1 Name of the medicinal product

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

2 Qualitative and quantitative composition

Active substances:
Amlodipine besylate: 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 besylate) and 80 mg of valsartan,
- 5 mg of amlodipine (as amlodipine besylate) and 160 mg of valsartan,
- 10 mg of amlodipine (as amlodipine besylate) and 160 mg of valsartan,

For a full list of excipients, see section List of excipients.

3 Pharmaceutical form

Film-coated tablets.

4 Clinical particulars

4.1 Therapeutic indications

Treatment of essential hypertension.
Exforge is indicated in patients whose blood pressure is not adequately controlled by monotherapy.

4.2 Posology and method of administration

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 Qualitative and quantitative composition). When clinically appropriate direct change from monotherapy to the fixed-dose combination may be considered (See **Special warnings and special precautions for use** 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.

In Elderly
Since both components of the combination are equally well tolerated when used at similar doses in elderly or younger patients, normal dosage regimens are recommended.

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

Renal and hepatic impairment
No dosage adjustment is required for patients with mild to moderate renal impairment but caution should be required when administering Exforge to patients with hepatic impairment or biliary obstructive disorders (see section Special warnings and special precautions for use).

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients.

Pregnancy, lactation (see section Pregnancy and lactation).

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.

4.4 Special warnings and special precautions for use

Sodium- and/or volume depleted patients

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.

Hyperkalaemia

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.

Beta-Blocker Withdrawal

Amlodipine is not a beta-blocker and therefore gives no protection against the dangers of abrupt beta-blocker withdrawal; any such withdrawal should be by gradual reduction of the dose of beta-blocker.

Renal artery stenosis

No data are available on the use of Exforge in patients with unilateral or bilateral renal artery stenosis, stenosis to a solitary kidney. Other drugs that affect the renin-angiotensin-aldosterone system (RAAS) may increase blood urea and serum creatinine in patients with unilateral or bilateral renal artery stenosis, and monitoring of such patients is therefore recommended as a precautionary measure.

Renal impairment

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

Kidney transplantation

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

kidney transplantation.

Hepatic impairment
Valsartan is mostly eliminated unchanged via the bile whereas amlodipine is extensively metabolized by the liver. Particular caution should be required when administering Exforge to patients with hepatic impairment or biliary obstructive disorders.

Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy
As with all other vasodilators, special caution is indicated in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy.

4.5 Interaction with other medicinal products and other forms of interaction
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.

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
Studies in 20 healthy volunteers have shown that concomitant administration of 240 ml grapefruit juice and a single dose of amlodipine (5 mg or 10 mg) results in a slight increase in the C_{max} and AUC of amlodipine.

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
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.

Valsartan is only metabolized to a slight extent, so no clinically relevant drug interactions – in the form of metabolic induction or inhibition of the cytochrome P450 system – are to be expected.

Although valsartan is extensively bound to plasma proteins, *in vitro* studies have not shown any interaction at this level with a range of other substances that are extensively bound to plasma proteins (e.g. diclofenac, furosemide and warfarin).

There is no experience with concomitant use of valsartan and lithium. Regular monitoring of serum lithium levels is therefore recommended in the event of concomitant administration of lithium and valsartan.
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.

4.6 Pregnancy and lactation

Pregnancy

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. As for any drug that also acts directly on the RAAS, Exforge must not be used during pregnancy (see section Contraindications) or 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. If pregnancy is detected during therapy, Exforge must be discontinued as soon as possible.

Lactation

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 contraindicated for women who are breast-feeding to use Exforge.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. When driving vehicles or using machines it should be taken into account that occasionally dizziness or weariness may occur.

4.8 Undesirable effects

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 (Table 1) 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

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 in clinical trials with amlodipine monotherapy, irrespective of their causal association with the study drug, were as follows:

Adverse effects that were uncommon, or rarely reported, were insomnia, mood disorder, mood changes, tremor, dysgeusia, syncope, hypoaesthesia, dyspnoea, rhinitis, vomiting, dyspepsia, altered bowel habits, dry mouth, alopecia, purpura, skin discoloration, increased sweating, rash, photosensitization, myalgia, disturbances of micturition, nocturia, increased urinary frequency, impotence, gynaecomastia, asthenia, pain, malaise, weight gain, weight loss.

Adverse effects that were very rarely reported were leucopenia, thrombocytopenia, allergic reactions, hyperglycaemia, peripheral neuropathy, vasculitis, pancreatitis, gastritis, gingival hyperplasia, hepatitis, jaundice, elevated liver enzyme counts (usually consistent with cholestasis), vascular oedema, erythema multiforme, urticaria, muscle stiffness or muscle tension.

In a long-term, placebo controlled study (PRAISE-2) of amlodipine in patients with NYHA III and IV heart failure of nonischaemic aetiology, amlodipine was associated with increased reports of

pulmonary oedema despite no significant difference in the incidence of worsening heart failure as compared to placebo.

Risk of Myocardial Infarction or Increased Angina: Rarely, patients, particularly those with severe obstructive coronary artery disease, have developed increased frequency, duration or severity of angina or acute myocardial infarction on starting calcium channel blocker therapy or at the time of dosage increase. Arrhythmia (including ventricular tachycardia and atrial fibrillation) has also been reported with calcium channel blocker therapy. These adverse events may not be distinguishable from the natural history of the underlying disease.

Valsartan

Other additional adverse experiences reported in clinical trials with valsartan monotherapy in the hypertension indication, irrespective of their causal association with the study drug, were as follows:

Adverse effects that were frequently reported were viral infections, elevated blood levels of creatinine and urea.
Adverse effects that were uncommon, or rarely reported, were upper respiratory tract infections, impaired renal function, fatigue.
Adverse effects that were very rarely reported were neutropenia, thrombocytopenia, insomnia, reduced libido, light-headedness, arrhythmia, rhinitis, sinusitis, pharyngitis, vomiting, angioedema, vasculitis, rash, myalgia, fetal complications, elevated levels of bilirubin, reduced blood levels of haemoglobin/ haematocrit, abnormal liver function values.

Neutropenia was observed in 1.9% of patients treated with valsartan versus 1.6% of patients treated with an ACE inhibitor.

In heart failure patients, greater than 50% increases in creatinine were observed in 3.9% of valsartan-treated patients compared to 0.9% of placebo-treated patients. In post-myocardial infarction patients, doubling of serum creatinine was observed in 4.2% of valsartan-treated patients and 3.4% of captopril-treated patients.

In heart failure patients, greater than 20% increases in serum potassium were observed in 10% of valsartan-treated patients compared to 5.1% of placebo-treated patients.

In heart failure patients, greater than 50% increases in BUN were observed in 16.6% of valsartan-treated patients compared to 6.3% of placebo-treated patients.

4.9 Overdose

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.

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.

Clinically significant hypotension due to Exforge overdose calls for active cardiovascular support including frequent monitoring of cardiac and respiratory function, elevation of extremities, and attention to circulating fluid volume and urine output. A vasoconstrictor may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade.

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

5 Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: angiotensin II antagonists, plain (valsartan) combinations with dihydropyridine derivatives (amlodipine), ATC code: CO9DB01.

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 reduction in 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 effects 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.

Valsartan/Amlodipine

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 besylate/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 multicentre, randomised, double-blind, active-controlled, parallel-group trial showed normalisation 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 multicentre, randomised, double-blind, active-controlled, parallel-group trial showed normalisation 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 two long-term follow-up studies the effect of Exforge was maintained for over one year.

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

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

5.2 Pharmacokinetic properties

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 in hypertensive patients.

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

Excretion: 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 1/2α <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 does not distribute 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.

Excretion: 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.

Elderly
Time to peak plasma amlodipine concentrations is similar in young and elderly patients. In elderly patients, amlodipine clearance tends to decline, causing increases in AUC and elimination half-life.

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 Posology and method of administration)

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 Posology and method of administration and section Special warnings and special precautions for use).

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 Posology and method of administration and section Special warnings and special precautions for use).

Preclinical safety data
Animal studies lasting 13 weeks have been conducted with the combination in rats and marmosets, as well as studies in rats to investigate embryofoetal development toxicity. There were no toxicological findings observed that were of relevance to human therapeutic use.

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.

6 Pharmaceutical particulars

6.1 List of 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)

6.2 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.

6.3 Nature and contents of container
Alu/Alu blisters.

6.4 Instructions for use and handling, and disposal
No special requirements.

6.5 Package
Exforge® 5 mg/80 mg FCT :
Box, 1 Blisters @ 14 Film-coated Tablets Reg. No. DKI0767506517A1
Box, 2 Blisters @ 14 Film-coated Tablets Reg. No. DKI0767506517A1

Exforge® 5 mg/160 mg FCT:
Box, 1 Blisters @ 14 Film-coated Tablets Reg. No. DKI0767506517B1
Box, 2 Blisters @ 14 Film-coated Tablets Reg. No. DKI0767506517B1

Exforge®10 mg/160 mg FCT:
Box, 1 Blisters @ 14 Film-coated Tablets Reg. No. DKI0767506517C1
Box, 2 Blisters @ 14 Film-coated Tablets Reg. No. DKI0767506517C1

Harus Dengan Resep Dokter

To be dispensed only on the prescription of a physician.

Manufactured by Novartis Pharma Stein AG, Stein, Switzerland for Novartis Pharma AG, Basel, Switzerland. Imported by PT Novartis Indonesia, Pasar Rebo, Jakarta, Indonesia.