NOVARTIS

TRADE NAME

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

DESCRIPTION AND COMPOSITION

Pharmaceutical form

Film-coated tablet.

Active substances:

Amlodipine besylate

Valsartan

Three strengths are available. One film-coated tablet of Exforge contains:

- 5 mg of amlodipine (as amlodipine besylate) and 80 mg of valsartan, dark yellow, round film-coated tablet with bevelled edges, imprinted with “NVR” on one side and “NV” on the other side.

- 5 mg of amlodipine (as amlodipine besylate) and 160 mg of valsartan, dark yellow, ovaloid film-coated tablet with bevelled edges, imprinted with “NVR” on one side and “ECE” on the other side.

- 10 mg of amlodipine (as amlodipine besylate) and 160 mg of valsartan, light yellow, ovaloid film-coated tablet with bevelled edges, imprinted with “NVR” on one side and “UIC” on the other side.

For a full list of excipients, see section Excipients.

Exforge FCT are non-divisible and cannot be divided into equal doses.

Excipients

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

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

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

INDICATIONS

Treatment of essential hypertension.

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

DOSAGE REGIMEN AND ADMINISTRATION

Dosage regimen

General target population

The recommended dose of Exforge is one tablet per day.

A patient whose blood pressure is not adequately controlled on monotherapy may be switched to combination therapy with Exforge. When clinically appropriate, direct change from monotherapy to the fixed-dose combination may be considered. Individual dose titration with the components (i.e. amlodipine and valsartan) is recommended before changing to the fixed dose combination.

Exforge may be used as initial therapy in patients who are likely to need multiple drugs to achieve blood pressure goals. The choice of Exforge as initial therapy for hypertension should be based on an assessment of potential benefits and risks.

For initial therapy, the usual starting dose is Exforge 5/80 mg once daily. The dosage can be increased after 1 to 2 weeks of therapy to a maximum of one 10/320 mg tablet once daily as needed to control blood pressure. Exforge is not recommended as initial therapy in patients with intravascular volume depletion (see Special Warnings and Precautions).

The maximum dose is 10/320 mg. Exforge can be used with or without food. It is recommended to take Exforge with some water.

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

Special populations

Renal impairment

No dosage adjustment is required for patients with mild to moderate renal impairment. Monitoring of potassium levels and creatinine is advised in moderate renal impairment.

Hepatic impairment

Due to amlodipine and valsartan,caution should be exercised when administering Exforge to patients with hepatic impairment or biliary obstructive disorders. Starting with the lowest available dose of amlodipine should be considered. The lowest strength of Exforge contains 5 mg of amlodipine. (See Warnings and Precautions and Clinical Pharmacology). In patients with mild to moderate hepatic impairment without cholestasis, the maximum recommended dose is 80 mg valsartan.

Geriatric patients (aged 65 years or above)

In elderly patients, no dose adjustment of the starting dose is required. Starting with the lowest available dose of amlodipine should be considered. The lowest strength of Exforge contains 5 mg of amlodipine. However, caution is required when increasing the dosage. (See section CLINICAL PHARMACOLOGY).

Pediatric patients (below 18 years)

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

CONTRAINDICATIONS

- Known hypersensitivity to amlodipine, valsartan, to dihydropyridine derivatives, or to any of the excipients.
- Severe hepatic impairment, biliary cirrhosis or cholestasis.
- Severe renal impairment (GFR <30 ml/min/1.73 m^2) and patients undergoing dialysis.
- Pregnancy (see section PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL)
- The concomitant use of Exforge with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73m^2) (see section INTERACTIONS).

WARNINGS AND PRECAUTIONS

Patients with sodium- and/or volume-depletion

Excessive hypotension was seen in 0.4% of patients with uncomplicated hypertension treated with Exforge in placebo-controlled studies. In patients with an activated renin-angiotensin system (such as volume- and/or salt-depleted patients receiving high doses of diuretics) who are receiving angiotensin receptor blockers, symptomatic hypotension may occur. Correction of this condition prior to administration of Exforge or close medical supervision at the start of treatment is recommended.

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

Hyperkalemia

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

Patients with renal artery stenosis

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

Patients with kidney transplantation

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

Patients with hepatic impairment

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

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

Patients with 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.

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

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.

Patients with heart failure/post –myocaradial infarction

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

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

In 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.

Patients with acute myocardial infarction

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

Patients with aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy

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

Angioedema

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

Exforge has not been studied in any patient population other than hypertension.

Dual Blockade of the Renin-Angiotensin System (RAS)

There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended (see INTERACTIONS). If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure. ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

ADVERSE DRUG REACTIONS

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

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

Infections and infestations	
Common:	Nasopharyngitis, influenza
Immune system disorders	
Rare:	Hypersensitivity
Eye disorders	
Rare:	Visual disturbance
Psychiatric disorders	
Rare:	Anxiety
Nervous system disorders	
Common:	Headache
Uncommon:	Dizziness, somnolence, dizziness postural, paraesthesia
Ear and labyrinth disorders	
Uncommon:	Vertigo
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:	Diarrhea, 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:

% of patients who experienced peripheral		**Valsartan (mg)**				
		0	40	80	160	320
Amlodipine (mg)	0	3.0	5.5	2.4	1.6	0.9
	2.5	8.0	2.3	5.4	2.4	3.9
	5	3.1	4.8	2.3	2.1	2.4
	10	10.3	NA	NA	9.0	9.5

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

Laboratory evaluation

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

Additional information on the individual components

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

Amlodipine

Other additional adverse events reported in with amlodipine monotherapy, irrespective of their causal association with the study medication, are presented in Table 1:

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

Table 1 Adverse experiences with amlodipine monotherapy

Eye disorders	
Uncommon	Diplopia
Blood and lymphatic system disorders	
Very rare	Thrombocytopenia, leucocytopenia
Immune system disorders	
Very rare	Allergic reactions
Metabolism and nutrition disorders	
Very rare	Hyperglycemia
Psychiatric disorders	
Uncommon	Insomnia, mood changes
Nervous system disorders	
Uncommon Very rare	Tremor, hypoesthesia, dysgeusia Peripheral neuropathy, hypertonia
Cardiac disorders	
Very rare	Arrhythmia, bradycardia, atrial fibrillation, ventricular tachycardia, myocardial infarction
Vascular disorders	
Very rare	Vasculitis
Respiratory, thoracic and mediastinal disorders	
Uncommon	Dyspnea, rhinitis
Gastrointestinal disorders	
Uncommon Very rare	Vomiting, dyspepsia Pancreatitis, gastritis, gingival hyperplasia
Hepatobiliary disorders	
Very rare	Hepatitis, jaundice
Skin and subcutaneous tissue disorders	
Uncommon Very rare	Alopecia, purpura, skin discoloration, photosensitivity Angioedema, urticaria, erythema multiforme, Steven Johnson syndrome
Musculoskeletal and connective tissue disorders	
Uncommon	Myalgia
Renal and urinary disorders	
Uncommon	Micturition disorder, nocturia
Reproductive system and breast disorders	
Uncommon	Gynecomastia
General disorders and administration site conditions	
Uncommon	Pain, malaise, chest pain
Investigations	
Uncommon Very rare	Weight decreased, weight increased Hepatic enzyme increased (mostly consistent with cholestasis)

Valsartan

Other ADRs reported from clinical studies, post-marketing experience and laboratory findings in hypertension indication are presented in Table 2 according to system organ class.

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

Table 2 Adverse drug reactions with valsartan monotherapy

Blood and lymphatic system disorders	
Not known	Hemoglobin decreased, Hematocrit decreased, Neutropenia, Thrombocytopenia
Immune system disorders	
Not known	Hypersensitivity including serum sickness
Metabolism and nutrition disorders	
Not known	Blood potassium increased
Vascular disorders	
Not known	Vasculitis
Hepato-biliary disorders	
Not known	Liver function test abnormal including blood bilirubin increase
Skin and subcutaneous tissue disorders	
Not known	Angioedema, dermatitis bullous
Musculoskeletal and connective tissue disorders	
Not known	Myalgia
Renal and urinary disorders	
Not known	Renal failure and impairment, Blood creatinine increased

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

The following serious adverse events, irrespective of causality and with unknown frequency, have been reported from clinical studies or post-marketing experiences: Toxic epidermal necrolysis (TEN), Stevens-Johnsons syndrome (SJS), erythema multiforme (EM), toxic skin eruption, skin necrosis, exfoliative rash, pemphigus and pemphigoid.

INTERACTIONS

Amlodipine

Simvastatin: Co-administration of multiple doses of 10 mg of amlodipine with 80 mg simvastatin resulted in a 77% increase in exposure to simvastatin compared to simvastatin alone. It is recommended to limit the dose of simvastatin to 20 mg daily in patients on amlodipine.

CYP3A4 Inhibitors: Co-administration of a 180 mg daily dose of diltiazem with 5 mg amlodipine in elderly hypertensive patients resulted in a 1.6 fold increase in amlodipine systemic exposure. However, strong inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, ritonavir) may increase the

plasma concentrations of amlodipine to a greater extent than diltiazem. Caution should therefore be exercised when co-administering amlodipine with CYP3A4 inhibitors.

Grapefruit Juice: The exposure of amlodipine may be increased when co-administered with grapefruit juice due to CYP3A4 inhibition. However, co-administration of 240 mL of grapefruit juice with a single oral dose of amlodipine 10 mg in 20 healthy volunteers had no significant effect on the pharmacokinetics of amlodipine.

CYP3A4 Inducers: No information is available on the quantitative effects of CYP3A4 inducers on amlodipine. Patients should be monitored for adequate clinical effect when amlodipine is co-administered with CYP3A4 inducers (e.g. rifampicin, hypericum perforatum).

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 drugs (aluminium hydroxide gel, magnesium hydroxide, simeticone), cimetidine, non-steroidal anti-inflammatory drugs, antibiotics and oral hypoglycaemic drugs.

Valsartan

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

The concomitant use of ARBs - including valsartan - or ACEIs with aliskiren is contraindicated in patients with Type 2 diabetes or renal impairment (GFR < 60ml/min/1.73m^2) (see CONTRAINDICATIONS).

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

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.

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, in patients who are elderly, volume-depleted (including those on diuretic therapy), or have compromised renal function, concomitant use of angiotensin II antagonists and NSAIDs may lead to an increased risk of worsening of renal function. Therefore, monitoring of renal function is recommended when initiating or modifying the treatment in patients on valsartan who are taking NSAIDs concomitantly.

Transporters: The results from an in vitro study with human liver tissue indicate that valsartan is a substrate of the hepatic uptake transporter OATP1B1 and the hepatic efflux transporter MRP2. Co-

administration of inhibitors of the uptake transporter (e.g, rifampin, ciclosporin) or efflux transporter (e.g., ritonavir) may increase the systemic exposure to valsartan.

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

Interactions common to the combination

No drug interaction studies were 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.

PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Pregnancy

Risk summary

As for any drug that acts directly on the RAAS, Exforge must not be used during pregnancy (see section CONTRAINDICATIONS). Due to the mechanism of action of angiotensin II antagonists, a risk to the foetus cannot be excluded. Administration of angiotensin converting enzyme (ACE) inhibitors (a specific class of drugs acting on the renin-angiotensin-aldosterone system, RAAS) to pregnant women during the second and third trimesters has been reported to cause injury and death to the developing foetus. In addition, in retrospective data, first trimester use of ACE inhibitors has been associated with a potential risk of birth defects. There have been reports of spontaneous abortion, oligohydramnios and newborn renal dysfunction when pregnant women have inadvertently taken valsartan.

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

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

Clinical considerations

Disease-associated maternal and/or embryo/fetal risk

Hypertension in pregnancy increases the maternal risk for pre-eclampsia, gestational diabetes, premature delivery, and delivery complications (e.g., need for cesarean section, and post-partum hemorrhage). Hypertension increases the fetal risk for intrauterine growth restriction and intrauterine death.

Fetal/Neonatal Risk

Oligohydramnios in pregnant women who use drugs affecting the renin-angiotensin system in the second and third trimesters of pregnancy can result in the following: reduced fetal renal function leading to anuria and renal failure, fetal lung hypoplasia, skeletal deformations, including skull hypoplasia, hypotension and death.

In case of accidental exposure to ARB therapy, appropriate fetal monitoring should be considered.

Infants whose mothers have taken ARB therapy in the first trimester,should be closely observed for hypotension.

Animal data

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

Valsartan: In embryofetal development studies in mice, rats and rabbits, fetotoxicity was observed in association with maternal toxicity in rats at valsartan doses of 600 mg/kg/day approximately 6 times the maximum recommended human dose on a mg/m^2 basis (calculations assume an oral dose of 320 mg/day and a 60-kg patient) and in rabbits at doses of 10 mg/kg/day approximately 0.6 times the maximum recommended human dose on a mg/m^2 basis (calculations assume an oral dose of 320 mg/day and a 60-kg patient). There was no evidence of maternal toxicity or fetotoxicity in mice up to a dose level of 600 mg/kg/day approximately 9 times the maximum recommended human dose on a mg/m^2 basis (calculations assume an oral dose of 320 mg/day and a 60-kg patient).

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

Lactation

It is not known whether valsartan is excreted in human milk. It is reported that amlodipine is excreted in human milk. The proportion of the maternal dose received by the infant has been estimated with an interquartile range of 3 – 7%, with a maximum of 15%. The effect of amlodipine on infants is unknown. Valsartan was excreted in the milk of lactating rats. It is therefore not advisable for women who are breast-feeding to use Exforge.

Females and males of reproductive potential

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

Infertility

There is no information on the effects of amlodipine or valsartan on human fertility. Studies in rats did not show any effects of amlodipine or valsartan on fertility (see section NON-CLINICAL SAFETY DATA).

OVERDOSAGE

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

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

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

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

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

Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade.

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

CLINICAL PHARMACOLOGY

Pharmacotherapeutic group, ATC

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

Pharmacodynamics (PD)

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

Amlodipine

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

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

Amlodipine has demonstrated beneficial clinical effects in patients with chronic stable angina, vasospastic angina and angiographically documented coronary artery disease.

Valsartan

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

Valsartan does not inhibit ACE, also known as kininase II, which converts angiotensin I to angiotensin II and degrades bradykinin. Since there is no effect on ACE and no potentiation of bradykinin or substance P, angiotensin II antagonists are unlikely to be associated with 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 reduction of blood pressure is achieved within 4–6 hours. The

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

In patients with chronic heart failure (NYHA class II-IV), valsartan has been demonstrated to significantly reduce hospitalizations in patients with chronic heart failure (NYHA class II-IV). The benefits were greatest in patients not receiving either an ACE inhibitor or a beta blocker. In post-MI patients, valsartan has also been shown to reduce cardiovascular mortality in clinically stable patients with left ventricular failure or left ventricular dysfunction following myocardial infarction.

Pharmacokinetics (PK)

Linearity

Valsartan and amlodipine exhibit linear pharmacokinetics.

Amlodipine

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

Distribution: Volume of distribution is approximately 21 L/kg. In vitro studies with amlodipine have shown that approximately 97.5% of circulating drug is bound to plasma proteins. Amlodipine crosses the placenta and is excreted into breast milk.

Biotransformation: Amlodipine is extensively (approximately 90%) metabolized 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%. Food decreases exposure (as measured by AUC) to valsartan by about 40% and peak plasma concentration (Cmax) 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 liters, indicating that valsartan is not distributed into tissues extensively. Valsartan is highly bound to serum proteins (94–97%), mainly serum albumin.

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

Elimination: Valsartan shows multiexponential decay kinetics (t 1/2α <1h and t 1/2 ß about 9 h). 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.

Valsartan/Amlodipine

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

Special populations

Geriatric patients

The time to reach peak plasma concentrations of amlodipine is similar in elderly and younger patients. Amlodipine clearance tends to be decreased with resulting increases in AUC and elimination half life in elderly patients. Systemic exposure to valsartan is slightly elevated in the elderly as compared to the young, but this has not been shown to have any clinical significance.

Renal impairment

The pharmacokinetics of amlodipine is not significantly influenced by renal impairment. There is no correlation between renal function (measured by creatinine clearance) and exposure (measured by AUC) to valsartan in patients with different degrees of renal impairment. Patients with mild to moderate renal impairment may therefore receive the usual initial dose. (see section DOSAGE REGIMEN AND ADMINISTRATION and WARNINGS AND PRECAUTIONS)

Hepatic impairment

Patients with hepatic impairment have decreased clearance of amlodipine with resulting increase in AUC of approximately 40–60%. On average, in patients with mild to moderate chronic liver disease exposure (measured by AUC values) to valsartan is twice that found in healthy volunteers (matched by age, sex and weight). Caution should be exercised in patients with liver disease (see section DOSAGE REGIMEN AND ADMINISTRATION and WARNINGS AND PRECAUTIONS).

CLINICAL STUDIES

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.

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.

A multicenter randomized, double-blind, active-controlled, parallel-group trial showed normalization 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 /160 mg and 62% of patients treated with amlodipine/valsartan 5 /160 mg, compared to 53% of patients remaining on valsartan 160 mg. The addition of amlodipine 10 mg and 5 mg produced an additional reduction in systolic/diastolic blood pressure of 6.0/4.8 mmHg and 3.9/2.9 mmHg, respectively, compared to patients who remained on valsartan 160 mg only.

A multicenter, randomized, double-blind, active-controlled, parallel-group trial showed normalization of blood pressure (trough sitting diastolic 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 /160 mg, compared to 67% of patients remaining on amlodipine 10 mg. The addition of valsartan 160 mg produced an additional reduction in systolic/diastolic blood pressure of 2.9/2.1 mmHg compared to patients who remained on amlodipine 10 mg only. Exforge was also studied in an active-controlled study of 130 hypertensive patients with diastolic blood pressure ≥110 mmHg and <120 mmHg. In this study (baseline blood pressure 171/113 mmHg), an Exforge regimen of 5 /160 mg titrated to 10 /160 mg reduced sitting blood pressure by 36/29 mmHg as compared to 32/28 mmHg with a regimen of lisinopril/hydrochlorothiazide 10/12.5 mg titrated to 20 /12.5 mg.

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

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

In patients not adequately controlled on amlodipine 5 mg, amlodipine/valsartan 5 mg/80 mg may achieve blood pressure control similar to amlodipine 10 mg with less oedema. In patients adequately controlled on amlodipine 10 mg but who experience unacceptable oedema, amlodipine/valsartan 5 mg/80 mg may achieve similar blood pressure control with less oedema.

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

Efficacy in subgroup populations

In double-blind controlled studies, age, gender, race and/or body mass index (⩾30 kg/m², <30 kg/m²) did not influence the response to Exforge.

Two double-blind, active-controlled studies were conducted in which Exforge was administered as initial therapy. In 1 study, a total of 572 black patients with moderate to severe hypertension were randomized to receive either the combination amlodipine/valsartan or amlodipine monotherapy for 12 weeks. The initial dose of amlodipine/valsartan was 5/160 mg for 2 weeks with forced titration to 10/160 mg for 2 weeks, followed by optional titration to 10/320 mg for 4 weeks and optional addition of HCTZ 12.5 mg for 4 weeks. The initial dose of amlodipine was 5 mg for 2 weeks with forced titration to 10 mg for 2 weeks, followed by optional titration to 10 mg for 4 weeks and optional addition of HCTZ 12.5 mg for 4 weeks. At the primary endpoint of

8 weeks, the treatment difference between amlodipine/valsartan and amlodipine was 6.7/2.8 mmHg.

In the other study of similar design, a total of 646 patients with moderate to severe hypertension (MSSBP of ⩾160 mmHg and <200 mmHg) were randomized to receive either the combination amlodipine/valsartan or amlodipine monotherapy for 8 weeks. The initial dose of amlodipine/valsartan was 5/160 mg for 2 weeks with forced titration to 10/160 mg for 2 weeks, followed by the optional addition of HCTZ 12.5 mg for 4 weeks. The initial dose of amlodipine was 5 mg for 2 weeks with forced titration to 10 mg for 2 weeks, followed by the optional addition of HCTZ 12.5 mg for 4 weeks. At the primary endpoint of 4 weeks, the treatment difference between amlodipine/valsartan and amlodipine was 6.6/3.9 mmHg.

EXCITE (EXperienCe of amlodIpine and valsarTan in hypErtension) Study

In an open, uncontrolled study, 9,794 hypertensive patients across 13 countries in the Middle East and Asia were treated according to routine clinical practice and prospectively observed for 26 weeks. A total of 8,603 were prescribed amlodipine/valsartan and 1,191 prescribed amlodipine/valsartan/hydrochlorothiazide. Among these, 15.5% were elderly, 32.5% were obese, 31.3% had diabetes, and 9.8% had isolated systolic hypertension. Both amlodipine/valsartan and amlodipine/valsartan/hydrochlorothiazide single-pill combinations, respectively, were associated with clinically relevant and significant mean sitting systolic/diastolic BP reductions in the overall population (-31.0/-16.6 mmHg and -36.6/-17.8 mmHg, respectively. These results were consistent regardless of age, body mass index, and diabetic status. Similarly, clinically relevant and significant systolic BP reductions were observed in patients with isolated systolic hypertension (−25.5 mmHg and −30.2 mmHg, respectively).

Asian studies (in Chinese and Taiwanese patients)

Three Asian studies including more than 12,000 patients with hypertension, mostly of Chinese origin, have shown similar efficacy and safety of Exforge compared to the global registration studies in mixed, but predominantly Caucasian patients.

In a multicenter, open-label, prospective, observational study in China, with 11,422 enrolled hypertensive patients including 16.5% with diabetes and 3.1% with renal impairment, Exforge provided clinically meaningful and statistically significant reductions in mean sitting systolic blood pressure (MSSBP) and mean sitting diastolic BP (MSDBP) (mean reductions of 27.1 and 15.2 mmHg, respectively; p <0.0001) after 8 weeks of treatment. The BP goal originally defined as <130/80 mmHg for patients with diabetes or renal impairment, and <140/90 mmHg for all other patients was achieved by 66.1% of patients at Week 8.The unified defined BP goal (<140/90 mmHg for all patients) was achieved by 76.8% of patients at Week 8.

In a multicenter, randomized, open-label, active-control, parallel group study in China of Exforge compared with nifedipine gastrointestinal therapeutic system (GITS), with 564 hypertensive patients including 9.2% (Exforge arm) and 9.7% (nifedipine GITS arm) of patients with diabetes, Exforge resulted in 5.8 and 4.0 mmHg greater mean reductions in MSSBP and MSDBP (p <0.0001) compared with nifedipine GITS (mean reductions of 16.6 and 8.6 mmHg with Exforge vs. 10.8 and 4.6 mmHg with nifedipine GITS) after 12 weeks of treatment. The percentage of patients achieving the BP

target (<140/90 or <130/80 mmHg in the absence or presence of diabetes mellitus, respectively) was significantly higher with Exforge (79.0%) vs. nifedipine GITS (57.4%; p<0.0001).

In a multicenter, open-label, prospective, observational study in Taiwan, with 1,029 enrolled hypertensive patients including 39.8% with diabetes, Exforge (administered alone or as add-on therapy) resulted in mean reductions of 12.5 and 6.5 mmHg in MSSBP and MSDBP, respectively, after 12 weeks of treatment. Overall, 48.3% patients receiving Exforge achieved the desired therapeutic BP goal.

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.

NON-CLINICAL SAFETY DATA

Amlodipine:Valsartan

In a variety of preclinical safety studies conducted in several animal species with amlodipine:valsartan, there were no findings that would exclude the use of therapeutic doses of amlodipine: valsartan in humans. Animal studies lasting 13 weeks have been conducted with amlodipine:valsartan combination in rats and marmosets, as well as studies in rats to investigate embryofetal development toxicity.

In a 13-week oral toxicity study in rats, amlodipine/valsartan-related inflammation of the glandular stomach was observed in males at doses ≥3/48 mg/kg/day and in female at doses ≥7.5 /120mg/kg/day. No such effects have been observed in the 13-week marmoset study at any dose, although inflammation of the large intestine was observed in the high-dose marmosets only (no effects at dose ≤5/80 mg/kg/day). The gastrointestinal adverse effects observed in clinical trials with Exforge were no more frequent with the combination than with the respective monotherapies.

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

Amlodipine

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

There was no effect on the fertility of rats treated with amlodipine (males for 64 days and females 14 days prior to mating) at doses up to 10 mg/kg/day (8 times the maximum recommended human dose of 10 mg on a mg/m^2 basis, based on patient weight of 50 kg).

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

Valsartan

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

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

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

Reproductive toxicity: In a rat fertility study, Valsartan had no adverse effects on the reproductive performance of male or female rats at oral doses up to 200 mg/kg/day, 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).

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

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

PHARMACEUTICAL INFORMATION

Incompatibilities

Not applicable.

Special precautions for storage

Do not store above 30°C.

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

Information might differ in some countries.

Keep out of the reach and sight of children.

Instructions for use and handling

No special requirements.

Pack size

Box of 14 tablets and 28 tablets

Manufacturer

See folding box.

Country Specific Package Leaflet

Information issued: September 2018.SIN

® = registered trademark

Novartis Pharma AG, Basel, Switzerland