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

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
VALDUO 5/320 film coated tablet
VALDUO 10/320 film coated tablet

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 base and 320 mg valsartan.
VALDUO 10/320: Each film coated tablet contains amlodipine besilate equivalent to 10 mg amlodipine base and 320 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, and **5/320** also contain iron oxide red (colourant).
VALDUO is sugar free.

CATEGORY AND CLASS

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 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 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 4-6 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.

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 **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.

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.

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 ($t_{1/2}$ α < 1 hour and $t_{1/2}$ 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.

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.

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 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 **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 **HUMAN REPRODUCTION**).
- Concomitant use of **VALDUO** with aliskiren-containing products (see **WARNINGS AND SPECIAL PRECAUTIONS** and **INTERACTIONS**).
- 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.

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 HUMAN REPRODUCTION).

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.

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 **CONTRAINDICATIONS**). 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 with impaired hepatic 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 hepatic 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 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.

CYP3A4 inducers (anticonvulsant medicines [e.g. carbamazepine, phenobarbitone, 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 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.

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 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 **CONTRAINDICATIONS** and **WARNINGS AND SPECIAL PRECAUTIONS**).

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.

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.

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.

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 **CONTRAINDICATIONS**).

HUMAN REPRODUCTION

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.

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.

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.
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.

PRESENTATION

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.

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
VALDUO 5/320: 53/7.1.3/0179
VALDUO 10/320:53/7.1.3/0180

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

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