:
Minder dikwels: Angio-edeem, multivorm eriteem.

Metabolisme en voedingversteurings:
Minder dikwels: Hiperglukemie.

Psigiatriese versteurings:
Minder dikwels: Depressie, gemoedsveranderings.

Senuweestelselversteurings:
Dikwels: Hoofpyn, slaperigheid, duiseligheid, migraine.
Minder dikwels: Perifere neuropatie, tremor.

Oogversteurings:
Minder dikwels: Visuele steurnisse, oogpyn.

Oor- en labirintversteurings:
Minder dikwels: Vertigo.

Kardiale versteurings:
Dikwels: Hartkloppings, tagikardie.
Minder dikwels: Angina, bradikardie.

Vaskulêre versteurings:
Dikwels: Blosing.
Minder dikwels: Vaskulitis, sinkopee, hipotensie, ortostatiese hipotensie.

Respiratoriese, torakale en mediastinale versteurings:
Minder dikwels: Dispnee, rinitis.

Gastro-intestinale versteurings:
Dikwels: Naarheid, braking, buikpyn.
Minder dikwels: Verandering in dermgewoontes, dispepsie, gastritis, tandvleishiperplasie, droë mond, hardlywigheid.

Hepato-biliêre versteurings:
Minder dikwels: Pankreatitis, hepatitis, geelsug.

Vel- en subkutaneweefselversteurings:
Minder dikwels: Alopecia, pruritus, uitslag.

Spier-, bindweefsel- en beenversteurings:
Minder dikwels: Myalgie, artralgie, rugpyn, spierkrampe.

Nier- en urienwegversteurings:
Minder dikwels: Toename in urinêre frekwensie, mikturisie.

Voortplantingstelsel- en borsversteurings:
Minder dikwels: Ginekomastie, impotensie

Algemene versteurings en toestande by gebied van toediening:
Dikwels: Moegheid, edeem.
Minder dikwels: Verhoogde sweet, malaise, astenie.

Valsartaan
Infeksies en besmettings:
Dikwels: Virale infeksies.

Bloed- en limfstelsel versteurings:
Dikwels: Neutropenie.
Minder dikwels: Trombositopen.

Immuunstelselversteurings:
Minder dikwels: Hipersensitiwiteit insluitend serumsiekte, angio-edeem.

Metabolisme- en voedingversteurings:
Minder dikwels: Hiperkalemie.

Psigiatriese versteurings:
Minder dikwels: Slaaploosheid.

Senuweestelselversteurings:
Dikwels: Posturale duiseligheid.
Minder dikwels: Duiseligheid, hoofpyn.

Oogversteurings:
Minder dikwels: Versteurde visie.

Oor- en labirintversteurings:
Minder dikwels: Vertigo.

Kardiale versteurings:
Minder dikwels: Hartversaking.

Vaskulêre versteurings:
Dikwels: Ortostatiese hipotensie.
Minder dikwels: Hipotensie, vaskulitis, sinkopee.

Respiratoriese, torakale en mediastinale versteurings:
Minder dikwels: Boonstelugweginfeksie, faringitis, sinusitis, rinitis, hoes.

Gastro-intestinale versteurings:
Minder dikwels: Diarree, buikpyn, naarheid.

Hepato-biliêre versteurings:
Frekwensie onbekend: Hepatitis.

Vel- en subkutaneweefselversteurings:
Minder dikwels: Uitslag, pruritus, alopesie, urtikaria.

Spier-, bindweefsel- en beenversteurings:
Minder dikwels: Rugpyn, artralgie, mialgia, rabdomiolise.

Nier- en urienwegversteurings:
Minder dikwels: Belemmerde nierfunksie, akute nierversaking, renale ontoereikendheid.

Voortplantingstelsel- en borsversteurings:
Minder dikwels: Verminderde libido.

Algemene versteurings en toestande by gebied van toediening:
Minder dikwels: Moegheid, astenie, edeem.

BEKENDE SIMPTOME VAN OORDOSERING EN BESONDERHEDE VIR DIE BEHANDELING DAARVAN
Simptome
Amlodipien
Oordosering met amlodipien kan lei tot die volgende:
- Oormatige perifere vasodilatasie.
- Moontlike refleks tagikardie.
- Bradikardie.
- Potensieel verlengde sistemiese hipotensie met skok, met dodelike uitkoms.

Valsartaan
Oordosering met valsartaan kan lei tot die volgende:
- Uitgesproke hipotensie.
- Duiseligheid.
- Tagikardie.
- Bradikardie.

Behandeling
Dit is aangetoon dat toediening van geaktiveerde houtskool onmiddellik of tot twee uur na inname van amlodipien die absorpsie van amlodipien beduidend verlaag.

Aktiewe kardiovaskulêre ondersteuning, in kliniese beduidende hipotensie, insluitende gereelde monitering van die hart- en respiratoriese funksie, oplig van ledemate, aandag aan sirkulerende vloeistofvolume en urienuitsette.

'n Bloedvatvernouer kan nuttig wees om vaskulêre tonus en bloeddruk te herstel, op voorwaarde dat daar geen kontra-indikasie vir die gebruik daarvan is nie. Intraveneuse kalsiumglukonaat kan voordelig wees om die effekte van 'n kalsiumkanaalblokker om te keer.

Dit is onwaarskynlik dat sowel amlodipien as valsartaan deur hemodialise verwyder sal word.

IDENTIFIKASIE
VALDUO 5/80: Liggeel, ronde, bikonvekse, filmbedekte tablet, glad aan beide kante.
VALDUO 5/160: Donkergeel, ovaalvormige, bikonvekse, filmbedekte tablet, met 'L298' aan die een kant ingepers en ongemerk aan die ander kant.
VALDUO 10/160: Liggeel, ovaalvormige, bikonvekse, filmbedekte tablet, met 'L300' aan die een kant ingepers en ongemerk aan die ander kant.

AANBIEDING
Silwer aluminium/aluminium stulpstrook wat 10 tablette per stulpstrook bevat. Die stulpstroke word in 'n kartonhouer verpak.

Verpakkingsgrootte: 30 filmbedekte tablette.

BERGINGSINSTRUKSIES
Bewaar teen of onder 30 °C.
Hou die stulpstroke in die buitenste karton tot nodig vir gebruik.
Beskerm teen vog.
HOU BUITE BEREIK VAN KINDERS.

REGISTRASIENOMMERS
VALDUO 5/80: 51/7.1.3/0067
VALDUO 5/160: 51/7.1.3/0068
VALDUO 10/160: 51/7.1.3/0069

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PASIËNTINLIGTINGSBLAD VIR VALDUO 5/80, 5/160 EN 10/160

SKEDULERINGSTATUS
Skedule 3

EIENDOMSNAAM, STERKTE EN DOSEERVORM
VALDUO 5/80 filmbedekte tablet
VALDUO 5/160 filmbedekte tablet
VALDUO 10/160 filmbedekte tablet

Lees die hele inligtingsblad aandagtig deur voordat u begin om VALDUO te gebruik.
- Hou hierdie inligtingsblad. Dit is moontlik dat u dit weer sal wil deurlees.
- Indien u nog vrae het, vra asseblief u dokter of apteker.
- **VALDUO** is vir u persoonlik voorgeskryf en u moet nie medisyne met ander mense deel nie. Dit kan skadelik vir hulle wees, selfs al het hulle dieselfde simptome as u.

1. WAT VALDUO BEVAT
VALDUO 5/80: Die aktiewe bestanddeel in elke filmbedekte tablet is amlodipienbesilaat gelykstaande aan 5 mg amlodipien basis en 80 mg valsartaan.
VALDUO 5/160: Die aktiewe bestanddeel in elke filmbedekte tablet is amlodipienbesilaat gelykstaande aan 5 mg amlodipien basis en 160 mg valsartaan.
VALDUO 10/160: Die aktiewe bestanddeel in elke filmbedekte tablet is amlodipienbesilaat gelykstaande aan 10 mg amlodipien basis en 160 mg valsartaan.

Die ander bestanddele is kolloïdale anhidriese silika, krospovidoon, magnesiumstearaat, mikrokristallyne sellulose, Opadry geel (hipromellose, geel ysteroksied (kleurmiddel), makrogol, talk, titaandioksied (kleurmiddel)).
VALDUO 5/160 bevat ook rooi ysteroksied (kleurmiddel).
VALDUO (5/80, 5/160, 10/160) is suikervry.

2. WAARVOOR VALDUO GEBRUIK WORD
VALDUO bevat twee aktiewe bestanddele naamlik amlodipien en valsartaan. Albei van hierdie bestanddele word gebruik om hoë bloeddruk te behandel
- Amlodipien behoort aan 'n groep wat kalsiumkanaalblokkers genoem word.
- Valsartaan behoort aan 'n groep wat angiotensienreseptorblokkers (ARBs) genoem word.

VALDUO word gebruik om hoë bloeddruk te behandel by volwasse pasiënte wie se bloeddruk nie alleen met amlodipien of valsartaan beheer word nie.

3. VOORDAT U VALDUO NEEM
Moet nie VALDUO neem nie
- Indien u hipersensitief (allergies) is vir amlodipienbesilaat, valsartaan of enige van die ander bestanddele van **VALDUO** (sien **WAT VALDUO BEVAT**).
- Indien u swelling in u gesig of keel ondervind het toe u ander medisyne gebruik het (insluitend angiotensienreseptorblokkers (ARBs)). Indien hierdie simptome voorkom, moet behandeling met **VALDUO** dadelik gestaak word en u dokter gekontak word. U moet nooit weer **VALDUO** gebruik nie.
- Indien u dokter u ingelig het dat die dikte van u hartspier abnormaal toegeneem het (obstruktiewe hipertrofiese kardiomiopatie (HOCM)) of dat die kleppe in u hart vernou is (aortiese stenose).
- Indien u 'n nieroorplanting gehad het, indien u nierslagare vernou is of as u ernstige nierprobleme het.
- Indien u porfirie het ('n seldsame oorerflike siekte waarin daar 'n abnormale metabolisme van die bloedpigment hemoglobien in u bloed voorkom).
- Indien u swanger is of borsvoed (sien **Swangerskap en borsvoeding**).
- Indien u ernstige lae bloeddruk (hipotensie) het.
- Indien u aan 'n toestand ly waar u hart nie genoeg bloed aan die liggaam kan lewer nie (kardiogeniese skok).
- Indien u aan hartversaking ly ná 'n hartaanval.
- Indien u enige van die volgende medisyne gebruik (sien **Gebruik van ander medisyne met VALDUO**):
  - Renieninhibeerders soos aliskiren (wat gebruik word om hoë bloeddruk te behandel).
  - Litium (wat gebruik word om sekere tipes depressie te behandel).
  - Kaliumbesparende diuretika soos spironolaktoon, triamtereen, amiloried (watertablette).

Wees versigtig met VALDUO

Indien u swanger raak moet u dadelik die gebruik van VALDUO staak en u dokter skakel. VALDUO kan 'n ongebore baba skade aandoen en selfs dood veroorsaak. As u van plan is om swanger te raak, praat met u dokter oor ander behandelingsopsies om u bloeddruk te verlaag voordat u VALDUO gebruik (sien Moet nie VALDUO neem nie).

- Indien u nierprobleme het.
- Indien u lewerprobleme het.
- Indien u lae bloeddruk het.
- Indien u siek was (braking of diarree).
- Indien u 18 jaar of jonger is.

Die neem van VALDUO met kos en vloeistof
VALDUO kan met of sonder kos geneem word. Neem **VALDUO** met water. Moenie pomelo's eet of pomelosap drink terwyl u **VALDUO** neem nie. Pomelo's of pomelosap kan die bloeddrukverlagende effek van **VALDUO** verhoog.

Swangerskap en borsvoeding
Indien u swanger is of u baba borsvoed, raadpleeg u dokter, apteker of ander gesondheidsorgkundige voordat u **VALDUO** gebruik.
Moet nie **VALDUO** neem indien u swanger is of borsvoed nie.

Bestuur en gebruik van masjinerie
VALDUO kan newe-effekte veroorsaak, soos duiseligheid, slaperigheid en visuele steurnisse en kan u vermoë om 'n voertuig te bestuur en masjiene te hanteer, beïnvloed (sien **MOONTLIKE NEWE-EFFEKTE**). Moenie 'n voertuig bestuur, masjinerie hanteer of iets anders doen wat u aandag vereis totdat u weet hoe **VALDUO** u affekteer nie.

Gebruik van ander medisyne saam met VALDUO
Vertel altyd u gesondheidsorgkundige indien u enige ander medisyne gebruik. (Dit sluit aanvullende of tradisionele medisyne in.)
Sê vir u dokter of apteker indien u tans die volgende gebruik: (sien **Moet nie VALDUO neem nie**)
- Angiotensienomskakelingsensiem (ACE) inhibeerders, angiotensien II-reseptorblokkers (ARB's) of renien-inhibeerders, soos aliskiren (wat gebruik word om hoë bloeddruk te behandel).
- Litium (gebruik om sekere tipes depressie te behandel).
- Kaliumbesparende diuretikas soos spironolaktoon, triamtereen, amiloried (gebruik om oortollige vloeistof uit u liggaam te verwyder).
- Kaliumaanvullings, soutvervangers wat kalium bevat en ander stowwe wat kaliumvlakke kan verhoog.
- Sekere tipes pynstillers genaamd nie-steroïede anti-inflammatoriese medisyne (NSAID's, soos aspirien, diklofenak, ibuprofeen) of selektiewe siklo-oksigenase-2 inhibeerders (COX-2 inhibeerders, soos rofekoksib, selekoksib).
- Antikonvulsante medisyne (soos karbamasepien, fenobarbitaal, fenitoïen, fosfenitoïen, primidoon).
- Johanneskruid ('n kruiemedisyne wat gebruik word om depressie te behandel).
- Medisyne wat gebruik word vir MIV/VIGS (soos ritonavir, indinavir, nelfinavir).
- Medisyne wat gebruik word om swaminfeksies te behandel (soos ketokonasool, itrakonasool).
- Medisyne wat gebruik word om bakteriese infeksies te behandel (soos rifampisien, eritromisien, klaritromisien, telitromisien)
- Verapamiel, diltiasem (hartmedisyne).
- Simvastatien ('n medisyne wat gebruik word om hoë cholesterolvlakke te beheer).
- Dantroleen (infusie om ernstige abnormaliteite in die liggaamstemperatuur te behandel).
- Medisyne wat gebruik word om teen verwerping van oorgeplante organe te beskerm (siklosporien).

4. HOE OM VALDUO TE GEBRUIK
Moet nie medisyne wat aan u voorgeskryf is met ander mense deel nie. Neem **VALDUO** presies soos u dokter dit vir u voorgeskryf het. Indien u nie seker is nie, vra u dokter of apteker.

Volwassenes
Die gewone dosis is een tablet daagliks, dieselfde tyd elke dag. Neem die tablet met water. Indien u die indruk kry dat die effek van **VALDUO** te sterk of te swak is, sê vir u dokter of apteker.

Indien u meer VALDUO neem as wat u moet
In die geval van oordosering, raadpleeg u dokter of apteker. Indien nie een van hulle beskikbaar is nie, kontak die naaste hospitaal of gifsentrum.
Neem hierdie inligtingsblad en die res van die oorblywende **VALDUO** saam sodat die dokter weet wat u geneem het.

Indien u vergeet om VALDUO te neem
Indien u 'n dosis met slegs 'n paar uur gemis het, neem die dosis wat u vergeet het sodra u onthou. Indien dit amper tyd is vir die volgende dosis, slaan die gemiste dosis oor en neem **VALDUO** op die volgende gereelde geskeduleerde tyd. Moenie 'n dubbeldosis neem om op te maak vir die vergete individuele dosis nie.

Effekte wanneer behandeling met VALDUO gestop word
U dokter sal u inlig hoe lank u **VALDUO** moet neem. U toestand kan terugkeer indien die gebruik van **VALDUO** gestaak word voordat u aangeraai is om dit te doen.

5. MOONTLIKE NEWE-EFFEKTE
VALDUO kan newe-effekte hê.
Nie alle newe-effekte wat vir **VALDUO** aangemeld is, is by hierdie inligtingsblad ingesluit nie. Indien u algemene gesondheid agteruitgaan of u enige ongunstige effekte ervaar terwyl u **VALDUO** gebruik, raadpleeg asseblief u dokter, apteker of ander gesondheidsorgdeskundige.

Indien enige van die volgende gebeur, moet die gebruik van **VALDUO** dadelik gestaak word en moet u die dokter onmiddellik inlig of na die ongevalle-afdeling by u naaste hospitaal gaan:
- Swelling van u hande, voete, enkels, gesig, lippe, mond of keel, wat probleme kan veroorsaak om te sluk of asem te haal.
- Uitslag of jeuk.
- Floute.

Hierdie is almal baie ernstige newe-effekte. Indien u dit ervaar, het u moontlik 'n ernstige allergiese reaksie teen **VALDUO** gehad. U benodig dringende mediese aandag of hospitalisasie.

Lig u dokter dadelik in of gaan na die ongevalle-afdeling by die naaste hospitaal indien u enige van die volgende oplet:
Dikwels:
- Gereelde infeksies soos koors, erge kouekoors, seer keel of mondsere.
- Veranderinge in die manier waarop u hart klop (vinniger klop of slae oorslaan).

Minder dikwels:
- Bloei of kneus makliker as gewoonlik.
- Hoë kaliumvlakke in u bloed (abdominale pyn, verwarring, onreëlmatige hartklop, naarheid en braking), senuweeagtigheid, gevoelloosheid of tinteling in u hande, voete of lippe, kortasemheid, moeilike asemhaling, swakheid of swaar gevoel in u bene).
- Perifere neuropatie (tinteling of gevoelloosheid in u hande of voete, laat val gereeld goed van u hande, gevoel van swakheid of swaarheid in u arms en bene, skerp steekpyne).
- Hartversaking (kortasemheid, moegheid en swakheid, swelling van u bene, enkels en voete, vinnige of onreëlmatige hartklop, aanhoudende hoes met wit of pienk slym).
- Veranderinge in die manier waarop u hart klop (klop stadiger as normaal), borspyn.
- Vaskulitis (koors, hoofpyn, moegheid, gewigsverlies, algemene pyne, nagswete, senuweeprobleme soos gevoelloosheid of swakheid).
- Gastritis (pyn, naarheid, braking, braak bloed, bloed in die stoelgang).
- Pankreatitis (naarheid, braking, koors, pyn in u maagarea wat na u rug uitstraal).
- Vergeling van die vel en oë, ook genoem geelsug.
- Multivorm eriteem (rooi, dikwels jeukerige kolle, soortgelyk aan die uitslag van masels wat op u ledemate begin en soms op die gesig en die res van u liggaam, die kolle kan blase vorm of kan vorder om verhoogde, rooi merke met 'n vaal middel gedeelte te vorm, ander simptome sluit in koors, seer keel, hoofpyn en/of diarree).
- Hoë suiker (glukose) vlakke in u bloed (uitskei van groot hoeveelhede urine, oormatige dors, droë mond en vel).
- Nierversaking (slaperigheid, kortasem, moegheid, verwarring, naarheid, stuipe, skei minder urine uit as normaalweg).
- Skei meer urine uit as wat normaal is vir u, verhoogde frekwensie van urinering, veral gedurende die dag.

Hierdie is almal baie ernstige newe-effekte. U mag dringende mediese aandag benodig.

Vertel u dokter so gou as moontlik indien u enige van die volgende oplet:
Dikwels:
- Hoofpyn en erge hoofpyne (migraine).
- Lighoofdigheid wanneer u opstaan vanuit 'n lêende of sitposisie.
- Duiseligheid, slaperigheid.
- Influensa- of virusinfeksies (koors, hoes, algemene gevoel van ongemak of siekte, hoofpyn, gewrigspyn, spierpyne en pyn, verlies aan eetlus, sweet).
- Nasofaringitis (seer keel, loopneus of geblokkeerde neus, nies, spierpyn, hoofpyn).
- Naarheid, braking, maagpyn.
- Vel en gesig word rooi en warm.
- Ongewone moegheid of swakheid.

Minder dikwels:
- Voel angstig en/of depressief, met gemoedskommelings, onvermoë om te slaap.
- Verminderde eetlus.
- Abnormale bloedtoetsresultate wat hoë vlakke van vet in u bloed (hiperlipidemie), hoë bloedsuikervlakke (hiperglukemie) of lae bloedsuikervlakke (hipoglukemie) toon.
- Bloedtoetsresultate wat abnormale vlakke van natrium, kalium, kalsium of ureum in u bloed toon.
- Tinteling of gevoelloosheid van u hande en voete (naalde en spelde).
- Bewing (onwillekeurige bewe of skud van u hande en voete).
- Visuele steurnisse, pyn in die oog, versteurde visie.
- Vertigo (draaisensasie), gesing in die ore.
- Lae bloeddruk.
- Boonstelugweginfeksie (hoes, koors, seer keel, nies).
- Rinitis (loopneus of geblokte neus, nies), seer keel, hoes.
- Sinusitis (pyn en teerheid rondom u oë en wangbene, koors, geblokte of loopneus, hoofpyn, hoes).
- Diarree, hardlywigheid, droë mond, spysvertering.
- Gingivale hiperplasie (toename in die grootte van u tandvleisweefsel).
- Veranderinge in u dermgewoontes (verskuiwing in u stoelgangfrekwensie en konsekwentheid).
- Rooiheid van u vel en slymvliese, jeukerige uitslag.
- Haarverlies (tydelik).
- Pynlike geswelde gewrigte, spierkrampe en -pyn, rugpyn, gevoel van swaarheid.
- Tydelike verlamming of swakheid van spiere.
- Borsvergroting by mans.
- Erektiele disfunksie (die onvermoë om 'n ereksie te ontwikkel en te hou).
- Verhoogde sweetafskeiding.
- Abnormale fisiese swakheid of gebrek aan energie, oor die algemeen ongesteld voel.
- Verlies van libido.

Indien u enige newe-effekte oplet wat nie in hierdie inligtingsblad genoem word nie, moet u asseblief u dokter of apteker inlig.

6. BERGING EN WEGDOENING VAN VALDUO
- Bewaar by of onder 30 °C.
- Hou die stulpstroke in die buitenste karton totdat dit benodig word.
- Beskerm teen vog.
- BEWAAR ALLE MEDISYNE BUITE BEREIK VAN KINDERS.
- Moet nie gebruik na die vervaldatum wat op die karton gedruk is nie.
- Stuur ongebruikte medisyne na u apteker terug.
- Moet nie ongebruikte medisyne in dreine en rioolstelsels (bv. toilette) weggooi nie.

7. AANBIEDING VAN VALDUO
Silwer aluminium/aluminium stulpstrook wat 10 tablette per stulpstrook bevat. Die stulpstroke word in 'n kartonhouer verpak.
Verpakkingsgrootte: 30 filmbedekte tablette.

8. IDENTIFIKASIE VAN VALDUO
VALDUO 5/80: Liggeel, ronde, bikonvekse, filmbedekte tablet, glad aan beide kante.
VALDUO 5/160: Donkergeel, ovaalvormige, bikonvekse, filmbedekte tablet, met 'L298' aan die een kant ingepers en ongemerk aan die ander kant.
VALDUO 10/160: Liggeel, ovaalvormige, bikonvekse, filmbedekte tablet, met 'L300' aan die een kant ingepers en ongemerk aan die ander kant.

9. REGISTRASIENOMMERS
VALDUO 5/80: 51/7.1.3/0067
VALDUO 5/160: 51/7.1.3/0068
VALDUO 10/160: 51/7.1.3/0069

10. NAAM EN ADRES VAN REGISTRASIEHOUER
Forrester Pharma (Edms.) Bpk.
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