EXFORGE®

(amlodipine besilate/valsartan)

film-coated tablets 5 mg/80 mg, 5 mg/160 mg, and 10 mg/160 mg

LEAFLET

Trade name

EXFORGE® 5 mg/80 mg, 5 mg/160 mg and 10 mg/160 mg film-coated tablets.

Description and composition

Active substances:

Amlodipine besilate: 3-Ethyl-5-methyl (±)-2-[(2-minoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate, mono-benzenesulphonate.

Valsartan: (*S*)-N-valeryl-N-{[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl}-valine.

Three strengths are available. One tablet of Exforge contains:

- 5 mg of amlodipine (as amlodipine besilate) and 80 mg of valsartan, dark yellow, round shaped film-coated tablet with bevelled edges, debossed with “NVR” on one side and “NV” on the reverse side.
- 5 mg of amlodipine (as amlodipine besilate) and 160 mg of valsartan, dark yellow, ovaloid shaped film-coated tablet with bevelled edges, debossed with “NVR” on one side and “ECE” on the reverse side.
- 10 mg of amlodipine (as amlodipine besilate) and 160 mg of valsartan, light yellow, ovaloid shaped film-coated tablet with bevelled edges, debossed with “NVR” on one side and “UIC” on the reverse side.

Excipients

Exforge 5/80 mg: Cellulose microcrystalline; crospovidone; silica, colloidal anhydrous; magnesium stearate; hypromellose, macrogol 4000, talc, titanium dioxide (E171), iron oxide, yellow (E172)

Exforge 5/160 mg: Cellulose microcrystalline; crospovidone; silica, colloidal anhydrous; magnesium stearate; hypromellose, macrogol 4000, talc, titanium dioxide (E171), iron oxide, yellow (E172)

Exforge 10/160 mg: Cellulose microcrystalline; crospovidone; silica, colloidal anhydrous, magnesium stearate, hypromellose, macrogol 4000, talc, titanium dioxide (E171), iron oxide, yellow (E172), iron oxide, red (E172)

Pharmaceutical form

Film-coated tablets.

Indications

Treatment of essential hypertension.

Exforge is indicated in patients whose blood pressure is not adequately controlled by monotherapy.

Dosage and administration

Dosage

General target population

A patient whose blood pressure is not adequately controlled on monotherapy may be switched to combination therapy with Exforge. The recommended dose is one tablet per day (the strengths are listed in section Description and composition). When clinically appropriate direct change from monotherapy to the fixed-dose combination may be considered (See Warnings and precautions with regard to withdrawal of beta-blockers).

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

Both amlodipine and valsartan monotherapy can be taken with or without food. It is recommended to take Exforge with some water.

Special populations

Geriatric patients

Since both components of the combination are equally well tolerated when used at similar doses in elderly (aged 65 years or above) or younger patients, no dose adjustment of the starting dose is required (see section Clinical pharmacology).

Pediatric patients

Exforge is not recommended for use in patients aged below 18 years due to a lack of data on safety and efficacy.

Renal impairment

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

Monitoring of potassium levels and creatinine is advised in moderate renal impairment.

Hepatic impairment

Due to amlodipine and valsartan, caution should be required when administering Exforge to patients with hepatic impairment or biliary obstructive disorders (see section Warnings and precautions and Clinical pharmacology).

Contraindications

Known hypersensitivity to the amlodipine, valsartan or to any of the excipients.

Severe hepatic impairment, biliary cirrhosis, or cholestasis.

Pregnancy, breast-feeding (see section Women of child-bearing potential, pregnancy, breast-feeding and fertility, WOCPB).

There are no data on patients with severe renal impairment (creatinine clearance < 10 ml/minute). Exforge is contraindicated in patients with hereditary angioedema or in those in whom angioedema developed during earlier treatment with an ACE inhibitor or an angiotensin II receptor antagonist.

Concomitant use of angiotensin receptor antagonists (ARBs) - including valsartan - or of angiotensin - converting enzyme inhibitors (ACEIs) with aliskiren in patients with Type 2 diabetes (see section Interactions, subsection dual blockade of the RAS).

Warnings and precautions

Patients with sodium- and/or volume depletion

Excessive hypotension was seen in 0.4% of patients with uncomplicated hypertension treated with Exforge in placebo-controlled studies. In patients with an activated renin-

angiotensin system (such as volume- and/or salt-depleted patients receiving high doses of diuretics) who are receiving angiotensin receptor blockers, symptomatic hypotension may occur. Correction of this condition prior to administration of Exforge or close medical supervision at the start of treatment is recommended.

If hypotension occurs with Exforge, the patient should be placed in the supine position and, if necessary, given an i.v. infusion of normal saline. Treatment can be continued once blood pressure has been stabilized.

Hyperkalemia

Concomitant use with potassium supplements, potassium sparing diuretics, salt substitutes containing potassium, or other drugs that may increase potassium levels (heparin, etc.) should be used with caution and with frequent monitoring of potassium levels.

Patients with renal artery stenosis

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

No data are available on the use of Exforge in patients with unilateral or bilateral RAS, stenosis to a solitary kidney.

Patients with renal impairment

No data is available for severe cases (creatinine clearance < 10 mL/min.) and caution is therefore advised. No dosage adjustment of Exforge is required for patients with mild to moderate renal impairment.

The use of ARBs - including valsartan - or of ACEIs with aliskiren should be avoided in patients with severe renal impairment (GFR < 30 mL/min) (see section Interactions, subsection dual blockade of the RAS).

Patients with kidney transplantation

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

Patients with hepatic impairment

Valsartan is mostly eliminated unchanged via the bile whereas amlodipine is extensively metabolized by the liver. Particular caution should be exercised when administering Exforge to patients with hepatic impairment or biliary obstructive disorders (see section Clinical pharmacology).

Angioedema

Angioedema, including swelling of the larynx and glottis, causing airway obstruction and/or swelling of the face, lips, pharynx, and/or tongue has been reported in patients treated with valsartan; some of these patients previously experienced angioedema with other drugs including ACE inhibitors. Exforge should be immediately discontinued in patients who develop angioedema, and Exforge should not be re-administered.

Patients with heart failure/post-myocardial infarction

In general, calcium channel blockers including amlodipine should be used with caution in patients with serious congestive heart failure (New York Heart Association (NYHA) functional class III-IV).

In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (e.g. patients with severe congestive heart failure), treatment with angiotensin converting enzyme inhibitors or angiotensin receptor antagonists has been associated with oliguria and/or progressive azotemia, and in rare cases with acute renal failure and/or death. Evaluation of patients with heart failure or post-myocardial infarction should always include assessment of renal function.

Patients with acute myocardial infarction

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

Patients with aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy

As with all other vasodilators, special caution is required when using amlodipine in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy.

Dual Blockade of the Renin-Angiotensin System (RAS)

Caution is required while co-administering ARBs, including valsartan, with other agents blocking the RAS such as ACEIs or aliskiren (see section Interactions, subsection dual blockade of the RAS).

Interactions

Amlodipine

Amlodipine may be concomitantly administered with thiazide diuretics, alpha-blockers, beta-blockers, ACE inhibitors, long-acting nitrates, sublingual glyceryl trinitrate (nitroglycerin), NSAIDs, antibiotics and oral antidiabetics.

Calcium channel blockers may interfere with the cytochrome-P450-dependent metabolism of theophylline and ergotamine. Neither *in vitro* nor *in vivo* interaction studies are thus far available for amlodipine in combination with theophylline or ergotamine, and regular monitoring of theophylline or ergotamine blood levels is therefore recommended at the start of concomitant administration with amlodipine.

In vitro studies with human plasma show that amlodipine does not affect the protein binding of digoxin, phenytoin, coumarin, warfarin or indometacin.

Simvastatin: Co-administration of multiple doses of 10 mg of 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.

CYP3A4 Inhibitors: Co-administration of a 180 mg daily dose of diltiazem with 5 mg amlodipine in elderly hypertensive patients resulted in a 1.6 fold increase in amlodipine systemic exposure. However, strong inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, ritonavir) may increase the plasma concentrations of amlodipine to a greater extent than diltiazem. Caution should therefore be exercised when co-administering amlodipine with CYP3A4 inhibitors.

CYP3A4 Inducers: No information is available on the quantitative effects of CYP3A4 inducers on amlodipine. Patients should be monitored for adequate clinical effect when amlodipine is co-administered with CYP3A4 inducers.

Special studies: Effects of other active substances on amlodipine

Cimetidine

Concomitant administration of amlodipine and cimetidine does not alter the pharmacokinetics of amlodipine.

Grapefruit juice

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

Aluminium/magnesium (antacids)

Concomitant administration of aluminium/magnesium antacids and a single dose of amlodipine had no significant effect on the pharmacokinetics of amlodipine.

Sildenafil

In patients with essential hypertension, a single dose of sildenafil (100 mg) had no effect on the pharmacokinetic parameters of amlodipine. When amlodipine and sildenafil were co-administered, each active substance independently exerted its own antihypertensive effect.

Special studies: Effects of amlodipine on other active substances

Atorvastatin

Concomitant administration of several doses of amlodipine (10 mg) with atorvastatin (80 mg) did not result in any significant changes in the steady-state pharmacokinetic parameters of atorvastatin.

Digoxin

Studies in healthy volunteers have shown that concomitant administration of amlodipine and digoxin does not result in any changes in digoxin plasma levels or renal digoxin clearance.

Ethanol (alcohol)

Single and multiple doses of amlodipine (10 mg) had no significant effect on the pharmacokinetics of ethanol.

Warfarin

Concomitant administration of amlodipine did not significantly alter the effect of warfarin on prothrombin time in healthy male volunteers.

Ciclosporin

Pharmacokinetic studies with ciclosporin have shown that amlodipine does not significantly alter the pharmacokinetics of ciclosporin.

Valsartan

Dual blockade of the Renin-Angiotensin-System (RAS) with ARBs, ACEIs, or aliskiren: The concomitant use of ARBs, including valsartan, with other agents acting on the RAS is associated with an increased incidence of hypotension, hyperkalemia, and changes in renal function compared to monotherapy. It is recommended to monitor blood pressure, renal function and electrolytes in patients on Exforge and other agents that affect the RAS (see section Warnings and precautions).

The concomitant use of ARBs - including valsartan - or of ACEIs with aliskiren, should be avoided in patients with severe renal impairment (GFR < 30 mL/min) (see section Warnings and precautions).

The concomitant use of ARBs - including valsartan - or of ACEIs with aliskiren is contraindicated in patients with Type 2 diabetes (see section Contraindications).

Potassium: Concomitant use with potassium supplements, potassium-sparing diuretics, salt substitutes containing potassium, or other drugs that may increase potassium levels (heparin, etc.) requires caution and frequent monitoring of potassium levels.

Non-Steroidal Anti-Inflammatory Agents (NSAIDs) including Selective Cyclooxygenase-2 Inhibitors (COX-2 Inhibitors): When angiotensin II antagonists are administered simultaneously with NSAIDs, attenuation of the antihypertensive effect may occur. Furthermore, in patients who are elderly, volume-depleted (including those on diuretic therapy), or have compromised renal function, concomitant use of angiotensin II antagonists and NSAIDs may lead to an increased risk of worsening of renal function. Therefore, monitoring of renal function is recommended when initiating or modifying the treatment in patients on valsartan who are taking NSAIDs concomitantly.

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

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

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

Women of child-bearing potential, pregnancy, breast feeding and fertility (WOCPB)

Women of child-bearing potential

As for any drug that also acts directly on the RAAS, Exforge must not be used in women planning to become pregnant. Healthcare professionals prescribing any agents acting on the RAAS should counsel women of childbearing potential about the potential risk of these agents during pregnancy.

Pregnancy

As for any drug that also acts directly on the RAAS, Exforge must not be used during pregnancy (see section Contraindications). Due to the mechanism of action of angiotensin II antagonists, a risk to the foetus cannot be excluded. Administration of angiotensin converting enzyme (ACE) inhibitors (a specific class of drugs acting on the renin-angiotensin-aldosterone system, RAAS) to pregnant women during the second

and third trimesters has been reported to cause injury and death to the developing foetus. In addition, in retrospective data, first trimester use of ACE inhibitors has been associated with a potential risk of birth defects. There have been reports of spontaneous abortion, oligohydramnios and newborn renal dysfunction when pregnant women have inadvertently taken valsartan.

There are no adequate clinical data with amlodipine in pregnant women. Animal studies with amlodipine have shown reproductive toxicity at dose 8 times the maximum recommended dose of 10 mg (see section Non-clinical safety data). The potential risk to humans is unknown.

If pregnancy is detected during therapy, Exforge must be discontinued as soon as possible (see section Non-clinical safety data).

Breast-feeding

It is not known whether valsartan and/or amlodipine are excreted in human milk. Valsartan was excreted in the milk of lactating rats. It is therefore not advisable for women who are breast-feeding to use Exforge.

Fertility

There is no information on the effects of amlodipine or valsartan on human fertility. Studies in rats did not show any effects of amlodipine or valsartan on fertility (see section 13 Non-clinical safety data).

Adverse drug reactions

The safety of Exforge has been evaluated in five controlled clinical studies with 5,175 patients, 2,613 of whom received valsartan in combination with amlodipine.

Adverse drug reactions or adverse experiences (Table-1 and -2) are ranked under heading of frequency, the most frequent first, using the following convention: very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000) very rare (< 1/10,000), including isolated reports. Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.

Table 1 Adverse drug reactions with Exforge

Infections and infestations	
Common:	Nasopharyngitis, influenza
Uncommon:	Bronchitis, pharyngitis, urinary tract infection, gastroenteritis, pharyngotonsilitis, bronchitis acute, viral infection, tooth abscess, cystitis, pneumonia
Immune system disorders	

Rare:	Hypersensitivity
Eye disorders	
Rare	Visual disturbance
Psychiatric disorders	
Rare:	Anxiety
Nervous system disorders	
Common:	Headache
Uncommon:	Dizziness, somnolence, dizziness postural, paraesthesia
Ear and labyrinth disorders	
Uncommon:	Vertigo, ear pain
Rare:	Tinnitus
Cardiac disorders	
Uncommon:	Tachycardia, palpitations
Rare:	Syncope
Vascular disorders	
Uncommon:	Orthostatic hypotension
Rare:	Hypotension
Respiratory, thoracic and mediastinal disorders	
Uncommon:	Cough, pharyngolaryngeal pain
Gastrointestinal disorders	
Uncommon:	Diarrhoea, nausea, abdominal pain, constipation, dry mouth, dyspepsia, gastritis, vomiting, abdominal discomfort, hemorrhoids, abdominal distention, flatulence, toothache, colitis
Skin and subcutaneous tissue disorders	
Uncommon:	Rash, erythema
Rare:	Hyperhidrosis, exanthema, pruritus
Musculoskeletal and connective tissue disorders	
Uncommon:	Joint swelling, back pain, arthralgia
Rare:	Muscle spasm, sensation of heaviness
Renal and urinary disorders	
Rare:	Pollakiuria, polyuria
Reproductive system and breast disorders	
Rare:	Erectile dysfunction
Blood and lymphatic system disorders	
Uncommon:	Lymphadenopathy
General disorders and administration site conditions	
Common:	oedema, pitting oedema, facial oedema, oedema peripheral, fatigue, flushing, asthenia, hot flush
Uncommon:	Chest pain, pyrexia, and pain

Additional information on the combination

In double-blind, active- or placebo-controlled completed clinical trials, the incidence of peripheral oedema was statistically lower in patients treated with the combination (5.8%) than in patients treated with amlodipine monotherapy (9%).

Laboratory evaluation

Very few hypertensive patients treated with valsartan/amlodipine showed notable changes in laboratory test results from baseline. There was a slightly higher incidence of notably increased blood urea nitrogen in the amlodipine/valsartan (5.5 %) and valsartan monotherapy (5.5%) groups as compared to the placebo group (4.5%).

Additional information on individual components

Adverse reactions previously reported with one of the individual components may occur with EXFORGE even if not observed in clinical trials.

Amlodipine

Other additional adverse experiences reported with amlodipine monotherapy, irrespective of their causal association with the study drug, are presented in Table-2:

Because amlodipine clinical trials were conducted under widely varying conditions, adverse experience rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Table -2 Adverse experiences with amlodipine monotherapy

Eye disorders	
Uncommon	Diplopia
Blood and lymphatic system disorders	
Very rare	Thrombocytopenia, leucocytopenia
Immune system disorders	
Very rare	Allergic reactions
Metabolism and nutrition disorders	
Very rare	Hyperglycemia
Psychiatric disorders	
Uncommon	Insomnia, mood changes
Nervous system disorders	
Uncommon Very rare	Tremor, hypoesthesia, dysgeusia Peripheral neuropathy, hypertonia
Cardiac disorders	
Very rare	Arrhythmia, bradycardia, atrial fibrillation, ventricular tachycardia, myocardial infarction
Vascular disorders	
Very rare	Vasculitis
Respiratory, thoracic and mediastinal disorders	

Uncommon	Dyspnea, rhinitis
Gastrointestinal disorders	
Uncommon Very rare	Vomiting, dyspepsia Pancreatitis, gastritis, gingival hyperplasia
Hepatobiliary disorders	
Very rare	Hepatitis, jaundice
Skin and subcutaneous tissue disorders	
Uncommon Very rare	Alopecia, purpura, skin discoloration, photosensitivity Angioedema, urticaria, erythema multiforme, Steven Johnson syndrome
Musculoskeletal and connective tissue disorders	
Uncommon	Myalgia
Renal and urinary disorders	
Uncommon	Micturition disorder, nocturia
Reproductive system and breast disorders	
Uncommon	Gynecomastia
General disorders and administration site conditions	
Uncommon	Pain, malaise, chest pain
Investigations	
Uncommon Very rare	Weight decreased, weight increased Hepatic enzyme increased (mostly consistent with cholestasis)

Valsartan

Other ADRs reported from clinical studies, post-marketing experience and laboratory findings in hypertension indication are presented in Table 7-3 according to system organ class

For all the ADRs reported from post-marketing experience and laboratory findings, it is not possible to apply any ADR frequency and therefore they are mentioned with a "not known" frequency.

Table -3 Adverse drug reactions with valsartan monotherapy

Blood and lymphatic system disorders	
Not known	Hemoglobin decreased, hematocrit decreased, Neutropenia, Thrombocytopenia
Immune system disorders	
Not known	Hypersensitivity including serum sickness
Metabolism and nutrition disorders	
Not known	Blood potassium increased
Vascular disorders	

Not known	Vasculitis
Hepato-biliary disorders	
Not known	Liver function test abnormal including blood bilirubin increase
Skin and subcutaneous tissue disorders	
Not known	Angioedema, dermatitis bullous
Musculoskeletal and connective tissue disorders	
Not known	Myalgia
Renal and urinary disorders	
Not known	Renal failure and impairment, Blood creatinine increased

The following events have also been observed during clinical trials in hypertensive patients irrespective of their causal association with the study drug: Insomnia, libido decrease, pharyngitis, rhinitis, sinusitis, upper respiratory tract infection, viral infections.

Overdosage

There is no experience of overdose with Exforge yet. The major symptom of overdose with valsartan is probably pronounced hypotension with dizziness. Overdose with amlodipine may result in excessive peripheral vasodilatation and possibly reflex tachycardia. Marked and potentially prolonged systemic hypotension up to and including shock with fatal outcome have been reported.

Overdosage with amlodipine may result in excessive peripheral vasodilatation and possibly reflex tachycardia. Marked and potentially prolonged systemic hypotension up to and including shock with fatal outcome have been reported. Clinically significant hypotension due to amlodipine overdosage calls for active cardiovascular support including frequent monitoring of cardiac and respiratory function, elevation of extremities and attention to circulating fluid volume and urine output.

A vasoconstrictor may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use.

If the ingestion is recent, induction of vomiting or gastric lavage may be considered.

Administration of activated charcoal to healthy volunteers immediately or up to two hours after ingestion of amlodipine has been shown to significantly decrease amlodipine absorption.

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

Clinical pharmacology

Pharmacotherapeutic group, ATC

Pharmacotherapeutic group: angiotensin II antagonists, plain (valsartan) combinations with dihydropyridine derivatives (amlodipine), ATC code: C09DB01.

Pharmacodynamics (PD)

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

Amlodipine

The amlodipine component of Exforge inhibits the transmembrane entry of calcium ions into cardiac and vascular smooth muscle cells. The mechanism of the antihypertensive action of amlodipine is due to a direct relaxant effect on vascular smooth muscle, causing reductions in peripheral vascular resistance and blood pressure. Experimental data suggest that 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.

Following administration of therapeutic doses to patients with hypertension, 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.

As with other calcium channel blockers, haemodynamic measurements of cardiac function at rest and during exercise (or pacing) in patients with normal ventricular function treated with amlodipine have generally demonstrated a small increase in cardiac index without significant influence on dP/dt or on left ventricular end diastolic pressure or volume. In haemodynamic studies, amlodipine has not been associated with a negative inotropic effect when administered in the therapeutic dose range to intact animals and humans, even when co-administered with beta blockers to humans.

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

Valsartan

Valsartan is an orally active, potent, and specific angiotensin II receptor antagonist. It acts selectively on the AT1 receptor subtype, which is responsible for the known actions of angiotensin II. The increased plasma levels of angiotensin II following AT1 receptor blockade with valsartan may stimulate the unblocked AT2 receptor, which appears to counterbalance the effect of the AT1 receptor. Valsartan does not exhibit any partial agonist activity at the AT1 receptor and has much (about 20,000 fold) greater affinity for the AT1 receptor than for the AT2 receptor.

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

Administration of Valsartan to patients with hypertension results in reduction of blood pressure without affecting pulse rate.

In most patients, after administration of a single oral dose, onset of antihypertensive activity occurs within 2 hours, and the peak reduction of blood pressure is achieved

within 4-6 hours. The antihypertensive effect persists over 24 hours after administration. During repeated administration, the maximum reduction in blood pressure with any dose is generally attained within 2-4 weeks and is sustained during long-term therapy. Abrupt withdrawal of Valsartan has not been associated with rebound hypertension or other adverse clinical events.

Pharmacokinetics (PK)

Linearity

Valsartan and amlodipine exhibit linear pharmacokinetics.

Amlodipine

***Absorption**:* After oral administration of therapeutic doses of amlodipine alone, peak plasma concentrations of amlodipine are reached in 6–12 hours. Absolute bioavailability has been calculated as between 64% and 80%. Amlodipine bioavailability is unaffected by food ingestion.

***Distribution**:* Volume of distribution is approximately 21 l/kg. *In vitro* studies with amlodipine have shown that approximately 97.5% of circulating drug is bound to plasma proteins.

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

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

Valsartan

***Absorption**:* Following oral administration of valsartan alone, peak plasma concentrations of valsartan are reached in 2-4 hours. Mean absolute bioavailability is 23% (range 23%±7). Valsartan shows multiexponential decay kinetics ($t_{1/2}\alpha$ <1h and t 1/2 ß about 9 h). Food decreases the exposure (as measured by AUC) to valsartan by about 48% and peak plasma concentration (Cmax) by about 59%, although from about 8 h 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, and valsartan can therefore be given either with or without food.

Distribution: The steady-state volume of distribution of valsartan after intravenous administration is about 17 litres indicating that valsartan is not distributed into tissues extensively. Valsartan is highly bound to serum proteins (94-97%), mainly serum albumin.

Biotransformation: Valsartan is not transformed to a high extent as only about 20% of dose is recovered as metabolites. A hydroxy metabolite has been identified in plasma at low concentrations (less than 10 % of the valsartan AUC). This metabolite is pharmacologically inactive.

Elimination: Valsartan shows multiexponential decay kinetics ($t_{1/2}\alpha$ <1h and t 1/2 ß about 9 h). Valsartan is primarily eliminated unchanged in faeces (about 83% of dose) and urine (about 13% of dose) mainly as unchanged drug. Following intravenous administration, plasma clearance of valsartan is about 2 L/h and its renal clearance is 0.62 L/h (about 30% of total clearance). The half-life of valsartan is 6 hours.

Valsartan/Amlodipine

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

Special populations

Pediatric

No pharmacokinetic data are available in the paediatric population.

Geriatrics

The time to reach peak plasma concentrations of amlodipine is similar in elderly and younger subjects. Amlodipine clearance tends to be decreased with resulting increases in AUC and elimination half life in elderly patients.

Systemic exposure to valsartan is slightly elevated in the elderly as compared to the young, but this has not been shown to have any clinical significance. Since the two

components are equally well tolerated in younger and elderly patients, normal dose regimens are recommended (see section Dosage and andministration).

Renal impairment

The pharmacokinetics of amlodipine is not significantly influenced by renal impairment. There is no apparent 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 therefore receive the usual initial dose (see section Dosage and administration and section Warnings and precautions).

Hepatic impairment

Patients with hepatic insufficiency have decreased clearance of amlodipine with resulting increase in AUC of approximately 40-60% in AUC. On average, in patients with mild to moderate chronic liver disease exposure (measured by AUC values) to valsartan is twice that found in healthy volunteers (matched by age, sex and weight). Caution should be exercised in patients with liver disease (see section Dosage and administration and section Warnings and precautions).

Clinical studies

Over 1400 hypertensive patients received Exforge once daily in two placebo-controlled trials. The antihypertensive effect of a single dose of the combination persisted for 24 hours.

Exforge (amlodipine besilate/valsartan) was studied in 2 placebo-controlled trials in hypertensive patients with a diastolic blood pressure ≥95 mmHg and < 110 mmHg. In the first study (baseline blood pressure 153/99 mmHg), Exforge in doses of 5/80 mg, 5/160 mg and 5/320 mg reduced blood pressure 20-23/14-16 mmHg compared to 7/7 mmHg with placebo. In the second study (baseline blood pressure 157/99 mmHg), Exforge in doses of 10/160 mg and 10/320 mg reduced blood pressure 28/18-19 mmHg compared to 13/9 mmHg with placebo.

A multicenter, randomized, double-blind, active-controlled, parallel-group trial showed normalization of blood pressure (trough sitting diastolic BP <90 mmHg at the end of the trial) in patients not adequately controlled on valsartan 160 mg in 75% of patients treated with amlodipine/valsartan 10 mg/160 mg and 62% of patients treated with

amlodipine/valsartan 5 mg/160 mg, compared to 53% of patients remaining on valsartan 160 mg. The addition of amlodipine 10 mg and 5 mg produced an additional reduction in systolic/diastolic blood pressure of 6.0/4.8 mmHg and 3.9/2.9 mmHg, respectively, compared to patients who remained on valsartan 160 mg only.

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

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

In other studies, the probability of achieving systolic or diastolic blood pressure control was greater with combination therapy than valsartan and amlodipine monotherapy at all levels of baseline blood pressure.

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

In patients whose blood pressure is adequately controlled with amlodipine but who experience unacceptable edema, combination therapy may achieve similar blood pressure control with less edema.

Age, gender and race did not influence the response to Exforge.

Non-clinical safety data

Amlodipine:Valsartan

In a variety of preclinical safety studies conducted in several animal species with amlodipine:valsartan, there were no findings that would exclude the use of therapeutic doses of amlodipine: valsartan in humans. Animal studies lasting 13 weeks have been

conducted with amlodipine:valsartan combination in rats and marmosets, as well as studies in rats to investigate embryofetal development toxicity.

In a 13-week oral toxicity study in rats, amlodipine/valsartan-related inflammation of the glandular stomach was observed in males at doses ≥3/48 mg/kg/day. No such effects were observed in female rats at dose ≥3/48 mg/kg/day or in the 13-week marmoset study at any dose, although inflammation of the large intestine was observed in the high-dose marmosets only (no effects at dose ≤5/80 mg/kg/day). The gastrointestinal adverse effects observed in clinical trials with Exforge were no more frequent with the combination than with the respective monotherapies.

In an oral embryo-fetal development study in rats with dose levels of 5:80 mg/kg/day, amlodipine:valsartan, 10:160 mg/kg/day amlodipine:valsartan, and 20:320 mg/kg/day amlodipine:valsartan, treatment-related maternal and fetal effects (developmental delays and alterations noted in the presence of significant maternal toxicity) were noted with the high dose combination. The no-observed-adverse-effect level (NOAEL) for embryo-fetal effects was 10:160 mg/kg/day amlodipine:valsartan. These doses are, respectively, 4.3 and 2.7 times the systemic exposure in humans receiving the MRHD (10/320 mg/60 kg).

The combination amlodipine:valsartan was not tested for mutagenicity, clastogenicity, reproductive performance or carcinogenicity as there was no evidence for any interaction between the two compounds.

Amlodipine

Safety data for amlodipine are well established both clinically and non-clinically. No relevant findings were observed in carcinogenicity studies, mutagenicity studies.

There was no effect on the fertility of rats treated with amlodipine (males for 64 days and females 14 days prior to mating) at doses up to 10 mg/kg/day (8 times the maximum recommended human dose of 10 mg on a mg/m2 basis, based on patient weight of 50 kg).

No evidence of teratogenicity or embryo/fetal toxicity was found when pregnant rats and rabbits were treated orally with amlodipine maleate at doses up to 10 mg amlodipine/kg/day during their respective periods of major organogenesis. However, litter size was significantly decreased (by about 50%) and the number of intrauterine deaths was significantly increased (about 5-fold). Amlodipine has been shown to prolong both the gestation period and the duration of labor in rats at this dose.

Amlodipine has been tested individually for mutagenicity, clastogenicity, reproductive performance and carcinogenicity with negative results.

Valsartan

Precilinal data revealed no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity, carcinogenic potential and effects on fertility.

Safety pharmacology and Long term toxicity: In a variety of preclinical safety studies conducted in several animal species, there were no findings that would exclude the use of therapeutic doses of valsartan in humans.

In preclinical safety studies, high doses of valsartan (200 to 600 mg/kg/day body weight) caused in rats a reduction of red blood cell parameters (erythrocytes, hemoglobin, hematocrit) and evidence of changes in renal hemodynamics (slightly raised blood urea nitrogen, and renal tubular hyperplasia and basophilia in males). These doses in rats (200 and 600 mg/kg/day) are approximately 6 and 18 times the maximum recommended human dose on a mg/m2 basis (calculations assume an oral dose of 320 mg/day and a 60-kg patient). In marmosets at comparable doses, the changes were similar though more severe, particularly in the kidney where the changes developed to a nephropathy including raised blood urea nitrogen and creatinine. Hypertrophy of the renal juxtaglomerular cells was also seen in both species. All changes were considered to be caused by the pharmacological action of valsartan which produces prolonged hypotension, particularly in marmosets. For therapeutic doses of valsartan in humans, the hypertrophy of the renal juxtaglomerular cells does not seem to have any relevance.

Reproductive toxicity: Valsartan had no adverse effects on the reproductive performance of male or female rats at oral doses up to 200 mg/kg/day. In embryofetal development studies (Segment II) in mice, rats and rabbits, fetotoxicity was observed in association with maternal toxicity in rats at valsartan doses of ≥600 mg/kg/day and in rabbits at doses of 10 mg/kg/day. In a peri- and postnatal development toxicity (segment III) study, the offspring of rats given 600 mg/kg/day during the last trimester and during lactation showed a slightly reduced survival rate and a slight developmental delay.

Mutagenicity: Valsartan was devoid of mutagenic potential at either the gene or chromosome level when investigated in various standard in vitro and in vivo genotoxicity studies.

Carcinogenicity: There was no evidence of carcinogenicity when valsartan was administered in the diet to mice and rats for 2 years at doses up to 160 and 200 mg/kg/day, respectively.

Pharmaceutical information

Special precautions for storage

Do not store above 30°C, store in the original package in order to protect from moisture.

Keep out of the reach and sight of children.

Shelf-life

The expiry date is indicated on the packaging.

Nature and contents of container

Alu/Alu blisters.

Instructions for use and handling, and disposal

No special requirements.

Package

Exforge® 5 mg/80 mg FCT:

Box, 2 Blisters @ 14 Film-coated Tablets Reg. No.

Exforge® 5 mg/160 mg FCT:

Box, 4 Blisters @ 7 Film-coated Tablets Reg. No.

Exforge®10 mg/160 mg FCT:

Box, 4 Blisters @ 7 Film-coated Tablets Reg. No.

HARUS DENGAN RESEP DOKTER

To be dispensed only on the prescription of a physician.

Manufactured by Novartis Farma S.p.A, Torre Annunziata, Italy for Novartis Pharma AG, Basel, Switzerland.

Imported by PT Novartis Indonesia, Jakarta, Indonesia.

Leaflet is made based on CDS 03 Dec 2014_Torre