ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS
1. NAME OF THE MEDICINAL PRODUCT

Exforge 5 mg/80 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 5 mg of amlodipine (as amlodipine besylate) and 80 mg of valsartan. For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

Dark yellow, round film-coated tablet with bevelled edges, imprinted with “NVR” on one side and “NV” on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of essential hypertension.

Exforge is indicated in adults whose blood pressure is not adequately controlled on amlodipine or valsartan monotherapy.

4.2 Posology and method of administration

Posology
The recommended dose of Exforge is one tablet per day.

Exforge 5 mg/80 mg may be administered in patients whose blood pressure is not adequately controlled with amlodipine 5 mg or valsartan 80 mg alone.

Exforge can be used with or without food.

Individual dose titration with the components (i.e. amlodipine and valsartan) is recommended before changing to the fixed dose combination. When clinically appropriate, direct change from monotherapy to the fixed-dose combination may be considered.

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

Renal impairment
Exforge is contraindicated in patients with severe renal impairment (see section 4.3).

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
Exforge is contraindicated in patients with severe hepatic impairment (see section 4.3).

Caution should be exercised when administering Exforge to patients with hepatic impairment or biliary obstructive disorders (see section 4.4). In patients with mild to moderate hepatic impairment without cholestasis, the maximum recommended dose is 80 mg valsartan.

Elderly (age 65 years or over)
In elderly patients, caution is required when increasing the dosage.

Paediatric population
The safety and efficacy of Exforge in children aged below 18 years have not been established. No data are available.

Method of administration
Oral use.
It is recommended to take Exforge with some water.

4.3 Contraindications

- Hypersensitivity to the active substances, to dihydropyridine derivatives, or to any of the excipients listed in section 6.1.
- Severe hepatic impairment, biliary cirrhosis or cholestasis.
- Severe renal impairment (glomerular filtration rate (GFR) <30 ml/min/1.73 m²) and patients undergoing dialysis.
- Second and third trimesters of pregnancy (see sections 4.4 and 4.6).

4.4 Special warnings and precautions for use

Pregnancy
Angiotensin II Receptor Antagonists (AIIRAs) should not be initiated during pregnancy. Unless continued AIIRA therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with AIIRAs should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

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 intravenous infusion of normal saline. Treatment can be continued once blood pressure has been stabilised.

Hyperkalaemia
Concomitant use with potassium supplements, potassium-sparing diuretics, salt substitutes containing potassium, or other medicinal products that may increase potassium levels (heparin, etc.) should be undertaken with caution and with frequent monitoring of potassium levels.
Renal artery stenosis
No data are available on the use of Exforge in patients with bilateral renal artery stenosis or stenosis to a solitary kidney.

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 metabolised by the liver. Particular caution should be exercised when administering Exforge to patients with mild to moderate hepatic impairment or biliary obstructive disorders.

In patients with mild to moderate hepatic impairment without cholestasis, the maximum recommended dose is 80 mg valsartan.

Renal impairment
No dosage adjustment of Exforge is required for patients with mild to moderate renal impairment (GFR >30 ml/min/1.73 m²). Monitoring of potassium levels and creatinine is advised in moderate renal impairment.

Primary hyperaldosteronism
Patients with primary hyperaldosteronism should not be treated with the angiotensin II antagonist valsartan as their renin-angiotensin system is affected by the primary disease.

Heart failure
As a consequence of the inhibition of the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotaemia and (rarely) with acute renal failure and/or death. Similar outcomes have been reported with valsartan.

In a long-term, placebo-controlled study (PRAISE-2) of amlodipine in patients with NYHA (New York Heart Association Classification) III and IV heart failure of non-ischaemic 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.

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.

Exforge has not been studied in any patient population other than hypertension.
4.5 Interaction with other medicinal products and other forms of interaction

**Interactions common to the combination**
No drug-drug interaction studies have been performed with Exforge and other medicinal products.

**To be taken into account with concomitant use**

**Other antihypertensive agents**
Commonly used antihypertensive agents (e.g. alpha blockers, diuretics) and other medicinal products which may cause hypotensive adverse effects (e.g. tricyclic antidepressants, alpha blockers for treatment of benign prostate hyperplasia) may increase the antihypertensive effect of the combination.

**Interactions linked to amlodipine**

**Caution required with concomitant use**

**CYP3A4 inhibitors**
A study in elderly patients has shown that diltiazem inhibits the metabolism of amlodipine, probably via CYP3A4 (plasma concentration increases by approximately 50% and the effect of amlodipine is increased). The possibility that more potent inhibitors of CYP3A4 (i.e. ketoconazole, itraconazole, ritonavir) may increase the plasma concentration of amlodipine to a greater extent than diltiazem cannot be excluded.

CYP3A4 inducers (anticonvulsant agents [e.g. carbamazepine, phenobarbital, phenytoin, fosphenytoin, primidone], rifampicin, Hypericum perforatum)
Co-administration may lead to reduced plasma concentrations of amlodipine. Clinical monitoring is indicated, with possible dosage adjustment of amlodipine during the treatment with the inducer and after its withdrawal.

**To be taken into account with concomitant use**

**Others**
In monotherapy, amlodipine has been safely administered with thiazide diuretics, beta blockers, ACE inhibitors, long-acting nitrates, sublingual nitroglycerin, digoxin, warfarin, atorvastatin, sildenafil, anti-acid medicines (aluminium hydroxide gel, magnesium hydroxide, simeticone), cimetidine, non-steroidal anti-inflammatory medicines, antibiotics and oral hypoglycaemic medicines.

**Interactions linked to valsartan**

**Concomitant use not recommended**

**Lithium**
Reversible increases in serum lithium concentrations and toxicity have been reported during concurrent use of ACE inhibitors. Despite the lack of experience with concomitant use of valsartan and lithium, this combination is not recommended. If the combination proves necessary, careful monitoring of serum lithium levels is recommended (see section 4.4).

Potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium and other substances that may increase potassium levels
If a medicinal product that affects potassium levels is to be prescribed in combination with valsartan, monitoring of potassium plasma levels is advised.

**Caution required with concomitant use**

Non-steroidal anti-inflammatory medicines (NSAIDs), including selective COX-2 inhibitors, acetylsalicylic acid (>3 g/day), and non-selective NSAIDs
When angiotensin II antagonists are administered simultaneously with NSAIDs attenuation of the antihypertensive effect may occur. Furthermore, concomitant use of angiotensin II antagonists and NSAIDs may lead to an increased risk of worsening of renal function and an increase in serum potassium. Therefore, monitoring of renal function at the beginning of the treatment is recommended, as well as adequate hydration of the patient.
**Others**

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

### 4.6 Fertility, pregnancy and lactation

**Pregnancy**

**Amlodipine**

The safety of amlodipine in human pregnancy has not been established. In animal studies, reproductive toxicity was observed at high doses (see section 5.3). Use in pregnancy is only recommended when there is no safer alternative and when the disease itself carries greater risk for the mother and foetus.

**Valsartan**

The use of Angiotensin II Receptor Antagonists (AIIRAs) is not recommended during the first trimester of pregnancy (see section 4.4). The use of AIIRAs is contraindicated during the second and third trimesters of pregnancy (see sections 4.3 and 4.4).

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Whilst there is no controlled epidemiological data on the risk with Angiotensin II Receptor Antagonists (AIIRAs), similar risks may exist for this class of drugs. Unless continued AIIRA therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with AIIRAs should be stopped immediately, and, if appropriate, alternative therapy should be started.

Exposure to AIIRA therapy during the second and third trimesters is known to induce human foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (see section 5.3).

Should exposure to AIIRAs have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.

Infants whose mothers have taken AIIRAs should be closely observed for hypotension (see sections 4.3 and 4.4).

**Breast-feeding**

No information is available regarding the use of Exforge during breast-feeding, therefore Exforge is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

**Fertility**

There are no clinical studies on fertility with Exforge.

**Valsartan**

Valsartan had no adverse effects on the reproductive performance of male or female rats at oral doses up to 200 mg/kg/day. This dose is 6 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).

**Amlodipine**

Reversible biochemical changes in the head of spermatozoa have been reported in some patients treated by calcium channel blockers. Clinical data are insufficient regarding the potential effect of amlodipine on fertility. In one rat study, adverse effects were found on male fertility (see section 5.3).
4.7 Effects on ability to drive and use machines

When driving vehicles or using machines it should be taken into account that occasionally dizziness or weariness may occur.

4.8 Undesirable effects

Summary of the safety profile
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. The following adverse reactions were found to be the most frequently occurring or the most significant or severe: nasopharyngitis, influenza, hypersensitivity, headache, syncope, orthostatic hypotension, oedema, pitting oedema, facial oedema, oedema peripheral, fatigue, flushing, asthenia and hot flush.
Tabulated list of adverse reactions
Adverse reactions have been ranked under headings of frequency using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

<table>
<thead>
<tr>
<th>Infections and infestations</th>
<th>Common: Nasopharyngitis, influenza</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune system disorders</td>
<td>Rare: Hypersensitivity</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Rare: Anxiety</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Common: Headache</td>
</tr>
<tr>
<td></td>
<td>Uncommon: Dizziness, somnolence, dizziness postural, paraesthesia</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Rare: Visual disturbance</td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td>Uncommon: Vertigo</td>
</tr>
<tr>
<td></td>
<td>Rare: Tinnitus</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Uncommon: Tachycardia, palpitations</td>
</tr>
<tr>
<td></td>
<td>Rare: Syncope</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Uncommon: Orthostatic hypotension</td>
</tr>
<tr>
<td></td>
<td>Rare: Hypotension</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Uncommon: Cough, pharyngolaryngeal pain</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Uncommon: Diarrhoea, nausea, abdominal pain, constipation, dry mouth</td>
</tr>
<tr>
<td></td>
<td>Uncommon: Rash, erythema</td>
</tr>
<tr>
<td></td>
<td>Rare: Hyperhidrosis, exanthema, pruritus</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Uncommon: Joint swelling, back pain, arthralgia</td>
</tr>
<tr>
<td></td>
<td>Rare: Muscle spasm, sensation of heaviness</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Rare: Pollakisuria, polyuria</td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td>Rare: Erectile dysfunction</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Common: Oedema, pitting oedema, facial oedema, oedema peripheral, fatigue, flushing, asthenia, hot flush</td>
</tr>
</tbody>
</table>
Additional information on the combination
Peripheral oedema, a recognised side effect of amlodipine, was generally observed at a lower incidence in patients who received the amlodipine/valsartan combination than in those who received amlodipine alone. In double-blind, controlled clinical trials, the incidence of peripheral oedema by dose was as follows:

<table>
<thead>
<tr>
<th>% of patients who experienced peripheral oedema</th>
<th>Valsartan (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Amlodipine (mg)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>2.5</td>
</tr>
<tr>
<td></td>
<td>5</td>
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<td></td>
<td>10</td>
</tr>
</tbody>
</table>

The mean incidence of peripheral oedema evenly weighted across all doses was 5.1% with the amlodipine/valsartan combination.

Additional information on the individual components
Adverse reactions previously reported with one of the individual components (amlodipine or valsartan) may be potential adverse reactions with Exforge as well, even if not observed in clinical trials or during the post-marketing period.

**Amlodipine**

*Common*  Vomiting.

*Uncommon*  Alopecia, altered bowel habits, dyspepsia, dyspnoea, rhinitis, gastritis, gingival hyperplasia, gynaecomastia, hyperglycaemia, impotence, increased urinary frequency, leucopenia, malaise, mood changes, myalgia, peripheral neuropathy, pancreatitis, hepatitis, thrombocytopenia, vasculitis, angioedema and erythema multiforme.

*Rare*  Arrhythmia, myocardial infarction. 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. These adverse events may not be distinguishable from the natural history of the underlying disease.

*Very rare*  Cholestatic jaundice, AST and ALT increase, purpura, rash and pruritus. Exceptional cases of extrapyramidal syndrome have been reported.

**Valsartan**

*Not known*  Decrease in haemoglobin, decrease in haematocrit, neutropenia, thrombocytopenia, increase of serum potassium, elevation of liver function values including increase of serum bilirubin, renal failure and impairment, elevation of serum creatinine, angioedema, myalgia, vasculitis, hypersensitivity including serum sickness.
4.9 Overdose

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

Treatment
If 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: Agents acting on the renin-angiotensin system; angiotensin II antagonists, combinations; angiotensin II antagonists and calcium channel blockers, ATC code: C09DB01

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 antagonist class of medicines. The combination of these substances has an additive antihypertensive effect, reducing blood pressure to a greater degree than either component alone.

Amlodipine/Valsartan
The combination of amlodipine and valsartan produces dose-related additive reduction in blood pressure across its therapeutic dose range. The antihypertensive effect of a single dose of the combination persisted for 24 hours.

Placebo-controlled trials
Over 1,400 hypertensive patients received Exforge once daily in two placebo-controlled trials. Adults with mild to moderate uncomplicated essential hypertension (mean sitting diastolic blood pressure ≥95 and <110 mmHg) were enrolled. Patients with high cardiovascular risks – heart failure, type I and poorly controlled type II diabetes and history of myocardial infarction or stroke within one year – were excluded.

Active-controlled trials in patients who were non-responders to monotherapy
A multicentre, randomised, double-blind, active-controlled, parallel-group trial showed normalisation of blood pressure (trough sitting diastolic blood pressure <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 blood pressure <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 mean sitting 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. Abrupt withdrawal of Exforge has not been associated with a rapid increase in blood pressure.

Age, gender, race or body mass index (≥30 kg/m², <30 kg/m²) did not influence the response to Exforge.

Exforge has not been studied in any patient population other than hypertension. Valsartan has been studied in patients with post myocardial infarction and heart failure. Amlodipine has been studied in patients with chronic stable angina, vasospastic angina and angiographically documented coronary artery disease.

Amlodipine
The amlodipine component of Exforge 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 relaxant effect on vascular smooth muscle, causing reductions in peripheral vascular resistance and in blood pressure. Experimental data suggest that 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.

Following administration of therapeutic doses to patients with hypertension, amlodipine produces vasodilation, 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 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 receptor subtype AT_2, 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.

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 coughing. 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 coughing, 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 a drop in 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 drop in 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.

5.2 Pharmacokinetic properties

Linearity
Amlodipine and valsartan exhibit linear pharmacokinetics.

Amlodipine/Valsartan
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.

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.

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%. Valsartan shows multiexponential decay kinetics ($t_{1/2a} < 1$ h and $t_{1/2b}$ about 9 h). Food decreases exposure (as measured by AUC) to valsartan by about 40% and peak plasma concentration ($C_{max}$) by about 50%, although from about 8 h post dosing plasma valsartan concentrations are similar for the fed and fasted groups. This reduction in AUC is not, however, 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.

Elimination: Valsartan is primarily eliminated 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.

Special populations

Paediatric population (age below 18 years)
No pharmacokinetic data are available in the paediatric population.

Elderly (age 65 years or over)
Time to peak plasma amlodipine concentrations is similar in young and elderly patients. In elderly patients, amlodipine clearance tends to decline, causing increases in the area under the curve (AUC) and elimination half-life. Mean systemic AUC of valsartan is higher by 70% in the elderly than in the young, therefore caution is required when increasing the dosage.

Renal impairment
The pharmacokinetics of amlodipine are not significantly influenced by renal impairment. As expected for a compound where renal clearance accounts for only 30% of total plasma clearance, no correlation was seen between renal function and systemic exposure to valsartan.

Hepatic impairment
Patients with hepatic insufficiency have decreased clearance of amlodipine with resulting increase 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 4.2).

5.3 Preclinical safety data

Amlodipine/Valsartan
Adverse reactions observed in animal studies with possible clinical relevance were as follows: Histopathological signs of inflammation of the glandular stomach was seen in male rats at an exposure of about 1.9 (valsartan) and 2.6 (amlodipine) times the clinical doses of 160 mg valsartan and 10 mg amlodipine. At higher exposures, there were ulceration and erosion of the stomach mucosa in both females and males. Similar changes were also seen in the valsartan alone group (exposure 8.5–11.0 times the clinical dose of 160 mg valsartan).
An increased incidence and severity of renal tubular basophilia/hyalinisation, dilation and casts, as well as interstitial lymphocyte inflammation and arteriolar medial hypertrophy were found at an exposure of 8–13 (valsartan) and 7–8 (amlodipine) times the clinical doses of 160 mg valsartan and 10 mg amlodipine. Similar changes were found in the valsartan alone group (exposure 8.5–11.0 times the clinical dose of 160 mg valsartan).

In an embryo-foetal development study in the rat, increased incidences of dilated ureters, malformed sternebrae, and unossified forepaw phalanges were noticed at exposures of about 12 (valsartan) and 10 (amlodipine) times the clinical doses of 160 mg valsartan and 10 mg amlodipine. Dilated ureters were also found in the valsartan alone group (exposure 12 times the clinical dose of 160 mg valsartan). There were only modest signs of maternal toxicity (moderate reduction of body weight) in this study. The no-observed-effect-level for developmental effects was observed at 3- (valsartan) and 4- (amlodipine) fold the clinical exposure (based on AUC).

For the single compounds there was no evidence of mutagenicity, clastogenicity or carcinogenicity.

Amlodipine
Reproductive toxicology
Reproductive studies in rats and mice have shown delayed date of delivery, prolonged duration of labour and decreased pup survival at dosages approximately 50 times greater than the maximum recommended dosage for humans based on mg/kg.

Impairment of fertility
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). In another rat study in which male rats were treated with amlodipine besilate for 30 days at a dose comparable with the human dose based on mg/kg, decreased plasma follicle-stimulating hormone and testosterone were found as well as decreases in sperm density and in the number of mature spermatids and Sertoli cells.

Carcinogenesis, mutagenesis
Rats and mice treated with amlodipine in the diet for two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 mg/kg/day showed no evidence of carcinogenicity. The highest dose (for mice, similar to, and for rats twice* the maximum recommended clinical dose of 10 mg on a mg/m² basis) was close to the maximum tolerated dose for mice but not for rats.

Mutagenicity studies revealed no drug related effects at either the gene or chromosome levels.

* Based on patient weight of 50 kg

Valsartan
Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential.

In rats, maternally toxic doses (600 mg/kg/day) during the last days of gestation and lactation led to lower survival, lower weight gain and delayed development (pinna detachment and ear-canal opening) in the offspring (see section 4.6). These doses in rats (600 mg/kg/day) are approximately 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 non-clinical safety studies, high doses of valsartan (200 to 600 mg/kg body weight) caused in rats a reduction of red blood cell parameters (erythrocytes, haemoglobin, haematocrit) and evidence of changes in renal haemodynamics (slightly raised plasma urea, 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 similar doses, the changes were similar though more severe, particularly in the kidney where the changes developed to a nephropathy which included raised urea 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Cellulose microcrystalline
Crospovidone Type A
Silica, colloidal anhydrous
Magnesium stearate

Coating:
Hypermellose
Titanium dioxide (E171)
Iron oxide, yellow (E172)
Macrogol 4000
Talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 30°C.

Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

PVC/PVDC blisters. One blister contains 7, 10 or 14 film-coated tablets.
Pack sizes: 7, 14, 28, 30, 56, 90, 98 or 280 film-coated tablets and multipacks containing 280 (4x70 or 20x14) film-coated tablets.

PVC/PVDC perforated unit dose blisters. One blister contains 7, 10 or 14 film-coated tablets.
Pack sizes: 56, 98 or 280 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.
7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/370/001
EU/1/06/370/002
EU/1/06/370/003
EU/1/06/370/004
EU/1/06/370/005
EU/1/06/370/006
EU/1/06/370/007
EU/1/06/370/008
EU/1/06/370/025
EU/1/06/370/026
EU/1/06/370/027
EU/1/06/370/034
EU/1/06/370/037

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17.01.2007
Date of latest renewal: 17.01.2012

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu
1. NAME OF THE MEDICINAL PRODUCT

Exforge 5 mg/160 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 5 mg of amlodipine (as amlodipine besylate) and 160 mg of valsartan.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

Dark yellow, oval film-coated tablet, imprinted with “NVR” on one side and “ECE” on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of essential hypertension.

Exforge is indicated in adults whose blood pressure is not adequately controlled on amlodipine or valsartan monotherapy.

4.2 Posology and method of administration

Posology
The recommended dose of Exforge is one tablet per day.

Exforge 5 mg/160 mg may be administered in patients whose blood pressure is not adequately controlled with amlodipine 5 mg or valsartan 160 mg alone.

Exforge can be used with or without food.

Individual dose titration with the components (i.e. amlodipine and valsartan) is recommended before changing to the fixed dose combination. When clinically appropriate, direct change from monotherapy to the fixed-dose combination may be considered.

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

Renal impairment
Exforge is contraindicated in patients with severe renal impairment (see section 4.3).

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
Exforge is contraindicated in patients with severe hepatic impairment (see section 4.3).

Caution should be exercised when administering Exforge to patients with hepatic impairment or biliary obstructive disorders (see section 4.4). In patients with mild to moderate hepatic impairment without cholestasis, the maximum recommended dose is 80 mg valsartan.

Elderly (age 65 years or over)
In elderly patients, caution is required when increasing the dosage.

Paediatric population
The safety and efficacy of Exforge in children aged below 18 years have not been established. No data are available.

Method of administration
Oral use.
It is recommended to take Exforge with some water.

4.3 Contraindications

- Hypersensitivity to the active substances, to dihydropyridine derivatives, or to any of the excipients listed in section 6.1.
- Severe hepatic impairment, biliary cirrhosis or cholestasis.
- Severe renal impairment (glomerular filtration rate (GFR) <30 ml/min/1.73 m²) and patients undergoing dialysis.
- Second and third trimesters of pregnancy (see sections 4.4 and 4.6).

4.4 Special warnings and precautions for use

Pregnancy
Angiotensin II Receptor Antagonists (AIIRAs) should not be initiated during pregnancy. Unless continued AIIRA therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with AIIRAs should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

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 intravenous infusion of normal saline. Treatment can be continued once blood pressure has been stabilised.

Hyperkalaemia
Concomitant use with potassium supplements, potassium-sparing diuretics, salt substitutes containing potassium, or other medicinal products that may increase potassium levels (heparin, etc.) should be undertaken with caution and with frequent monitoring of potassium levels.
Renal artery stenosis
No data are available on the use of Exforge in patients with bilateral renal artery stenosis or stenosis to a solitary kidney.

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 metabolised by the liver. Particular caution should be exercised when administering Exforge to patients with mild to moderate hepatic impairment or biliary obstructive disorders.

In patients with mild to moderate hepatic impairment without cholestasis, the maximum recommended dose is 80 mg valsartan.

Renal impairment
No dosage adjustment of Exforge is required for patients with mild to moderate renal impairment (GFR >30 ml/min/1.73 m$^2$). Monitoring of potassium levels and creatinine is advised in moderate renal impairment.

Primary hyperaldosteronism
Patients with primary hyperaldosteronism should not be treated with the angiotensin II antagonist valsartan as their renin-angiotensin system is affected by the primary disease.

Heart failure
As a consequence of the inhibition of the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotaemia and (rarely) with acute renal failure and/or death. Similar outcomes have been reported with valsartan.

In a long-term, placebo-controlled study (PRAISE-2) of amlodipine in patients with NYHA (New York Heart Association Classification) III and IV heart failure of non-ischaemic 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.

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.

Exforge has not been studied in any patient population other than hypertension.
4.5 Interaction with other medicinal products and other forms of interaction

**Interactions common to the combination**

No drug-drug interaction studies have been performed with Exforge and other medicinal products.

**To be taken into account with concomitant use**

**Other antihypertensive agents**

Commonly used antihypertensive agents (e.g. alpha blockers, diuretics) and other medicinal products which may cause hypotensive adverse effects (e.g. tricyclic antidepressants, alpha blockers for treatment of benign prostate hyperplasia) may increase the antihypertensive effect of the combination.

**Interactions linked to amlodipine**

**Caution required with concomitant use**

**CYP3A4 inhibitors**

A study in elderly patients has shown that diltiazem inhibits the metabolism of amlodipine, probably via CYP3A4 (plasma concentration increases by approximately 50% and the effect of amlodipine is increased). The possibility that more potent inhibitors of CYP3A4 (i.e. ketoconazole, itraconazole, ritonavir) may increase the plasma concentration of amlodipine to a greater extent than diltiazem cannot be excluded.

**CYP3A4 inducers (anticonvulsant agents [e.g. carbamazepine, phenobarbital, phenytoin, fosphenytoin, primidone], rifampicin, Hypericum perforatum)**

Co-administration may lead to reduced plasma concentrations of amlodipine. Clinical monitoring is indicated, with possible dosage adjustment of amlodipine during the treatment with the inducer and after its withdrawal.

**To be taken into account with concomitant use**

**Others**

In monotherapy, amlodipine has been safely administered with thiazide diuretics, beta blockers, ACE inhibitors, long-acting nitrates, sublingual nitroglycerin, digoxin, warfarin, atorvastatin, sildenafil, anti-acid medicines (aluminium hydroxide gel, magnesium hydroxide, simeticone), cimetidine, non-steroidal anti-inflammatory medicines, antibiotics and oral hypoglycaemic medicines.

**Interactions linked to valsartan**

**Concomitant use not recommended**

**Lithium**

Reversible increases in serum lithium concentrations and toxicity have been reported during concurrent use of ACE inhibitors. Despite the lack of experience with concomitant use of valsartan and lithium, this combination is not recommended. If the combination proves necessary, careful monitoring of serum lithium levels is recommended (see section 4.4).

**Potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium and other substances that may increase potassium levels**

If a medicinal product that affects potassium levels is to be prescribed in combination with valsartan, monitoring of potassium plasma levels is advised.

**Caution required with concomitant use**

**Non-steroidal anti-inflammatory medicines (NSAIDs), including selective COX-2 inhibitors, acetylsalicylic acid (>3 g/day), and non-selective NSAIDs**

When angiotensin II antagonists are administered simultaneously with NSAIDs attenuation of the antihypertensive effect may occur. Furthermore, concomitant use of angiotensin II antagonists and NSAIDs may lead to an increased risk of worsening of renal function and an increase in serum potassium. Therefore, monitoring of renal function at the beginning of the treatment is recommended, as well as adequate hydration of the patient.
In monotherapy with valsartan, no interactions of clinical significance have been found with the following substances: cimetidine, warfarin, furosemide, digoxin, atenolol, indometacin, hydrochlorothiazide, amlodipine, glibenclamide.

4.6 Fertility, pregnancy and lactation

**Pregnancy**

**Amlodipine**
The safety of amlodipine in human pregnancy has not been established. In animal studies, reproductive toxicity was observed at high doses (see section 5.3). Use in pregnancy is only recommended when there is no safer alternative and when the disease itself carries greater risk for the mother and foetus.

**Valsartan**
The use of Angiotensin II Receptor Antagonists (AIIRAs) is not recommended during the first trimester of pregnancy (see section 4.4). The use of AIIRAs is contraindicated during the second and third trimesters of pregnancy (see sections 4.3 and 4.4).

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Whilst there is no controlled epidemiological data on the risk with Angiotensin II Receptor Antagonists (AIIRAs), similar risks may exist for this class of drugs. Unless continued AIIRA therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with AIIRAs should be stopped immediately, and, if appropriate, alternative therapy should be started.

Exposure to AIIRA therapy during the second and third trimesters is known to induce human foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (see section 5.3).

Should exposure to AIIRAs have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.

Infants whose mothers have taken AIIRAs should be closely observed for hypotension (see sections 4.3 and 4.4).

**Breast-feeding**
No information is available regarding the use of Exforge during breast-feeding, therefore Exforge is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

**Fertility**
There are no clinical studies on fertility with Exforge.

**Valsartan**
Valsartan had no adverse effects on the reproductive performance of male or female rats at oral doses up to 200 mg/kg/day. This dose is 6 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).

**Amlodipine**
Reversible biochemical changes in the head of spermatozoa have been reported in some patients treated by calcium channel blockers. Clinical data are insufficient regarding the potential effect of amlodipine on fertility. In one rat study, adverse effects were found on male fertility (see section 5.3).
4.7 Effects on ability to drive and use machines

When driving vehicles or using machines it should be taken into account that occasionally dizziness or weariness may occur.

4.8 Undesirable effects

Summary of the safety profile
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. The following adverse reactions were found to be the most frequently occurring or the most significant or severe: nasopharyngitis, influenza, hypersensitivity, headache, syncope, orthostatic hypotension, oedema, pitting oedema, facial oedema, oedema peripheral, fatigue, flushing, asthenia and hot flush.
Tabulated list of adverse reactions
Adverse reactions have been ranked under headings of frequency using the following convention:
very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

**Infections and infestations**
- Common: Nasopharyngitis, influenza

**Immune system disorders**
- Rare: Hypersensitivity

**Psychiatric disorders**
- Rare: Anxiety

**Nervous system disorders**
- Common: Headache
- Uncommon: Dizziness, somnolence, dizziness postural, paraesthesia

**Eye disorders**
- Rare: Visual disturbance

**Ear and labyrinth disorders**
- Uncommon: Vertigo
- 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

**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: Pollakisuria, polyuria

**Reproductive system and breast disorders**
- Rare: Erectile dysfunction

**General disorders and administration site conditions**
- Common: Oedema, pitting oedema, facial oedema, oedema peripheral, fatigue, flushing, asthenia, hot flush
Additional information on the combination
Peripheral oedema, a recognised side effect of amlodipine, was generally observed at a lower incidence in patients who received the amlodipine/valsartan combination than in those who received amlodipine alone. In double-blind, controlled clinical trials, the incidence of peripheral oedema by dose was as follows:

<table>
<thead>
<tr>
<th>% of patients who experienced peripheral oedema</th>
<th>Valsartan (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Amlodipine (mg)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>3.0</td>
</tr>
<tr>
<td>2.5</td>
<td>8.0</td>
</tr>
<tr>
<td>5</td>
<td>3.1</td>
</tr>
<tr>
<td>10</td>
<td>10.3</td>
</tr>
</tbody>
</table>

The mean incidence of peripheral oedema evenly weighted across all doses was 5.1% with the amlodipine/valsartan combination.

Additional information on the individual components
Adverse reactions previously reported with one of the individual components (amlodipine or valsartan) may be potential adverse reactions with Exforge as well, even if not observed in clinical trials or during the post-marketing period.

**Amlodipine**

*Common*  Vomiting.

*Uncommon*  Alopecia, altered bowel habits, dyspepsia, dyspnoea, rhinitis, gastritis, gingival hyperplasia, gynaecomastia, hyperglycaemia, impotence, increased urinary frequency, leucopenia, malaise, mood changes, myalgia, peripheral neuropathy, pancreatitis, hepatitis, thrombocytopenia, vasculitis, angioedema and erythema multiforme.

*Rare*  Arrhythmia, myocardial infarction. 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. These adverse events may not be distinguishable from the natural history of the underlying disease.

*Very rare*  Cholestatic jaundice, AST and ALT increase, purpura, rash and pruritus. Exceptional cases of extrapyramidal syndrome have been reported.

**Valsartan**

*Not known*  Decrease in haemoglobin, decrease in haematocrit, neutropenia, thrombocytopenia, increase of serum potassium, elevation of liver function values including increase of serum bilirubin, renal failure and impairment, elevation of serum creatinine, angioedema, myalgia, vasculitis, hypersensitivity including serum sickness.
4.9 Overdose

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

Treatment
If 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: Agents acting on the renin-angiotensin system; angiotensin II antagonists, combinations; angiotensin II antagonists and calcium channel blockers, ATC code: C09DB01

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 antagonist class of medicines. The combination of these substances has an additive antihypertensive effect, reducing blood pressure to a greater degree than either component alone.

Amlodipine/Valsartan
The combination of amlodipine and valsartan produces dose-related additive reduction in blood pressure across its therapeutic dose range. The antihypertensive effect of a single dose of the combination persisted for 24 hours.

Placebo-controlled trials
Over 1,400 hypertensive patients received Exforge once daily in two placebo-controlled trials. Adults with mild to moderate uncomplicated essential hypertension (mean sitting diastolic blood pressure ≥95 and <110 mmHg) were enrolled. Patients with high cardiovascular risks – heart failure, type I and poorly controlled type II diabetes and history of myocardial infarction or stroke within one year – were excluded.

Active-controlled trials in patients who were non-responders to monotherapy
A multicentre, randomised, double-blind, active-controlled, parallel-group trial showed normalisation of blood pressure (trough sitting diastolic blood pressure <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 (through sitting diastolic blood pressure <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 mean sitting 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. Abrupt withdrawal of Exforge has not been associated with a rapid increase in blood pressure.

Age, gender, race or body mass index (≥30 kg/m², <30 kg/m²) did not influence the response to Exforge.

Exforge has not been studied in any patient population other than hypertension. Valsartan has been studied in patients with post myocardial infarction and heart failure. Amlodipine has been studied in patients with chronic stable angina, vasospastic angina and angiographically documented coronary artery disease.

**Amlodipine**

The amlodipine component of Exforge 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 relaxant effect on vascular smooth muscle, causing reductions in peripheral vascular resistance and in blood pressure. Experimental data suggest that 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.

Following administration of therapeutic doses to patients with hypertension, amlodipine produces vasodilation, 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 receptor subtype AT\textsubscript{1}, which is responsible for the known actions of angiotensin II. The increased plasma levels of angiotensin II following AT\textsubscript{1} receptor blockade with valsartan may stimulate the unblocked receptor subtype AT\textsubscript{2}, which appears to counterbalance the effect of the AT\textsubscript{1} receptor. Valsartan does not exhibit any partial agonist activity at the AT\textsubscript{1} receptor and has much (about 20,000-fold) greater affinity for the AT\textsubscript{1} receptor than for the AT\textsubscript{2} 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 coughing. 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 coughing, 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 a drop in 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 drop in 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.

5.2 Pharmacokinetic properties

Linearity
Amlodipine and valsartan exhibit linear pharmacokinetics.

Amlodipine/Valsartan
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.

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.

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%. Valsartan shows multiexponential decay kinetics ($t_{1/2\alpha}$<1 h and $t_{1/2\beta}$ about 9 h). Food decreases exposure (as measured by AUC) to valsartan by about 40% and peak plasma concentration ($C_{\text{max}}$) by about 50%, although from about 8 h post dosing plasma valsartan concentrations are similar for the fed and fasted groups. This reduction in AUC is not, however, 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.

**Elimination:** Valsartan is primarily eliminated 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.

**Special populations**

**Paediatric population (age below 18 years)**
No pharmacokinetic data are available in the paediatric population.

**Elderly (age 65 years or over)**
Time to peak plasma amlodipine concentrations is similar in young and elderly patients. In elderly patients, amlodipine clearance tends to decline, causing increases in the area under the curve (AUC) and elimination half-life. Mean systemic AUC of valsartan is higher by 70% in the elderly than in the young, therefore caution is required when increasing the dosage.

**Renal impairment**
The pharmacokinetics of amlodipine are not significantly influenced by renal impairment. As expected for a compound where renal clearance accounts for only 30% of total plasma clearance, no correlation was seen between renal function and systemic exposure to valsartan.

**Hepatic impairment**
Patients with hepatic insufficiency have decreased clearance of amlodipine with resulting increase 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 4.2).

5.3 Preclinical safety data

**Amlodipine/Valsartan**
Adverse reactions observed in animal studies with possible clinical relevance were as follows: Histopathological signs of inflammation of the glandular stomach was seen in male rats at an exposure of about 1.9 (valsartan) and 2.6 (amlodipine) times the clinical doses of 160 mg valsartan and 10 mg amlodipine. At higher exposures, there were ulceration and erosion of the stomach mucosa in both females and males. Similar changes were also seen in the valsartan alone group (exposure 8.5–11.0 times the clinical dose of 160 mg valsartan).
An increased incidence and severity of renal tubular basophilia/hyalinisation, dilation and casts, as well as interstitial lymphocyte inflammation and arteriolar medial hypertrophy were found at an exposure of 8–13 (valsartan) and 7–8 (amlodipine) times the clinical doses of 160 mg valsartan and 10 mg amlodipine. Similar changes were found in the valsartan alone group (exposure 8.5–11.0 times the clinical dose of 160 mg valsartan).

In an embryo-foetal development study in the rat, increased incidences of dilated ureters, malformed sternebrae, and unossified forepaw phalanges were noticed at exposures of about 12 (valsartan) and 10 (amlodipine) times the clinical doses of 160 mg valsartan and 10 mg amlodipine. Dilated ureters were also found in the valsartan alone group (exposure 12 times the clinical dose of 160 mg valsartan). There were only modest signs of maternal toxicity (moderate reduction of body weight) in this study. The no-observed-effect-level for developmental effects was observed at 3- (valsartan) and 4- (amlodipine) fold the clinical exposure (based on AUC).

For the single compounds there was no evidence of mutagenicity, clastogenicity or carcinogenicity.

Amlodipine
Reproductive toxicology
Reproductive studies in rats and mice have shown delayed date of delivery, prolonged duration of labour and decreased pup survival at dosages approximately 50 times greater than the maximum recommended dosage for humans based on mg/kg.

Impairment of fertility
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). In another rat study in which male rats were treated with amlodipine besilate for 30 days at a dose comparable with the human dose based on mg/kg, decreased plasma follicle-stimulating hormone and testosterone were found as well as decreases in sperm density and in the number of mature spermatids and Sertoli cells.

Carcinogenesis, mutagenesis
Rats and mice treated with amlodipine in the diet for two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 mg/kg/day showed no evidence of carcinogenicity. The highest dose (for mice, similar to, and for rats twice* the maximum recommended clinical dose of 10 mg on a mg/m² basis) was close to the maximum tolerated dose for mice but not for rats.

Mutagenicity studies revealed no drug related effects at either the gene or chromosome levels.

* Based on patient weight of 50 kg

Valsartan
Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential.

In rats, maternally toxic doses (600 mg/kg/day) during the last days of gestation and lactation led to lower survival, lower weight gain and delayed development (pinna detachment and ear-canal opening) in the offspring (see section 4.6). These doses in rats (600 mg/kg/day) are approximately 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 non-clinical safety studies, high doses of valsartan (200 to 600 mg/kg body weight) caused in rats a reduction of red blood cell parameters (erythrocytes, haemoglobin, haematocrit) and evidence of changes in renal haemodynamics (slightly raised plasma urea, 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 similar doses, the changes were similar though more severe, particularly in the kidney where the changes developed to a nephropathy which included raised urea 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
- Cellulose microcrystalline
- Crospovidone Type A
- Silica, colloidal anhydrous
- Magnesium stearate

Coating:
- Hypromellose
- Titanium dioxide (E171)
- Iron oxide, yellow (E172)
- Macrogol 4000
- Talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 30°C.

Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

PVC/PVDC blisters. One blister contains 7, 10 or 14 film-coated tablets.
Pack sizes: 7, 14, 28, 30, 56, 90, 98 or 280 film-coated tablets and multipacks containing 280 (4x70 or 20x14) film-coated tablets.

PVC/PVDC perforated unit dose blisters. One blister contains 7, 10 or 14 film-coated tablets.
Pack sizes: 56, 98 or 280 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.
7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/370/009
EU/1/06/370/010
EU/1/06/370/011
EU/1/06/370/012
EU/1/06/370/013
EU/1/06/370/014
EU/1/06/370/015
EU/1/06/370/016
EU/1/06/370/028
EU/1/06/370/029
EU/1/06/370/030
EU/1/06/370/035
EU/1/06/370/038

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17.01.2007
Date of latest renewal: 17.01.2012

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu
1. NAME OF THE MEDICINAL PRODUCT

Exforge 10 mg/160 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 10 mg of amlodipine (as amlodipine besylate) and 160 mg of valsartan.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

Light yellow, oval film-coated tablet, imprinted with “NVR” on one side and “UIC” on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of essential hypertension.

Exforge is indicated in adults whose blood pressure is not adequately controlled on amlodipine or valsartan monotherapy.

4.2 Posology and method of administration

Posology
The recommended dose of Exforge is one tablet per day.

Exforge 10 mg/160 mg may be administered in patients whose blood pressure is not adequately controlled with amlodipine 10 mg or valsartan 160 mg alone or with Exforge 5 mg/160 mg.

Exforge can be used with or without food.

Individual dose titration with the components (i.e. amlodipine and valsartan) is recommended before changing to the fixed dose combination. When clinically appropriate, direct change from monotherapy to the fixed-dose combination may be considered.

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

Renal impairment
Exforge is contraindicated in patients with severe renal impairment (see section 4.3).

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**
Exforge is contraindicated in patients with severe hepatic impairment (see section 4.3).

Caution should be exercised when administering Exforge to patients with hepatic impairment or biliary obstructive disorders (see section 4.4). In patients with mild to moderate hepatic impairment without cholestasis, the maximum recommended dose is 80 mg valsartan.

**Elderly (age 65 years or over)**
In elderly patients, caution is required when increasing the dosage.

**Paediatric population**
The safety and efficacy of Exforge in children aged below 18 years have not been established. No data are available.

**Method of administration**
Oral use.
It is recommended to take Exforge with some water.

### 4.3 Contraindications

- Hypersensitivity to the active substances, to dihydropyridine derivatives, or to any of the excipients listed in section 6.1.
- Severe hepatic impairment, biliary cirrhosis or cholestasis.
- Severe renal impairment (glomerular filtration rate (GFR) <30 ml/min/1.73 m²) and patients undergoing dialysis.
- Second and third trimesters of pregnancy (see sections 4.4 and 4.6).

### 4.4 Special warnings and precautions for use

**Pregnancy**
Angiotensin II Receptor Antagonists (AIIRAs) should not be initiated during pregnancy. Unless continued AIIRA therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with AIIRAs should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

**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 intravenous infusion of normal saline. Treatment can be continued once blood pressure has been stabilised.

**Hyperkalaemia**
Concomitant use with potassium supplements, potassium-sparing diuretics, salt substitutes containing potassium, or other medicinal products that may increase potassium levels (heparin, etc.) should be undertaken with caution and with frequent monitoring of potassium levels.
Renal artery stenosis
No data are available on the use of Exforge in patients with bilateral renal artery stenosis or stenosis to a solitary kidney.

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 metabolised by the liver. Particular caution should be exercised when administering Exforge to patients with mild to moderate hepatic impairment or biliary obstructive disorders.

In patients with mild to moderate hepatic impairment without cholestasis, the maximum recommended dose is 80 mg valsartan.

Renal impairment
No dosage adjustment of Exforge is required for patients with mild to moderate renal impairment (GFR >30 ml/min/1.73 m²). Monitoring of potassium levels and creatinine is advised in moderate renal impairment.

Primary hyperaldosteronism
Patients with primary hyperaldosteronism should not be treated with the angiotensin II antagonist valsartan as their renin-angiotensin system is affected by the primary disease.

Heart failure
As a consequence of the inhibition of the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotaemia and (rarely) with acute renal failure and/or death. Similar outcomes have been reported with valsartan.

In a long-term, placebo-controlled study (PRAISE-2) of amlodipine in patients with NYHA (New York Heart Association Classification) III and IV heart failure of non-ischaemic 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.

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.

Exforge has not been studied in any patient population other than hypertension.
4.5 Interaction with other medicinal products and other forms of interaction

Interactions common to the combination
No drug-drug interaction studies have been performed with Exforge and other medicinal products.

To be taken into account with concomitant use
Other antihypertensive agents
Commonly used antihypertensive agents (e.g. alpha blockers, diuretics) and other medicinal products which may cause hypotensive adverse effects (e.g. tricyclic antidepressants, alpha blockers for treatment of benign prostate hyperplasia) may increase the antihypertensive effect of the combination.

Interactions linked to amlodipine
Caution required with concomitant use
CYP3A4 inhibitors
A study in elderly patients has shown that diltiazem inhibits the metabolism of amlodipine, probably via CYP3A4 (plasma concentration increases by approximately 50% and the effect of amlodipine is increased). The possibility that more potent inhibitors of CYP3A4 (i.e. ketoconazole, itraconazole, ritonavir) may increase the plasma concentration of amlodipine to a greater extent than diltiazem cannot be excluded.

CYP3A4 inducers (anticonvulsant agents [e.g. carbamazepine, phenobarbital, phenytoin, fosphenytoin, primidone], rifampicin, Hypericum perforatum)
Co-administration may lead to reduced plasma concentrations of amlodipine. Clinical monitoring is indicated, with possible dosage adjustment of amlodipine during the treatment with the inducer and after its withdrawal.

To be taken into account with concomitant use
Others
In monotherapy, amlodipine has been safely administered with thiazide diuretics, beta blockers, ACE inhibitors, long-acting nitrates, sublingual nitroglycerin, digoxin, warfarin, atorvastatin, sildenafil, anti-acid medicines (aluminium hydroxide gel, magnesium hydroxide, simeticone), cimetidine, non-steroidal anti-inflammatory medicines, antibiotics and oral hypoglycaemic medicines.

Interactions linked to valsartan
Concomitant use not recommended
Lithium
Reversible increases in serum lithium concentrations and toxicity have been reported during concurrent use of ACE inhibitors. Despite the lack of experience with concomitant use of valsartan and lithium, this combination is not recommended. If the combination proves necessary, careful monitoring of serum lithium levels is recommended (see section 4.4).

Potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium and other substances that may increase potassium levels
If a medicinal product that affects potassium levels is to be prescribed in combination with valsartan, monitoring of potassium plasma levels is advised.

Caution required with concomitant use
Non-steroidal anti-inflammatory medicines (NSAIDs), including selective COX-2 inhibitors, acetylsalicylic acid (>3 g/day), and non-selective NSAIDs
When angiotensin II antagonists are administered simultaneously with NSAIDs attenuation of the antihypertensive effect may occur. Furthermore, concomitant use of angiotensin II antagonists and NSAIDs may lead to an increased risk of worsening of renal function and an increase in serum potassium. Therefore, monitoring of renal function at the beginning of the treatment is recommended, as well as adequate hydration of the patient.
**Others**
In monotherapy with valsartan, no interactions of clinical significance have been found with the following substances: cimetidine, warfarin, furosemide, digoxin, atenolol, indometacin, hydrochlorothiazide, amlodipine, glibenclamide.

**4.6 Fertility, pregnancy and lactation**

**Pregnancy**

**Amlodipine**
The safety of amlodipine in human pregnancy has not been established. In animal studies, reproductive toxicity was observed at high doses (see section 5.3). Use in pregnancy is only recommended when there is no safer alternative and when the disease itself carries greater risk for the mother and foetus.

**Valsartan**
The use of Angiotensin II Receptor Antagonists (AIIRAs) is not recommended during the first trimester of pregnancy (see section 4.4). The use of AIIRAs is contraindicated during the second and third trimesters of pregnancy (see sections 4.3 and 4.4).

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Whilst there is no controlled epidemiological data on the risk with Angiotensin II Receptor Antagonists (AIIRAs), similar risks may exist for this class of drugs. Unless continued AIIRA therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with AIIRAs should be stopped immediately, and, if appropriate, alternative therapy should be started.

Exposure to AIIRA therapy during the second and third trimesters is known to induce human foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (see section 5.3).

Should exposure to AIIRAs have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.

Infants whose mothers have taken AIIRAs should be closely observed for hypotension (see sections 4.3 and 4.4).

**Breast-feeding**
No information is available regarding the use of Exforge during breast-feeding, therefore Exforge is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

**Fertility**
There are no clinical studies on fertility with Exforge.

**Valsartan**
Valsartan had no adverse effects on the reproductive performance of male or female rats at oral doses up to 200 mg/kg/day. This dose is 6 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).

**Amlodipine**
Reversible biochemical changes in the head of spermatozoa have been reported in some patients treated by calcium channel blockers. Clinical data are insufficient regarding the potential effect of amlodipine on fertility. In one rat study, adverse effects were found on male fertility (see section 5.3).
4.7 Effects on ability to drive and use machines

When driving vehicles or using machines it should be taken into account that occasionally dizziness or weariness may occur.

4.8 Undesirable effects

Summary of the safety profile
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. The following adverse reactions were found to be the most frequently occurring or the most significant or severe: nasopharyngitis, influenza, hypersensitivity, headache, syncope, orthostatic hypotension, oedema, pitting oedema, facial oedema, oedema peripheral, fatigue, flushing, asthenia and hot flush.
Tabulated list of adverse reactions
Adverse reactions have been ranked under headings of frequency using the following convention:
very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

**Infections and infestations**
- Common: Nasopharyngitis, influenza

**Immune system disorders**
- Rare: Hypersensitivity

**Psychiatric disorders**
- Rare: Anxiety

**Nervous system disorders**
- Common: Headache
- Uncommon: Dizziness, somnolence, dizziness postural, paraesthesia

**Eye disorders**
- Rare: Visual disturbance

**Ear and labyrinth disorders**
- Uncommon: Vertigo
- 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

**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: Pollakisuria, polyuria

**Reproductive system and breast disorders**
- Rare: Erectile dysfunction

**General disorders and administration site conditions**
- Common: Oedema, pitting oedema, facial oedema, oedema peripheral, fatigue, flushing, asthenia, hot flush
Additional information on the combination
Peripheral oedema, a recognised side effect of amlodipine, was generally observed at a lower incidence in patients who received the amlodipine/valsartan combination than in those who received amlodipine alone. In double-blind, controlled clinical trials, the incidence of peripheral oedema by dose was as follows:

<table>
<thead>
<tr>
<th>% of patients who experienced peripheral oedema</th>
<th>Valsartan (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Amlodipine (mg)</td>
<td></td>
</tr>
<tr>
<td>0.0</td>
<td>3.0</td>
</tr>
<tr>
<td>2.5</td>
<td>8.0</td>
</tr>
<tr>
<td>5.0</td>
<td>3.1</td>
</tr>
<tr>
<td>10.0</td>
<td>10.3</td>
</tr>
</tbody>
</table>

The mean incidence of peripheral oedema evenly weighted across all doses was 5.1% with the amlodipine/valsartan combination.

Additional information on the individual components
Adverse reactions previously reported with one of the individual components (amlodipine or valsartan) may be potential adverse reactions with Exforge as well, even if not observed in clinical trials or during the post-marketing period.

**Amlodipine**
- **Common**
  - Vomiting.
- **Uncommon**
  - Alopecia, altered bowel habits, dyspepsia, dyspnoea, rhinitis, gastritis, gingival hyperplasia, gynaecomastia, hyperglycaemia, impotence, increased urinary frequency, leucopenia, malaise, mood changes, myalgia, peripheral neuropathy, pancreatitis, hepatitis, thrombocytopenia, vasculitis, angioedema and erythema multiforme.
- **Rare**
  - Arrhythmia, myocardial infarction, 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. These adverse events may not be distinguishable from the natural history of the underlying disease.
- **Very rare**
  - Cholestatic jaundice, AST and ALT increase, purpura, rash and pruritus. Exceptional cases of extrapyramidal syndrome have been reported.

**Valsartan**
- **Not known**
  - Decrease in haemoglobin, decrease in haematocrit, neutropenia, thrombocytopenia, increase of serum potassium, elevation of liver function values including increase of serum bilirubin, renal failure and impairment, elevation of serum creatinine, angioedema, myalgia, vasculitis, hypersensitivity including serum sickness.
4.9 Overdose

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

Treatment
If 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: Agents acting on the renin-angiotensin system; angiotensin II antagonists, combinations; angiotensin II antagonists and calcium channel blockers, ATC code: C09DB01

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 antagonist class of medicines. The combination of these substances has an additive antihypertensive effect, reducing blood pressure to a greater degree than either component alone.

Amlodipine/Valsartan
The combination of amlodipine and valsartan produces dose-related additive reduction in blood pressure across its therapeutic dose range. The antihypertensive effect of a single dose of the combination persisted for 24 hours.

Placebo-controlled trials
Over 1,400 hypertensive patients received Exforge once daily in two placebo-controlled trials. Adults with mild to moderate uncomplicated essential hypertension (mean sitting diastolic blood pressure ≥95 and <110 mmHg) were enrolled. Patients with high cardiovascular risks – heart failure, type I and poorly controlled type II diabetes and history of myocardial infarction or stroke within one year – were excluded.

Active-controlled trials in patients who were non-responders to monotherapy
A multicentre, randomised, double-blind, active-controlled, parallel-group trial showed normalisation of blood pressure (trough sitting diastolic blood pressure <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 blood pressure <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 mean sitting 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. Abrupt withdrawal of Exforge has not been associated with a rapid increase in blood pressure.

Age, gender, race or body mass index (≥30 kg/m², <30 kg/m²) did not influence the response to Exforge.

Exforge has not been studied in any patient population other than hypertension. Valsartan has been studied in patients with post myocardial infarction and heart failure. Amlodipine has been studied in patients with chronic stable angina, vasospastic angina and angiographically documented coronary artery disease.

Amlodipine

The amlodipine component of Exforge 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 relaxant effect on vascular smooth muscle, causing reductions in peripheral vascular resistance and in blood pressure. Experimental data suggest that 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.

Following administration of therapeutic doses to patients with hypertension, amlodipine produces vasodilation, 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 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 receptor subtype AT\(_2\), 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.

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 coughing. 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 coughing, 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 a drop in 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 drop in 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.

5.2 Pharmacokinetic properties

Linearity
Amlodipine and valsartan exhibit linear pharmacokinetics.

Amlodipine/Valsartan
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.

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.

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%. Valsartan shows multiexponential decay kinetics ($t_{1/2\alpha} < 1$ h and $t_{1/2\beta}$ about 9 h). Food decreases exposure (as measured by AUC) to valsartan by about 40% and peak plasma concentration ($C_{max}$) by about 50%, although from about 8 h post dosing plasma valsartan concentrations are similar for the fed and fasted groups. This reduction in AUC is not, however, 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.

Elimination: Valsartan is primarily eliminated 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.

Special populations

**Paediatric population (age below 18 years)**
No pharmacokinetic data are available in the paediatric population.

**Elderly (age 65 years or over)**
Time to peak plasma amlodipine concentrations is similar in young and elderly patients. In elderly patients, amlodipine clearance tends to decline, causing increases in the area under the curve (AUC) and elimination half-life. Mean systemic AUC of valsartan is higher by 70% in the elderly than in the young, therefore caution is required when increasing the dosage.

**Renal impairment**
The pharmacokinetics of amlodipine are not significantly influenced by renal impairment. As expected for a compound where renal clearance accounts for only 30% of total plasma clearance, no correlation was seen between renal function and systemic exposure to valsartan.

**Hepatic impairment**
Patients with hepatic insufficiency have decreased clearance of amlodipine with resulting increase 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 4.2).

5.3 Preclinical safety data

**Amlodipine/Valsartan**
Adverse reactions observed in animal studies with possible clinical relevance were as follows: Histopathological signs of inflammation of the glandular stomach was seen in male rats at an exposure of about 1.9 (valsartan) and 2.6 (amlodipine) times the clinical doses of 160 mg valsartan and 10 mg amlodipine. At higher exposures, there were ulceration and erosion of the stomach mucosa in both females and males. Similar changes were also seen in the valsartan alone group (exposure 8.5–11.0 times the clinical dose of 160 mg valsartan).
An increased incidence and severity of renal tubular basophilia/hyalinisation, dilation and casts, as well as interstitial lymphocyte inflammation and arteriolar medial hypertrophy were found at an exposure of 8–13 (valsartan) and 7–8 (amlodipine) times the clinical doses of 160 mg valsartan and 10 mg amlodipine. Similar changes were found in the valsartan alone group (exposure 8.5–11.0 times the clinical dose of 160 mg valsartan).

In an embryo-foetal development study in the rat, increased incidences of dilated ureters, malformed sternebrae, and unossified forepaw phalanges were noticed at exposures of about 12 (valsartan) and 10 (amlodipine) times the clinical doses of 160 mg valsartan and 10 mg amlodipine. Dilated ureters were also found in the valsartan alone group (exposure 12 times the clinical dose of 160 mg valsartan). There were only modest signs of maternal toxicity (moderate reduction of body weight) in this study. The no-observed-effect-level for developmental effects was observed at 3- (valsartan) and 4- (amlodipine) fold the clinical exposure (based on AUC).

For the single compounds there was no evidence of mutagenicity, clastogenicity or carcinogenicity.

**Amlodipine**

**Reproductive toxicology**

Reproductive studies in rats and mice have shown delayed date of delivery, prolonged duration of labour and decreased pup survival at dosages approximately 50 times greater than the maximum recommended dosage for humans based on mg/kg.

**Impairment of fertility**

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). In another rat study in which male rats were treated with amlodipine besilate for 30 days at a dose comparable with the human dose based on kg/kg, decreased plasma follicle-stimulating hormone and testosterone were found as well as decreases in sperm density and in the number of mature spermatids and Sertoli cells.

**Carcinogenesis, mutagenesis**

Rats and mice treated with amlodipine in the diet for two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 mg/kg/day showed no evidence of carcinogenicity. The highest dose (for mice, similar to, and for rats twice* the maximum recommended clinical dose of 10 mg on a mg/m² basis) was close to the maximum tolerated dose for mice but not for rats.

Mutagenicity studies revealed no drug related effects at either the gene or chromosome levels.

* Based on patient weight of 50 kg

**Valsartan**

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential.

In rats, maternally toxic doses (600 mg/kg/day) during the last days of gestation and lactation led to lower survival, lower weight gain and delayed development (pinna detachment and ear-canal opening) in the offspring (see section 4.6). These doses in rats (600 mg/kg/day) are approximately 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 non-clinical safety studies, high doses of valsartan (200 to 600 mg/kg body weight) caused in rats a reduction of red blood cell parameters (erythrocytes, haemoglobin, haematocrit) and evidence of changes in renal haemodynamics (slightly raised plasma urea, 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 similar doses, the changes were similar though more severe, particularly in the kidney where the changes developed to a nephropathy which included raised urea 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Cellulose microcrystalline
Crospovidone Type A
Silica, colloidal anhydrous
Magnesium stearate

Coating:
Hypermellose
Titanium dioxide (E171)
Iron oxide, yellow (E172)
Iron oxide, red (E172)
Macrogol 4000
Talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 30°C.

Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

PVC/PVDC blisters. One blister contains 7, 10 or 14 film-coated tablets.
Pack sizes: 7, 14, 28, 30, 56, 90, 98 or 280 film-coated tablets and multipacks containing 280 (4x70 or 20x14) film-coated tablets.

PVC/PVDC perforated unit dose blisters. One blister contains 7, 10 or 14 film-coated tablets.
Pack sizes: 56, 98 or 280 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.
7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/370/017
EU/1/06/370/018
EU/1/06/370/019
EU/1/06/370/020
EU/1/06/370/021
EU/1/06/370/022
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EU/1/06/370/031
EU/1/06/370/032
EU/1/06/370/033
EU/1/06/370/036
EU/1/06/370/039

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17.01.2007
Date of latest renewal: 17.01.2012

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu
ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION
A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Novartis Pharma GmbH
Roonstraße 25
D-90429 Nuremberg
Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORIZATION

Pharmacovigilance system
The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1. of the Marketing Authorisation, is in place and functioning before and whilst the product is on the market.
ANNEX III

LABELLING AND PACKAGE LEAFLET
A. LABELLING
PARTICULARS TO APPEAR ON THE OUTER PACKAGING
CARTON OF UNIT PACK

1. NAME OF THE MEDICINAL PRODUCT

Exforge 5 mg/80 mg film-coated tablets
amlodipine/valsartan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 5 mg amlodipine (as amlodipine besylate) and 80 mg valsartan.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

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5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

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13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Exforge 5 mg/80 mg
1. **NAME OF THE MEDICINAL PRODUCT**

Exforge 5 mg/80 mg film-coated tablets
amlodipine/valsartan

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**

Each tablet contains 5 mg amlodipine (as amlodipine besylate) and 80 mg valsartan.

3. **LIST OF EXCIPIENTS**

4. **PHARMACEUTICAL FORM AND CONTENTS**

70 film-coated tablets. Component of a multipack, not to be sold separately.
14 film-coated tablets. Component of a multipack, not to be sold separately.

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.
Oral use.

6. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**

8. **EXPIRY DATE**

EXP
9. **SPECIAL STORAGE CONDITIONS**

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

10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

11. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Novartis Europharm Limited
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

12. **MARKETING AUTHORISATION NUMBER(S)**

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13. **BATCH NUMBER**

Lot

14. **GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

15. **INSTRUCTIONS ON USE**

16. **INFORMATION IN BRAILLE**

Exforge 5 mg/80 mg
**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON OF MULTIPACK (WITH BLUE BOX)**

| 1. NAME OF THE MEDICINAL PRODUCT | Exforge 5 mg/80 mg film-coated tablets amlodipine/valsartan |
| 2. STATEMENT OF ACTIVE SUBSTANCE(S) | Each tablet contains 5 mg amlodipine (as amlodipine besylate) and 80 mg valsartan. |
| 3. LIST OF EXCIPIENTS | |
| 4. PHARMACEUTICAL FORM AND CONTENTS | Multipack: 280 (4 packs of 70) film-coated tablets  
Multipack: 280 (20 packs of 14) film-coated tablets |
| 5. METHOD AND ROUTE(S) OF ADMINISTRATION | Read the package leaflet before use.  
Oral use. |
| 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN | Keep out of the sight and reach of children. |
| 7. OTHER SPECIAL WARNING(S), IF NECESSARY | |
| 8. EXPIRY DATE | EXP |
9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/370/034 280 film-coated tablets (4x70)
EU/1/06/370/037 280 film-coated tablets (20x14)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Exforge 5 mg/80 mg
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<th>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS</th>
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| **1. NAME OF THE MEDICINAL PRODUCT**               |
| Exforge 5 mg/80 mg film-coated tablets             |
| amlodipine/valsartan                               |

| **2. NAME OF THE MARKETING AUTHORISATION HOLDER** |
| Novartis Europharm Limited                        |

| **3. EXPIRY DATE**                                 |
| EXP                                               |

| **4. BATCH NUMBER**                                |
| Lot                                               |

| **5. OTHER**                                       |
PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON OF UNIT PACK

1. NAME OF THE MEDICINAL PRODUCT

Exforge 5 mg/160 mg film-coated tablets
amlodipine/valsartan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 5 mg amlodipine (as amlodipine besylate) and 160 mg valsartan.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

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5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

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13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Exforge 5 mg/160 mg
**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**INTERMEDIATE CARTON OF MULTIPACK (WITHOUT BLUE BOX)**

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<tr>
<td>Exforge 5 mg/160 mg film-coated tablets</td>
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<td>amlodipine/valsartan</td>
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<table>
<thead>
<tr>
<th>2. STATEMENT OF ACTIVE SUBSTANCE(S)</th>
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<tr>
<td>Each tablet contains 5 mg amlodipine (as amlodipine besylate) and 160 mg valsartan.</td>
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<tr>
<th>3. LIST OF EXCIPIENTS</th>
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<tr>
<th>4. PHARMACEUTICAL FORM AND CONTENTS</th>
</tr>
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<tbody>
<tr>
<td>70 film-coated tablets. Component of a multipack, not to be sold separately.</td>
</tr>
<tr>
<td>14 film-coated tablets. Component of a multipack, not to be sold separately.</td>
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<tr>
<th>5. METHOD AND ROUTE(S) OF ADMINISTRATION</th>
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<tbody>
<tr>
<td>Read the package leaflet before use.</td>
</tr>
<tr>
<td>Oral use.</td>
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<tr>
<th>6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN</th>
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<tr>
<td>Keep out of the sight and reach of children.</td>
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<tr>
<th>7. OTHER SPECIAL WARNING(S), IF NECESSARY</th>
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<tr>
<th>8. EXPIRY DATE</th>
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<tbody>
<tr>
<td>EXP</td>
</tr>
</tbody>
</table>
9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Wimplehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/370/035 280 film-coated tablets (4x70)
EU/1/06/370/038 280 film-coated tablets (20x14)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Exforge 5 mg/160 mg
PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF MULTIPACK (WITH BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Exforge 5 mg/160 mg film-coated tablets
amlodipine/valsartan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 5 mg amlodipine (as amlodipine besylate) and 160 mg valsartan.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Multipack: 280 (4 packs of 70) film-coated tablets
Multipack: 280 (20 packs of 14) film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/370/035 280 film-coated tablets (4x70)
EU/1/06/370/038 280 film-coated tablets (20x14)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Exforge 5 mg/160 mg
<table>
<thead>
<tr>
<th>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS</th>
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</thead>
<tbody>
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**1. NAME OF THE MEDICINAL PRODUCT**

Exforge 5 mg/160 mg film-coated tablets
amlodipine/valsartan

**2. NAME OF THE MARKETING AUTHORISATION HOLDER**

Novartis Europharm Limited

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. OTHER**
PARTICULARS TO APPEAR ON THE OUTER PACKAGING
CARTON OF UNIT PACK

1. NAME OF THE MEDICINAL PRODUCT
Exforge 10 mg/160 mg film-coated tablets
amlodipine/valsartan

2. STATEMENT OF ACTIVE SUBSTANCE(S)
Each tablet contains 10 mg amlodipine (as amlodipine besylate) and 160 mg valsartan.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS
7 film-coated tablets
14 film-coated tablets
28 film-coated tablets
30 film-coated tablets
56 film-coated tablets
90 film-coated tablets
98 film-coated tablets
280 film-coated tablets
56x1 film-coated tablet (unit dose)
98x1 film-coated tablet (unit dose)
280x1 film-coated tablet (unit dose)

5. METHOD AND ROUTE(S) OF ADMINISTRATION
Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN
Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE
EXP
9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS
OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF
APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

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13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Exforge 10 mg/160 mg
PARTICULARS TO APPEAR ON THE OUTER PACKAGING
INTERMEDIATE CARTON OF MULTIPACK (WITHOUT BLUE BOX)

1. **NAME OF THE MEDICINAL PRODUCT**

Exforge 10 mg/160 mg film-coated tablets
amlodipine/valsartan

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**

Each tablet contains 10 mg amlodipine (as amlodipine besylate) and 160 mg valsartan.

3. **LIST OF EXCIPIENTS**

4. **PHARMACEUTICAL FORM AND CONTENTS**

70 film-coated tablets. Component of a multipack, not to be sold separately.
14 film-coated tablets. Component of a multipack, not to be sold separately.

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.
Oral use.

6. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**

8. **EXPIRY DATE**

EXP
9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/370/036 280 film-coated tablets (4x70)
EU/1/06/370/039 280 film-coated tablets (20x14)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Exforge 10 mg/160 mg
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Exforge 10 mg/160 mg film-coated tablets
amlodipine/valsartan

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**

Each tablet contains 10 mg amlodipine (as amlodipine besylate) and 160 mg valsartan.

3. **LIST OF EXCIPIENTS**

4. **PHARMACEUTICAL FORM AND CONTENTS**

Multipack: 280 (4 packs of 70) film-coated tablets
Multipack: 280 (20 packs of 14) film-coated tablets

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.
Oral use.

6. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**

8. **EXPIRY DATE**

EXP
9. **SPECIAL STORAGE CONDITIONS**

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

10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

11. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Novartis Europharm Limited  
Wimblehurst Road  
Horsham  
West Sussex, RH12 5AB  
United Kingdom

12. **MARKETING AUTHORISATION NUMBER(S)**

EU/1/06/370/036  280 film-coated tablets (4x70)  
EU/1/06/370/039  280 film-coated tablets (20x14)

13. **BATCH NUMBER**

Lot

14. **GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

15. **INSTRUCTIONS ON USE**

16. **INFORMATION IN BRAILLE**

Exforge 10 mg/160 mg
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<tr>
<td><strong>5. OTHER</strong></td>
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B. PACKAGE LEAFLET
Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet
1. What Exforge is and what it is used for
2. What you need to know before you take Exforge
3. How to take Exforge
4. Possible side effects
5. How to store Exforge
6. Contents of the pack and other information

1. What Exforge is and what it is used for

Exforge tablets contain two substances called amlodipine and valsartan. Both of these substances help to control high blood pressure.

- Amlodipine belongs to a group of substances called “calcium channel blockers”. Amlodipine stops calcium from moving into the blood vessel wall which stops the blood vessels from tightening.
- Valsartan belongs to a group of substances called “angiotensin-II receptor antagonists”. Angiotensin II is produced by the body and makes the blood vessels tighten, thus increasing the blood pressure. Valsartan works by blocking the effect of angiotensin II.

This means that both of these substances help to stop the blood vessels tightening. As a result, the blood vessels relax and blood pressure is lowered.

Exforge is used to treat high blood pressure in adults whose blood pressure is not controlled enough with either amlodipine or valsartan on its own.

2. What you need to know before you take Exforge

Do not take Exforge

- if you are allergic to amlodipine or other medicines of the dihydropyridine type,
- if you are allergic to valsartan or any of the other ingredients of this medicine (listed in section 6). If you think you may be allergic, talk to your doctor before taking Exforge.
- if you have severe liver problems or bile problems such as biliary cirrhosis or cholestasis.
- if you have severe kidney problems or if you are having dialysis.
- if you are more than 3 months pregnant. (It is also better to avoid Exforge in early pregnancy, see Pregnancy section).

If any of the above applies to you, do not take Exforge and talk to your doctor.
Warnings and precautions
Talk to your doctor before taking Exforge:

– if you have been sick (vomiting or diarrhoea).
– if you have liver or kidney problems.
– if you have had a kidney transplant or if you had been told that you have a narrowing of your kidney arteries.
– if you have a condition affecting the renal glands called “primary hyperaldosteronism”.
– if you have heart failure.
– if your doctor has told you that you have a narrowing of the valves in your heart (called “aortic or mitral stenosis”) or that the thickness of your heart muscle is abnormally increased (called “obstructive hypertrophic cardiomyopathy”).

If any of these apply to you, tell your doctor before taking Exforge.

Children and adolescents
The use of Exforge in children and adolescents is not recommended (aged below 18 years old).

Other medicines and Exforge
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Your doctor may need to change the dose or take other precautions. In some cases you may have to stop taking one of the medicines. This applies especially to the medicines listed below:

– diuretics (a type of medicine also called “water tablets” which increases the amount of urine you produce);
– lithium (a medicine used to treat some types of depression);
– potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium and other substances that may increase potassium levels;
– certain types of painkillers called non-steroidal anti-inflammatory medicines (NSAIDs) or selective cyclooxygenase-2 inhibitors (COX-2 inhibitors). Your doctor may also check your kidney function;
– anticonvulsant agents (e.g. carbamazepine, phenobarbital, phenytoin, fosphenytoin, primidone), rifampicin, St. John’s Wort;
– nitroglycerin and other nitrates, or other substances called “vasodilators”;
– medicines used for HIV/AIDS (e.g. ritonavir) or for treatment of fungal infections (e.g. ketoconazole);
– diltiazem (used in the treatment of hypertension, angina pectoris and some types of arrhythmia).

Pregnancy and breast-feeding
Pregnancy
You must tell your doctor if you think you are (or might become) pregnant. Your doctor will normally advise you to stop taking Exforge before you become pregnant or as soon as you know you are pregnant and will advise you to take another medicine instead of Exforge. Exforge is not recommended in early pregnancy (first 3 months), and must not be taken when more than 3 months pregnant, as it may cause serious harm to your baby if used after the third month of pregnancy.

Breast-feeding
Tell your doctor if you are breast-feeding or about to start breast-feeding. Exforge is not recommended for mothers who are breast-feeding, and your doctor may choose another treatment for you if you wish to breast-feed, especially if your baby is newborn, or was born prematurely.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
This medicine may make you feel dizzy. This can affect how well you can concentrate. So, if you are not sure how this medicine will affect you, do not drive, use machinery, or do other activities that you need to concentrate on.
3. **How to take Exforge**

Always take this medicine exactly as your doctor has told you. Check with your doctor if you are not sure. This will help you get the best results and lower the risk of side effects.

The usual dose of Exforge is one tablet per day.

- It is advisable to take your medicine at the same time each day, preferably in the morning.
- Swallow the tablets with a glass of water.
- You can take Exforge with or without food.

Depending on how you respond to the treatment, your doctor may suggest a higher or lower dose.

Do not exceed the prescribed dose.

**Exforge and older people (age 65 years or over)**

Your doctor should exercise caution when increasing your dose.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

**If you take more Exforge than you should**

If you have taken too many tablets of Exforge, or if someone else has taken your tablets, consult a doctor immediately.

**If you forget to take Exforge**

If you forget to take this medicine, take it as soon as you remember. Then take your next dose at its usual time. However, if it is almost time for your next dose, skip the dose you missed. Do not take a double dose to make up for a forgotten tablet.

4. **Possible side effects**

Like all medicines, this medicine can cause side effects, although not everybody gets them.

**Some side effects can be serious:**

A few patients have experienced these serious side effects *(may affect up to 1 in 1,000 people)*. If any of the following happen, **tell your doctor straight away**:

- Allergic reaction with symptoms such as rash, itching, swelling of face or lips or tongue, difficulty breathing, low blood pressure (feeling of faintness, light-headedness).

**Other possible side effects:**

*Common (may affect up to 1 in 10 people)*: Influenza (flu); blocked nose, sore throat and discomfort when swallowing; headache; swelling of arms, hands, legs, ankles or feet; tiredness; asthenia (weakness); redness and warm feeling of the face and/or neck.

*Uncommon (may affect up to 1 in 100 people)*: Dizziness; nausea and abdominal pain; dry mouth; drowsiness, tingling or numbness of the hands or feet; vertigo; fast heart beat including palpitations; dizziness on standing up; cough; diarrhoea; constipation; skin rash, redness of the skin; joint swelling, back pain; pain in joints.

*Rare (may affect up to 1 in 1,000 people)*: Feeling anxious; ringing in the ears (tinnitus); fainting; passing more urine than normal or feeling more of an urge to pass urine; inability to get or maintain an erection; sensation of heaviness; low blood pressure with symptoms such as dizziness, light-headedness; excessive sweating; skin rash all over your body; itching; muscle spasm.

If any of these affect you severely, **tell your doctor**.
Side effects with amlodipine or valsartan alone which can be serious:

**Amlodipine**

*Common (may affect up to 1 in 10 people):* Vomiting.

*Uncommon (may affect up to 1 in 100 people):* Hair loss; change in bowel habits, feeling bloated, indigestion, stomach discomfort after meal; stomach pain, nausea; bleeding, tender or enlarged gums; breathlessness; breast enlargement in men; runny or stuffy nose, sneezing; yellow skin and eyes, nausea, loss of appetite, light-coloured urine; high level of sugar in the blood; inability to achieve or maintain an erection; increased need to pass urine; fever, sore throat or mouth ulcers due to infections; mood swings; muscle pain; sensation of numbness or tingling in fingers and toes; severe upper stomach pain; spontaneous bleeding or bruising; rash, purplish-red spots, fever, itching; swelling mainly of the face and throat; skin reddening, blistering of lips, eyes or mouth, skin peeling.

*Rare (may affect up to 1 in 1,000 people):* Crushing chest pain, irregular heart beat, angina pain.

*Very rare (may affect up to 1 in 10,000 people):* Yellowing of the skin and eyes, changes in the results of some liver function tests; purple skin patches, rash and itching, stiff limbs, trembling hands.

**Valsartan**

*Not known (frequency cannot be estimated from the available data):* Decrease in red blood cells, fever, sore throat or mouth sores due to infections, spontaneous bleeding or bruising, high level of potassium in the blood, abnormal liver test results, decreased renal functions and severely decreased renal functions, swelling mainly of the face and the throat, muscle pain, rash, purplish-red spots, fever, itching, allergic reaction.

If you experience any of these, tell your doctor straight away.

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

5. **How to store Exforge**

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and blister.

Do not store above 30°C.

Store in the original package in order to protect from moisture.

Do not use any Exforge pack that is damaged or shows signs of tampering.
6. Contents of the pack and other information

What Exforge contains
- The active substances of Exforge are amlodipine (as amlodipine besylate) and valsartan. Each tablet contains 5 mg amlodipine and 80 mg valsartan.
- The other ingredients are cellulose microcrystalline; crospovidone type A; silica, colloidal anhydrous; magnesium stearate; hypromellose; macrogol 4000; talc, titanium dioxide (E171); iron oxide, yellow (E172).

What Exforge looks like and contents of the pack
Exforge 5 mg/80 mg tablets are round and dark yellow with “NVR” on one side and “NV” on the other side.

Exforge is available in packs containing 7, 14, 28, 30, 56, 90, 98 or 280 tablets and in multipacks comprising 4 cartons, each containing 70 tablets, or 20 cartons, each containing 14 tablets. All packs are available with standard blisters; the 56, 98 and 280 tablet packs are additionally available with perforated unit dose blisters. Not all pack sizes may be available in your country.

Marketing Authorisation Holder
Novartis Europharm Limited
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

Manufacturer
Novartis Pharma GmbH
Roonstraße 25
D-90429 Nuremberg
Germany
For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

**België/Belgique/Belgien**
Novartis Pharma N.V.
Tél/Tel: +32 2 246 16 11

**Luxembourg/Luxemburg**
Novartis Pharma GmbH
Tél/Tel: +49 911 273 0

**България**
Novartis Pharma Services Inc.
Tel.: +359 2 976 98 28

**Magyarország**
Novartis Hungária Kft. Pharma
Tel.: +36 1 457 65 00

**Česká republika**
Novartis s.r.o.
Tel: +420 225 775 111

**Malta**
Novartis Pharma Services Inc.
Tel: +356 2298 3217

**Danmark**
Novartis Healthcare A/S
Tlf: +45 39 16 84 00

**Nederland**
Novartis Pharma B.V.
Tel: +31 26 37 82 111

**Deutschland**
Novartis Pharma GmbH
Tel: +49 911 273 0

**Norge**
Novartis Norge AS
Tlf: +47 23 05 20 00

**Éestí**
Novartis Pharma Services Inc.
Tel: +372 66 30 810

**Österreich**
Novartis Pharma GmbH
Tel: +43 1 86 6570

**Ελλάδα**
Novartis (Hellas) A.E.B.E.
Τηλ: +30 210 281 17 12

**Polska**
Novartis Poland Sp. z o.o.
Tel.: +48 22 375 4888

**España**
Novartis Farmacéutica, S.A.
Tel: +34 93 306 42 00

**Portugal**
Novartis Farma - Produtos Farmacêuticos, S.A.
Tel: +351 21 000 8600

**France**
Novartis Pharma S.A.S.
Tél: +33 1 55 47 66 00

**România**
Novartis Pharma Services Romania SRL
Tel: +40 21 31299 01

**Ireland**
Novartis Ireland Limited
Tel: +353 1 260 12 55

**Slovenija**
Novartis Pharma Services Inc.
Tel: +386 1 300 75 50

**Ísland**
Vistor hf.
Símí: +354 535 7000

**Slovenská republika**
Novartis Slovakia s.r.o.
Tel: +421 2 5542 5439

**Italia**
Novartis Farma S.p.A.
Tel: +39 02 96 54 1

**Suomi/Finland**
Novartis Finland Oy
Puh/Tel: +358 (0)10 6133 200

**Κύπρος**
Novartis Pharma Services Inc.
Τηλ: +357 22 690 690

**Sverige**
Novartis Sverige AB
Tel: +46 8 732 32 00
This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu
Exforge 5 mg/160 mg film-coated tablets
amlodipine/valsartan

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
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- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
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What is in this leaflet
1. What Exforge is and what it is used for
2. What you need to know before you take Exforge
3. How to take Exforge
4. Possible side effects
5. How to store Exforge
6. Contents of the pack and other information

1. What Exforge is and what it is used for

Exforge tablets contain two substances called amlodipine and valsartan. Both of these substances help to control high blood pressure.
- Amlodipine belongs to a group of substances called “calcium channel blockers”. Amlodipine stops calcium from moving into the blood vessel wall which stops the blood vessels from tightening.
- Valsartan belongs to a group of substances called “angiotensin-II receptor antagonists”. Angiotensin II is produced by the body and makes the blood vessels tighten, thus increasing the blood pressure. Valsartan works by blocking the effect of angiotensin II.
This means that both of these substances help to stop the blood vessels tightening. As a result, the blood vessels relax and blood pressure is lowered.

Exforge is used to treat high blood pressure in adults whose blood pressure is not controlled enough with either amlodipine or valsartan on its own.

2. What you need to know before you take Exforge

Do not take Exforge
- if you are allergic to amlodipine or other medicines of the dihydropyridine type,
- if you are allergic to valsartan or any of the other ingredients of this medicine (listed in section 6). If you think you may be allergic, talk to your doctor before taking Exforge.
- if you have severe liver problems or bile problems such as biliary cirrhosis or cholestasis.
- if you have severe kidney problems or if you are having dialysis.
- if you are more than 3 months pregnant. (It is also better to avoid Exforge in early pregnancy, see Pregnancy section).

If any of the above applies to you, do not take Exforge and talk to your doctor.
Warnings and precautions
Talk to your doctor before taking Exforge:
- if you have been sick (vomiting or diarrhoea).
- if you have liver or kidney problems.
- if you have had a kidney transplant or if you had been told that you have a narrowing of your kidney arteries.
- if you have a condition affecting the renal glands called “primary hyperaldosteronism”.
- if you have had heart failure.
- if your doctor has told you that you have a narrowing of the valves in your heart (called “aortic or mitral stenosis”) or that the thickness of your heart muscle is abnormally increased (called “obstructive hypertrophic cardiomyopathy”).
If any of these apply to you, tell your doctor before taking Exforge.

Children and adolescents
The use of Exforge in children and adolescents is not recommended (aged below 18 years old).

Other medicines and Exforge
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Your doctor may need to change the dose or take other precautions. In some cases you may have to stop taking one of the medicines. This applies especially to the medicines listed below:
- diuretics (a type of medicine also called “water tablets” which increases the amount of urine you produce);
- lithium (a medicine used to treat some types of depression);
- potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium and other substances that may increase potassium levels;
- certain types of painkillers called non-steroidal anti-inflammatory medicines (NSAIDs) or selective cyclooxygenase-2 inhibitors (COX-2 inhibitors). Your doctor may also check your kidney function;
- anticonvulsant agents (e.g. carbamazepine, phenobarbital, phenytoin, fosphenytoin, primidone), rifampicin, St. John’s wort;
- nitroglycerin and other nitrates, or other substances called “vasodilators”;
- medicines used for HIV/AIDS (e.g. ritonavir) or for treatment of fungal infections (e.g. ketoconazole);
- diltiazem (used in the treatment of hypertension, angina pectoris and some types of arrhythmia).

Pregnancy and breast-feeding

Pregnancy
You must tell your doctor if you think you are (or might become) pregnant. Your doctor will normally advise you to stop taking Exforge before you become pregnant or as soon as you know you are pregnant and will advise you to take another medicine instead of Exforge. Exforge is not recommended in early pregnancy (first 3 months), and must not be taken when more than 3 months pregnant, as it may cause serious harm to your baby if used after the third month of pregnancy.

Breast-feeding
Tell your doctor if you are breast-feeding or about to start breast-feeding. Exforge is not recommended for mothers who are breast-feeding, and your doctor may choose another treatment for you if you wish to breast-feed, especially if your baby is newborn, or was born prematurely.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
This medicine may make you feel dizzy. This can affect how well you can concentrate. So, if you are not sure how this medicine will affect you, do not drive, use machinery, or do other activities that you need to concentrate on.
3. **How to take Exforge**

Always take this medicine exactly as your doctor has told you. Check with your doctor if you are not sure. This will help you get the best results and lower the risk of side effects.

The usual dose of Exforge is one tablet per day.

- It is advisable to take your medicine at the same time each day, preferably in the morning.
- Swallow the tablets with a glass of water.
- You can take Exforge with or without food.

Depending on how you respond to the treatment, your doctor may suggest a higher or lower dose.

Do not exceed the prescribed dose.

**Exforge and older people (age 65 years or over)**

Your doctor should exercise caution when increasing your dose.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

**If you take more Exforge than you should**

If you have taken too many tablets of Exforge, or if someone else has taken your tablets, consult a doctor immediately.

**If you forget to take Exforge**

If you forget to take this medicine, take it as soon as you remember. Then take your next dose at its usual time. However, if it is almost time for your next dose, skip the dose you missed. Do not take a double dose to make up for a forgotten tablet.

4. **Possible side effects**

Like all medicines, this medicine can cause side effects, although not everybody gets them.

**Some side effects can be serious:**

A few patients have experienced these serious side effects (*may affect up to 1 in 1,000 people*). **If any of the following happen, tell your doctor straight away:**

- Allergic reaction with symptoms such as rash, itching, swelling of face or lips or tongue, difficulty breathing, low blood pressure (feeling of faintness, light-headedness).

**Other possible side effects:**

- Common (*may affect up to 1 in 10 people*): Influenza (flu); blocked nose, sore throat and discomfort when swallowing; headache; swelling of arms, hands, legs, ankles or feet; tiredness; asthenia (weakness); redness and warm feeling of the face and/or neck.
- Uncommon (*may affect up to 1 in 100 people*): Dizziness; nausea and abdominal pain; dry mouth; drowsiness, tingling or numbness of the hands or feet; vertigo; fast heart beat including palpitations; dizziness on standing up; cough; diarrhoea; constipation; skin rash, redness of the skin; joint swelling, back pain; pain in joints.
- Rare (*may affect up to 1 in 1,000 people*): Feeling anxious; ringing in the ears (tinnitus); fainting; passing more urine than normal or feeling more of an urge to pass urine; inability to get or maintain an erection; sensation of heaviness; low blood pressure with symptoms such as dizziness, light-headedness; excessive sweating; skin rash all over your body; itching; muscle spasm.

**If any of these affect you severely, tell your doctor.**
Side effects with amlodipine or valsartan alone which can be serious:

**Amlodipine**

*Common (may affect up to 1 in 10 people):* Vomiting.
*Uncommon (may affect up to 1 in 100 people):* Hair loss; change in bowel habits, feeling bloated, indigestion, stomach discomfort after meal; stomach pain, nausea; bleeding, tender or enlarged gums; breathlessness; breast enlargement in men; runny or stuffy nose, sneezing; yellow skin and eyes, nausea, loss of appetite, light-coloured urine; high level of sugar in the blood; inability to achieve or maintain an erection; increased need to pass urine; fever, sore throat or mouth ulcers due to infections; mood swings; muscle pain; sensation of numbness or tingling in fingers and toes; severe upper stomach pain; spontaneous bleeding or bruising; rash, purplish-red spots, fever, itching; swelling mainly of the face and throat; skin reddening, blistering of lips, eyes or mouth, skin peeling.
*Rare (may affect up to 1 in 1,000 people):* Crushing chest pain, irregular heart beat, angina pain.
*Very rare (may affect up to 1 in 10,000 people):* Yellowing of the skin and eyes, changes in the results of some liver function tests; purple skin patches, rash and itching, stiff limbs, trembling hands.

**Valsartan**

*Not known (frequency cannot be estimated from the available data):* Decrease in red blood cells, fever, sore throat or mouth sores due to infections, spontaneous bleeding or bruising, high level of potassium in the blood, abnormal liver test results, decreased renal functions and severely decreased renal functions, swelling mainly of the face and the throat, muscle pain, rash, purplish-red spots, fever, itching, allergic reaction.

If you experience any of these, tell your doctor straight away.

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

5. **How to store Exforge**

Keep this medicine out of the sight and reach of children.
Do not use this medicine after the expiry date which is stated on the carton and blister.
Do not store above 30°C.
Store in the original package in order to protect from moisture.
Do not use any Exforge pack that is damaged or shows signs of tampering.
6. Contents of the pack and other information

What Exforge contains
- The active substances of Exforge are amlodipine (as amlodipine besylate) and valsartan. Each tablet contains 5 mg amlodipine and 160 mg valsartan.
- The other ingredients are cellulose microcrystalline; crospovidone type A; silica, colloidal anhydrous; magnesium stearate; hypromellose; macrogol 4000; talc, titanium dioxide (E171); iron oxide, yellow (E172).

What Exforge looks like and contents of the pack
Exforge 5 mg/160 mg tablets are oval and dark yellow “NVR” on one side and “ECE” on the other side.

Exforge is available in packs containing 7, 14, 28, 30, 56, 90, 98 or 280 tablets and in multipacks comprising 4 cartons, each containing 70 tablets, or 20 cartons, each containing 14 tablets. All packs are available with standard blisters; the 56, 98 and 280 tablet packs are additionally available with perforated unit dose blisters. Not all pack sizes may be available in your country.

Marketing Authorisation Holder
Novartis Europharm Limited
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

Manufacturer
Novartis Pharma GmbH
Roonstraße 25
D-90429 Nuremberg
Germany
For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

**België/Belgique/Belgien**
Novartis Pharma N.V.
Tél/Tel: +32 2 246 16 11

**Luxembourg/Luxemburg**
Novartis Pharma GmbH
Tel: +49 911 273 0

**България**
Novartis Pharma Services Inc.
Tel.: +359 2 976 98 28

**Magyarország**
Novartis Hungária Kft. Pharma
Tel.: +36 1 457 65 00

**Česká republika**
Novartis s.r.o.
Tel: +420 225 775 111

**Malta**
Novartis Pharma Services Inc.
Tel: +356 2298 3217

**Danmark**
Novartis Healthcare A/S
Tlf: +45 39 16 84 00

**Nederland**
Novartis Pharma B.V.
Tel: +31 26 37 82 111

**Deutschland**
Novartis Pharma GmbH
Tel: +49 911 273 0

**Norge**
Novartis Norge AS
Tlf: +47 23 05 20 00

**Eesti**
Novartis Pharma Services Inc.
Tel: +372 66 30 810

**Österreich**
Novartis Pharma GmbH
Tel: +43 1 86 6570

**Ελλάδα**
Novartis (Hellas) A.E.B.E.
Τηλ: +30 210 281 17 12

**Polska**
Novartis Poland Sp. z o.o.
Tel.: +48 22 375 4888

**España**
Novartis Farmacéutica, S.A.
Tel: +34 93 306 42 00

**Portugal**
Novartis Farma - Produtos Farmacêuticos, S.A.
Tel: +351 21 000 8600

**France**
Novartis Pharma S.A.S.
Tél: +33 1 55 47 66 00

**România**
Novartis Pharma Services Romania SRL
Tel: +40 21 31299 01

**Ireland**
Novartis Ireland Limited
Tel: +353 1 260 12 55

**Slovenija**
Novartis Pharma Services Inc.
Tel: +386 1 300 75 50

**Ísland**
Vistor hf.
Sím: +354 535 7000

**Slovenská republika**
Novartis Slovakia s.r.o.
Tel: +421 2 5542 5439

**Italia**
Novartis Farma S.p.A.
Tel: +39 02 96 54 1

**Suomi/Finland**
Novartis Finland Oy
Puh/Tel: +358 (0)10 6133 200

**Κέρκυρα**
Novartis Pharma Services Inc.
Τηλ: +357 22 690 690

**Sverige**
Novartis Sverige AB
Tel: +46 8 732 32 00
Latvija
Novartis Pharma Services Inc.
Tel: +371 67 887 070

Lietuva
Novartis Pharma Services Inc.
Tel: +370 5 269 16 50

United Kingdom
Novartis Pharmaceuticals UK Ltd.
Tel: +44 1276 698370

This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site:
http://www.ema.europa.eu
Exforge tablets contain two substances called amlodipine and valsartan. Both of these substances help to control high blood pressure.

– Amlodipine belongs to a group of substances called “calcium channel blockers”. Amlodipine stops calcium from moving into the blood vessel wall which stops the blood vessels from tightening.

– Valsartan belongs to a group of substances called “angiotensin-II receptor antagonists”. Angiotensin II is produced by the body and makes the blood vessels tighten, thus increasing the blood pressure. Valsartan works by blocking the effect of angiotensin II.

This means that both of these substances help to stop the blood vessels tightening. As a result, the blood vessels relax and blood pressure is lowered.

Exforge is used to treat high blood pressure in adults whose blood pressure is not controlled enough with either amlodipine or valsartan on its own.

2. What you need to know before you take Exforge

Do not take Exforge

– if you are allergic to amlodipine or other medicines of the dihydropyridine type,

– if you are allergic to valsartan or any of the other ingredients of this medicine (listed in section 6). If you think you may be allergic, talk to your doctor before taking Exforge.

– if you have severe liver problems or bile problems such as biliary cirrhosis or cholestasis.

– if you have severe kidney problems or if you are having dialysis.

– if you are more than 3 months pregnant. (It is also better to avoid Exforge in early pregnancy, see Pregnancy section).

If any of the above applies to you, do not take Exforge and talk to your doctor.
Warnings and precautions
Talk to your doctor before taking Exforge:
- if you have been sick (vomiting or diarrhoea).
- if you have liver or kidney problems.
- if you have had a kidney transplant or if you had been told that you have a narrowing of your kidney arteries.
- if you have a condition affecting the renal glands called “primary hyperaldosteronism”.
- if you have had heart failure.
- if your doctor has told you that you have a narrowing of the valves in your heart (called “aortic or mitral stenosis”) or that the thickness of your heart muscle is abnormally increased (called “obstructive hypertrophic cardiomyopathy”).

If any of these apply to you, tell your doctor before taking Exforge.

Children and adolescents
The use of Exforge in children and adolescents is not recommended (aged below 18 years old).

Other medicines and Exforge
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Your doctor may need to change the dose or take other precautions. In some cases you may have to stop taking one of the medicines. This applies especially to the medicines listed below:
- diuretics (a type of medicine also called “water tablets” which increases the amount of urine you produce);
- lithium (a medicine used to treat some types of depression);
- potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium and other substances that may increase potassium levels;
- certain types of painkillers called non-steroidal anti-inflammatory medicines (NSAIDs) or selective cyclooxygenase-2 inhibitors (COX-2 inhibitors). Your doctor may also check your kidney function;
- anticonvulsant agents (e.g. carbamazepine, phenobarbital, phenytoin, fosphenytoin, primidone), rifampicin, St. John’s wort;
- nitroglycerin and other nitrates, or other substances called “vasodilators”;
- medicines used for HIV/AIDS (e.g. ritonavir) or for treatment of fungal infections (e.g. ketoconazole);
- diltiazem (used in the treatment of hypertension, angina pectoris and some types of arrhythmia).

Pregnancy and breast-feeding

Pregnancy
You must tell your doctor if you think you are (or might become) pregnant. Your doctor will normally advise you to stop taking Exforge before you become pregnant or as soon as you know you are pregnant and will advise you to take another medicine instead of Exforge. Exforge is not recommended in early pregnancy (first 3 months), and must not be taken when more than 3 months pregnant, as it may cause serious harm to your baby if used after the third month of pregnancy.

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Tell your doctor if you are breast-feeding or about to start breast-feeding. Exforge is not recommended for mothers who are breast-feeding, and your doctor may choose another treatment for you if you wish to breast-feed, especially if your baby is newborn, or was born prematurely.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
This medicine may make you feel dizzy. This can affect how well you can concentrate. So, if you are not sure how this medicine will affect you, do not drive, use machinery, or do other activities that you need to concentrate on.
3. How to take Exforge

Always take this medicine exactly as your doctor has told you. Check with your doctor if you are not sure. This will help you get the best results and lower the risk of side effects.

The usual dose of Exforge is one tablet per day.
- It is advisable to take your medicine at the same time each day, preferably in the morning.
- Swallow the tablets with a glass of water.
- You can take Exforge with or without food.

Depending on how you respond to the treatment, your doctor may suggest a higher or lower dose.

Do not exceed the prescribed dose.

Exforge and older people (age 65 years or over)
Your doctor should exercise caution when increasing your dose.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

If you take more Exforge than you should
If you have taken too many tablets of Exforge, or if someone else has taken your tablets, consult a doctor immediately.

If you forget to take Exforge
If you forget to take this medicine, take it as soon as you remember. Then take your next dose at its usual time. However, if it is almost time for your next dose, skip the dose you missed. Do not take a double dose to make up for a forgotten tablet.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Some side effects can be serious:
A few patients have experienced these serious side effects (may affect up to 1 in 1,000 people). If any of the following happen, tell your doctor straight away:
Allergic reaction with symptoms such as rash, itching, swelling of face or lips or tongue, difficulty breathing, low blood pressure (feeling of faintness, light-headedness).

Other possible side effects:
Common (may affect up to 1 in 10 people): Influenza (flu); blocked nose, sore throat and discomfort when swallowing; headache; swelling of arms, hands, legs, ankles or feet; tiredness; asthenia (weakness); redness and warm feeling of the face and/or neck.
Uncommon (may affect up to 1 in 100 people): Dizziness; nausea and abdominal pain; dry mouth; drowsiness, tingling or numbness of the hands or feet; vertigo; fast heart beat including palpitations; dizziness on standing up; cough; diarrhoea; constipation; skin rash, redness of the skin; joint swelling, back pain; pain in joints.
Rare (may affect up to 1 in 1,000 people): Feeling anxious; ringing in the ears (tinnitus); fainting; passing more urine than normal or feeling more of an urge to pass urine; inability to get or maintain an erection; sensation of heaviness; low blood pressure with symptoms such as dizziness, light-headedness; excessive sweating; skin rash all over your body; itching; muscle spasm.
If any of these affect you severely, tell your doctor.
Side effects with amlodipine or valsartan alone which can be serious:

**Amlodipine**
*Common (may affect up to 1 in 10 people):* Vomiting.
*Uncommon (may affect up to 1 in 100 people):* Hair loss; change in bowel habits, feeling bloated, indigestion, stomach discomfort after meal; stomach pain, nausea; bleeding, tender or enlarged gums; breathlessness; breast enlargement in men; runny or stuffy nose, sneezing; yellow skin and eyes, nausea, loss of appetite, light-coloured urine; high level of sugar in the blood; inability to achieve or maintain an erection; increased need to pass urine; fever, sore throat or mouth ulcers due to infections; mood swings; muscle pain; sensation of numbness or tingling in fingers and toes; severe upper stomach pain; spontaneous bleeding or bruising; rash, purplish-red spots, fever, itching; swelling mainly of the face and throat; skin reddening, blistering of lips, eyes or mouth, skin peeling.
*Rare (may affect up to 1 in 1,000 people):* Crushing chest pain, irregular heart beat, angina pain.
*Very rare (may affect up to 1 in 10,000 people):* Yelling of the skin and eyes, changes in the results of some liver function tests; purple skin patches, rash and itching, stiff limbs, trembling hands.

**Valsartan**
*Not known (frequency cannot be estimated from the available data):* Decrease in red blood cells, fever, sore throat or mouth sores due to infections, spontaneous bleeding or bruising, high level of potassium in the blood, abnormal liver test results, decreased renal functions and severely decreased renal functions, swelling mainly of the face and the throat, muscle pain, rash, purplish-red spots, fever, itching, allergic reaction.

If you experience any of these, tell your doctor straight away.

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

5. **How to store Exforge**

Keep this medicine out of the sight and reach of children.
Do not use this medicine after the expiry date which is stated on the carton and blister.
Do not store above 30°C.
Store in the original package in order to protect from moisture.
Do not use any Exforge pack that is damaged or shows signs of tampering.
6. Contents of the pack and other information

What Exforge contains

– The active substances of Exforge are amlodipine (as amlodipine besylate) and valsartan. Each tablet contains 10 mg amlodipine and 160 mg valsartan.

– The other ingredients are cellulose microcrystalline; crospovidone type A; silica, colloidal anhydrous; magnesium stearate; hypromellose; macrogol 4000; talc, titanium dioxide (E171); iron oxide, yellow (E172), iron oxide, red (E172).

What Exforge looks like and contents of the pack

Exforge 10 mg/160 mg tablets are oval and light yellow with “NVR” on one side and “UIC” on the other side.

Exforge is available in packs containing 7, 14, 28, 30, 56, 90, 98 or 280 tablets and in multipacks comprising 4 cartons, each containing 70 tablets, or 20 cartons, each containing 14 tablets. All packs are available with standard blisters; the 56, 98 and 280 tablet packs are additionally available with perforated unit dose blisters. Not all pack sizes may be available in your country.

Marketing Authorisation Holder

Novartis Europharm Limited
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

Manufacturer

Novartis Pharma GmbH
Roonstraße 25
D-90429 Nuremberg
Germany
For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

**België/Belgique/Belgien**
Novartis Pharma N.V.
Tél/Tel: +32 2 246 16 11

**Luxembourg/Luxemburg**
Novartis Pharma GmbH
Tel: +49 911 273 0

**България**
Novartis Pharma Services Inc.
Тел.: +359 2 976 98 28

**Magyarország**
Novartis Hungária Kft. Pharma
Tel.: +36 1 457 65 00

**Česká republika**
Novartis s.r.o.
Tel: +420 225 775 111

**Malta**
Novartis Pharma Services Inc.
Tel: +356 2298 3217

**Danmark**
Novartis Healthcare A/S
Tlf: +45 39 16 84 00

**Nederland**
Novartis Pharma B.V.
Tel: +31 26 37 82 111

**Deutschland**
Novartis Pharma GmbH
Tel: +49 911 273 0

**Norge**
Novartis Norge AS
Tlf: +47 23 05 20 00

**Êстi**
Novartis Pharma Services Inc.
Tel: +372 66 30 810

**Österreich**
Novartis Pharma GmbH
Tel: +43 1 86 6570

**Ελλάδα**
Novartis (Hellas) A.E.B.E.
Τηλ.: +30 210 281 17 12

**Polska**
Novartis Poland Sp. z o.o.
Tel.: +48 22 375 4888

**España**
Novartis Farma, S.A.
Tel: +34 93 306 42 00

**Portugal**
Novartis Farma - Produtos Farmacêuticos, S.A.
Tel: +351 21 000 8600

**France**
Novartis Pharma S.A.S.
Tél: +33 1 55 47 66 00

**România**
Novartis Pharma Services Romania SRL
Tel: +40 21 31299 01

**Ireland**
Novartis Ireland Limited
Tel: +353 1 260 12 55

**Slovenija**
Novartis Pharma Services Inc.
Tel: +386 1 300 75 50

**Ísland**
Viðsok hf.
Sími: +354 535 7000

**Slovenská republika**
Novartis Slovakia s.r.o.
Tel: +421 2 5542 5439

**Italia**
Novartis Farma S.p.A.
Tel: +39 02 96 54 1

**Suomi/Finland**
Novartis Finland Oy
Puh/Tel: +358 (0)10 6133 200

**Κύπρος**
Novartis Pharma Services Inc.
Τηλ.: +357 22 690 690

**Sverige**
Novartis Sverige AB
Tel: +46 8 732 32 00
Latvija
Novartis Pharma Services Inc.
Tel: +371 67 887 070

United Kingdom
Novartis Pharmaceuticals UK Ltd.
Tel: +44 1276 698370

Lietuva
Novartis Pharma Services Inc.
Tel: +370 5 269 16 50

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http://www.ema.europa.eu