For the use of a Registered Medical Practitioner only

PRESCRIBING INFORMATION

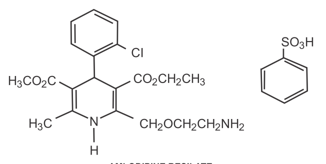
Carvals-AM Tablets
5/80 mg, 5/160 mg, 10/160 mg

Amlodipine Besilate and Valsartan Tablets

WARNING: FETAL TOXICITY [1, 2]
When pregnancy is detected, discontinue Carvals-AM Tablets as soon as possible (see WARNINGS AND PRECAUTIONS). Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus (see WARNINGS AND PRECAUTIONS).
The use of Angiotensin II Receptor Antagonists (AIIRAs) is not recommended during the first trimester of pregnancy (see WARNINGS AND PRECAUTIONS). The use of AIIRAs is contraindicated during the second and third trimesters of pregnancy (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS

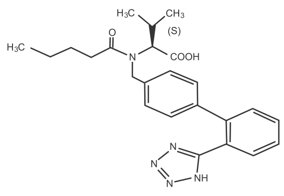
COMPOSITION
Carvals-AM Tablets 5/80, 5/160, 10/160 mg
For 5/80 mg Strength:
Each film coated tablet contains
Amlodipine Besilate Ph. Eur.
equivalent to Amlodipine ....5 mg
Valsartan Ph. Eur...80 mg
For 5/160 mg Strength:
Each film coated tablet contains
Amlodipine Besilate Ph. Eur.
equivalent to Amlodipine ....5 mg
Valsartan Ph. Eur...160 mg
For 10/160 mg Strength:
Each film coated tablet contains
Amlodipine Besilate Ph. Eur.
equivalent to Amlodipine ....10 mg
Valsartan Ph. Eur...160 mg
Inactive ingredients: Cellulose microcrystalline (Avicel PH 101), crospovidone, colloidal anhydrous Silica, Magnesium stearate, starch pregelatinized, cellulose microcrystalline (Avicel PH 102), Talc, Opadry 03G52389 Yellow, Opadry 03G54386 Pink, purified water.

DESCRIPTION [1]
Carvals-AM Tablet is a fixed combination of amlodipine and valsartan.
Fixed dose combination of amlodipine and valsartan contain the besylate salt of amlodipine, a dihydropyridine calcium-channel blocker (CCB). Amlodipine besylate's chemical name is 3-Ethyl 5-methyl (4RS)-2-[(2-aminoethoxy)methyl]-4-(2chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate benzenesulphonate. Its empirical formula is $C_{20}H_{25}ClN_2O_5C_6H_6O_3S$ and its molecular weight is 567.1. Its structural formula is:



AMLODIPINE BESILATE STRUCTURAL FORMULA

Valsartan is a nonpeptide, orally active and specific angiotensin II antagonist acting on the AT1 receptor subtype. Valsartan's chemical name is (2S)-3-Methyl-2-[pentanoyl[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]amino]butanoic acid. Its empirical formula is $C_{24}H_{29}N_5O_3$ and its molecular weight is 435.5. Its structural formula is:



VALSARTAN STRUCTURAL FORMULA

INDICATIONS [2]
Carvals-AM Tablet is indicated for the treatment of hypertension, to lower blood pressure in patients:
- whose blood pressure is not adequately controlled on monotherapy.
- whose blood pressure goals require initial therapy with multiple agents.

DOSE AND METHOD OF ADMINISTRATION [2]
The recommended dose of **Carvals-AM Tablets** is one tablet per day.
The dosage can be increased after 1 to 2 weeks of therapy to a maximum of one 10/320mg tablet once daily as needed to control blood pressure. The majority of the antihypertensive effect is attained within 2 weeks after initiation of therapy or a change in dose.
Fixed dose combination of amlodipine and valsartan 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 fixed dose combination of amlodipine and valsartan containing the same component doses.
Renal impairment
Carvals-AM Tablet is contraindicated in patients with severe renal impairment (see **CONTRAINDICATIONS**).
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
Carvals-AM Tablet is contraindicated in patients with severe hepatic impairment (see **CONTRAINDICATIONS**).
Caution should be exercised when administering fixed dose combination of amlodipine and valsartan to patients with hepatic impairment or biliary obstructive disorders (see section **WARNINGS AND PRECAUTIONS**). In patients with mild to moderate hepatic impairment without cholestasis, the maximum recommended dose is 80 mg valsartan. Amlodipine dosage recommendations have not been established in patients with mild to moderate hepatic impairment.
Elderly (age 65 years or over)
In elderly patients, caution is required when increasing the dosage.
Paediatric population
The safety and efficacy of **Carvals-AM Tablet** in children aged below 18 years have not been established. No data are available.
Method of administration
Oral use.
It is recommended to take **Carvals-AM Tablet** with some water.

USE IN SPECIAL POPULATIONS [1,2]
- **Pregnancy**

USFDA Pregnancy Category D
Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. When pregnancy is detected, discontinue fixed dose combination of amlodipine and valsartan as soon as possible. These adverse outcomes are usually associated with use of these drugs in the second and third trimester of pregnancy. Most epidemiologic studies examining fetal abnormalities after exposure to antihypertensive use in the first trimester have not distinguished drugs affecting the renin-angiotensin system from other antihypertensive agents. Appropriate management of maternal hypertension during pregnancy is important to optimize outcomes for both mother and fetus.
In the unusual case that there is no appropriate alternative to therapy with drugs affecting the renin-angiotensin system for a particular patient, apprise the mother of the potential risk to the fetus. Perform serial ultrasound examinations to assess the intra-amniotic environment. If oligohydramnios is observed, discontinue fixed dose combination of amlodipine and valsartan, unless it is considered lifesaving for the mother. Fetal testing may be appropriate, based on the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury. Closely observe infants with histories of *in utero* exposure to fixed dose combination of amlodipine and valsartan for hypotension, oliguria, and hyperkalemia
Amlodipine: The safety of amlodipine in human pregnancy has not been established. In animal studies, reproductive toxicity was observed at high doses. Use in pregnancy is only recommended when there is no safer alternative and when the disease itself carries greater risk for the mother and fetus.
Valsartan: 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 anti-hypertensive 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, and hyperkalaemia) (see **PHARMACODYNAMIC AND PHARMACOKINETIC PROPERTIES**).
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 **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS**).
Labor and Delivery
The effect of fixed dose combination of amlodipine and valsartan on labor and delivery has not been studied.
Fertility
There are no clinical studies on fertility with fixed dose combination of amlodipine and valsartan.
Amlodipine: Reversible biochemical changes in the head of spermatozoa have been reported in some patients treated by calcium channel blockers. Reported clinical data are insufficient regarding the potential effect of amlodipine on fertility. In one rat study, adverse effects were found on male fertility.
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/m^2 basis (calculations assume an oral dose of 320 mg/day and a 60-kg patient).
- **Lactation**

Because no information is available regarding the use of fixed dose combination of amlodipine and valsartan during breastfeeding, therefore, fixed dose combination of amlodipine and valsartan is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.
Amlodipine: It is not known whether amlodipine is excreted in human milk. In the absence of this information, it is recommended that nursing be discontinued while amlodipine is administered.
Valsartan: It is not known whether valsartan is excreted in human milk. Valsartan was excreted into the milk of lactating rats; however, animal breast milk drug levels may not accurately reflect human breast milk levels.
- **Pediatric**

Safety and effectiveness of fixed dose combination of amlodipine and valsartan in pediatric patients have not been established.
Neonates with a history of *in utero* exposure to fixed dose combination of amlodipine and valsartan:
If oliguria or hypotension occurs, direct attention toward support of blood pressure and renal perfusion. Exchange transfusions or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal function.
- **Geriatric**

In reported controlled clinical trials, 323 (22.5%) hypertensive patients treated with fixed dose combination of amlodipine and valsartan were ≥ 65 years and 79 (5.5%) were ≥ 75 years. No overall differences in the efficacy or safety of fixed dose combination of amlodipine and valsartan was observed in this patient population, but greater sensitivity of some older individuals cannot be ruled out.
Amlodipine: Reported clinical studies of amlodipine besylate tablets did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy. Elderly patients have decreased clearance of amlodipine with a resulting increase of AUC of approximately 40-60%, and a lower initial dose may be required.
Valsartan: In the reported controlled clinical trials of valsartan, 1214 (36.2%) of hypertensive patients treated with valsartan were ≥65 years and 265 (7.9%) were ≥75 years. No overall difference in the efficacy or safety of valsartan was observed in this patient population, but greater sensitivity of some older individuals cannot be ruled out.
- **Renal Impairment**

Safety and effectiveness of fixed dose combination of amlodipine and valsartan in patients with severe renal impairment (Cl_{Cr}< 30 mL/min) have not been established. No dose adjustment is required in patients with mild (60-90 mL/min) or moderate (Cl_{Cr} 30-60) renal impairment.
- **Hepatic Impairment**

Amlodipine: Exposure to amlodipine is increased in patients with hepatic insufficiency, thus consider using lower doses of fixed dose combination of amlodipine and valsartan (see **PHARMACOLOGICAL PROPERTIES**).
Valsartan: No dose adjustment is necessary for patients with mild-to-moderate disease. No dosing recommendations can be provided for patients with severe liver disease.

CONTRAINDICATIONS [1, 2]
Carvals-AM Tablet is contraindicated in the following conditions:
- Hypersensitivity to the active substances, 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.
- Second and third trimesters of pregnancy (see sections **WARNINGS AND PRECAUTIONS** and **USE IN SPECIAL POPULATIONS**).
- Severe hypotension.
- Shock (including cardiogenic shock).
- Obstruction of the outflow tract of the left ventricle (e.g. hypertrophic obstructive cardiomyopathy and high grade aortic stenosis).
- Haemodynamically unstable heart failure after acute myocardial infarction.

Do not co-administer aliskiren with **Carvals-AM Tablet** in patients with diabetes (see **DRUG INTERACTIONS**).

WARNINGS AND PRECAUTIONS [1,2]
The safety and efficacy of amlodipine in hypertensive crisis have not been established.
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 **CONTRAINDICATIONS** and **USE IN SPECIAL POPULATIONS**).
Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. When pregnancy is detected, discontinue fixed dose combination of amlodipine and valsartan as soon as possible (see **USE IN SPECIFIC POPULATIONS**).
Sodium- and/or volume-depleted patients
Excessive hypotension was seen in 0.4% of patients with uncomplicated hypertension treated with fixed dose combination of amlodipine and valsartan in reported 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 fixed dose combination of amlodipine and valsartan or close medical supervision at the start of treatment is recommended.
If hypotension occurs with fixed dose combination of amlodipine and valsartan, 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.
Drugs that inhibit the renin-angiotensin system can cause hyperkalemia. Monitor serum electrolytes periodically.
Some patients with heart failure have developed increases in potassium with valsartan therapy. These effects are usually minor and transient, and they are more likely to occur in patients with pre-existing renal impairment. Dosage reduction and/or discontinuation of fixed dose combination of amlodipine and valsartan may be required (see **UNDESIRABLE EFFECTS**).
Renal artery stenosis
Fixed dose combination of amlodipine and valsartan should be used with caution to treat hypertension in patients with unilateral or bilateral renal artery stenosis or stenosis to a solitary kidney since blood urea and serum creatinine may increase in such patients.
Kidney transplantation
To date there is no experience of the safe use of fixed dose combination of amlodipine and valsartan in patients who have had recent kidney transplantation.
Hepatic impairment
Valsartan is mostly eliminated unchanged via the bile. The half life of amlodipine is prolonged and AUC values are higher in patients with impaired liver function; dosage recommendations have not been established. Particular caution should be exercised when administering fixed dose combination of amlodipine and valsartan 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 fixed dose combination of amlodipine and valsartan 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.
Changes in renal function including acute renal failure can be caused by drugs that inhibit the renin-angiotensin system and by diuretics. Patients whose renal function may depend in part on the activity of the rennin-angiotensin system (e.g. patients with renal artery stenosis, chronic kidney disease, severe congestive heart failure, or volume depletion) may be at particular risk of developing acute renal failure on fixed dose combination of amlodipine and valsartan. Monitor renal function periodically in these patients. Consider withholding or discontinuing therapy in patients who develop a clinically significant decrease in renal function on fixed dose combination of amlodipine and valsartan (see **DRUG INTERACTIONS**).
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.
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 medicinal products, including angiotensin-converting enzyme (ACE) inhibitors. Fixed dose combination of amlodipine and valsartan should be discontinued immediately in patients who develop angioedema and should not be re-administered.
Heart failure/post-myocardial infarction or Increased Angina
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 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. Evaluation of patients with heart failure or post-myocardial infarction should always include assessment of renal function.
Initiate therapy cautiously in patients with heart failure or recent myocardial infarction and in patients undergoing surgery or dialysis. Patients with heart failure or post-myocardial infarction patients given valsartan commonly have some reduction in blood pressure, but discontinuation of therapy because of continuing symptomatic hypotension usually is not necessary when dosing instructions are followed. In reported controlled trials in heart failure patients, the incidence of hypotension in valsartan-treated patients was 5.5% compared to 1.8% in placebo-treated patients. In the Valsartan in Acute Myocardial Infarction Trial (VALIANT), hypotension in post-myocardial infarction patients led to permanent discontinuation of therapy in 1.4% of valsartan-treated patients and 0.8% of captopril-treated patients.
In a reported 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.
Calcium channel blockers, including amlodipine, should be used with caution in patients with congestive heart failure, as they may increase the risk of future cardiovascular events and mortality.
Aortic and mitral valve stenosis
Since the vasodilation induced by amlodipine is gradual in onset, acute hypotension has rarely been reported after oral administration. As with all other vasodilators, special caution is indicated in patients suffering from mitral stenosis or significant aortic stenosis that is not high grade.
Fixed dose combination of amlodipine and valsartan has not been studied in any patient population other than hypertension
Effects on ability to drive and use machines
Patients taking fixed dose combination of amlodipine and valsartan, and driving vehicles or using machines should take into account that dizziness or weariness may occasionally occur.
Amlodipine can have mild or moderate influence on the ability to drive and use machines. If patients taking amlodipine suffer from dizziness, headache, fatigue or nausea the ability to react may be impaired.

DRUG INTERACTIONS [1,2]
Interactions common to the combination
No drug-drug interaction studies have been performed with fixed dose combination of amlodipine and valsartan and other medicinal products.
<u>*To be taken into account with concomitant use*</u>
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
<u>*Concomitant use not recommended*</u>
Grapefruit or grapefruit juice
Administration of amlodipine with grapefruit or grapefruit juice is not recommended as bioavailability may be increased in some patients, resulting in increased blood pressure lowering effects.
<u>*Caution required with concomitant use*</u>
CYP3A4 inhibitors
Concomitant use of amlodipine with strong or moderate CYP3A4 inhibitors (protease inhibitors, azole antifungals, macrolides like erythromycin or clarithromycin, verapamil or diltiazem) may give rise to significant increase in amlodipine exposure warranting dose reduction. The clinical translation of these pharmacokinetic variations may be more pronounced in the elderly. Clinical monitoring for symptoms of hypotension and edema and dose adjustment may thus be required.
CYP3A4 inducers (anticonvulsant agents [e.g. carbamazepine, phenobarbital, phenytoin, fosphenytoin, primidone], rifampicin, Hypericum perforatum)
There is no data available regarding the effect of CYP3A4 inducers on amlodipine. The concomitant use of CYP3A4 inducers (e.g. rifampicin, *Hypericum perforatum*) may give a lower plasma concentration of amlodipine. Amlodipine should be used with caution together with CYP3A4 inducers. Blood pressure should be monitored when amlodipine is co-administered with CYP3A4 inducers.
Simvastatin
Co-administration of multiple doses of 10 mg amlodipine with 80 mg simvastatin resulted in a 77% increase in exposure to simvastatin compared to simvastatin alone. It is recommended to limit the dose of simvastatin to 20 mg daily in patients on amlodipine.
Dantrolene (infusion)
In animals, lethal ventricular fibrillation and cardiovascular collapse are observed in association with hyperkalaemia after administration of verapamil and intravenous dantrolene. Due to risk of hyperkalaemia, it is recommended that the co-administration of calcium channel blockers such as amlodipine be avoided in patients susceptible to malignant hyperthermia and in the management of malignant hyperthermia.
<u>*To be taken into account with concomitant use*</u>
Others
In clinical interaction studies, amlodipine did not affect the pharmacokinetics of atorvastatin, digoxin, warfarin or ciclosporin.
Interactions linked to valsartan
No clinically significant pharmacokinetic interactions were observed when valsartan was co-administered with amlodipine, atenolol, cimetidine, digoxin, furosemide, glyburide, hydrochlorothiazide, or indomethacin. The valsartan-atenolol combination was more antihypertensive than either component, but it did not lower the heart rate more than atenolol alone.
<u>*Concomitant use not recommended*</u>
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.
Potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium and other substances that may increase potassium levels
Concomitant use of valsartan with other agents that block the renin-angiotensin system, potassium sparing diuretics (e.g., spironolactone, triamterene, amiloride), potassium supplements, or salt substitutes containing potassium may lead to increases in serum potassium and in heart failure patients to increases in serum creatinine. If a medicinal product that affects potassium levels is to be prescribed in combination with valsartan, monitoring of potassium plasma levels is advised.
<u>*Caution required with concomitant use*</u>
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.
In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, co-administration of NSAIDs, including selective COX-2 inhibitors, with angiotensin II receptor antagonists, including valsartan, may result in deterioration of renal function, including possible acute renal failure and an increase in serum potassium. These effects are usually reversible. Therefore, monitoring of renal function at the beginning of the treatment is recommended, as well as adequate hydration of the patient.
Inhibitors of the uptake transporter (rifampicin, ciclosporin) or efflux transporter (ritonavir)
The results of an *in vitro* study with human liver tissue indicate that valsartan is a substrate of the hepatic uptake transporter OATP1B1 and of the hepatic efflux transporter MRP2. Co-administration of inhibitors of the uptake transporter (rifampicin, ciclosporin) or efflux transporter (ritonavir) may increase the systemic exposure to valsartan.
Dual Blockade of the Renin-Angiotensin System (RAS): Dual blockade of the RAS with angiotensin receptor blockers, ACE inhibitors, or aliskiren is associated with increased risks of hypotension, hyperkalemia, and changes in renal function (including acute renal failure) compared to monotherapy. Closely monitor blood pressure, renal function, and electrolytes in patients on fixed dose combination of amlodipine and valsartan and other agents that affect the RAS.
Do not co-administer aliskiren with fixed dose combination of amlodipine and valsartan in patients with diabetes. Avoid use of aliskiren with fixed dose combination of amlodipine and valsartan in patients with renal impairment (GFR <60 mL/min).
Warfarin
Co-administration of valsartan and warfarin did not change the pharmacokinetics of valsartan or the time-course of the anticoagulant properties of warfarin.
CYP 450 Interactions
In vitro metabolism studies indicate that CYP 450 mediated drug interactions between valsartan and co-administered drugs are unlikely because of low extent of metabolism.
Others
In monotherapy with valsartan, no interactions of clinical significance have been found with the following substances: cimetidine, furosemide, digoxin, atenolol, indometacin, hydrochlorothiazide, amlodipine, glibenclamide.

UNDESIRABLE EFFECTS [1,2]
Summary of the safety profile
The safety of fixed dose combination of amlodipine and valsartan 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).

MedDRA System organ class	Adverse reactions	Frequency		
		Fixed dose combination of amlodipine and valsartan	Amlodipine	Valsartan
Infections and infestations	Nasopharyngitis	Common	-	-
	Influenza	Common	-	-
Blood and lymphatic system disorders	Decrease in haemoglobin and in haematocrit	-	-	Not known
	Leukopenia	-	Very rare	-
	Neutropenia	-	-	Not known
	Thrombocytopenia, sometimes with purpura	-	Very rare	Not known
Immune system disorders	Hypersensitivity	Rare	Very rare	Not known
Metabolism and nutrition disorders	Anorexia	Uncommon	-	-
	Hypercalcaemia	Uncommon	-	-
	Hyperglycaemia	-	Very rare	-
	Hyperlipidaemia	Uncommon	-	-
	Hyperuricaemia	Uncommon	-	-
	Hypokalaemia	Common	-	-
	Hyponatraemia	Uncommon	-	-
Psychiatric disorders	Depression	-	Uncommon	-
	Anxiety	Rare	-	-
	Insomnia/sleep disturbances	-	Uncommon	-
	Mood swings	-	Uncommon	-
	Confusion	-	Rare	-
Nervous system disorders	Coordination abnormal	Uncommon	-	-
	Dizziness	Uncommon	Common	-
	Dizziness postural	Uncommon	-	-
	Dysgeusia	-	Uncommon	-
	Extrapyramidal syndrome	-	Not known	-
	Headache	Common	Common	-
	Hypertonia	-	Very rare	-
	Paraesthesia	Uncommon	Uncommon	-
	Peripheral neuropathy, neuropathy	-	Very rare	-
	Somnolence	Uncommon	Common	-
	Syncope	-	Uncommon	-
	Tremor	-	Uncommon	-
	Hypoesthesia	-	Uncommon	-
Eye disorders	Visual disturbance	Rare	Uncommon	--
	Visual impairment	Uncommon	Uncommon	-
Ear and labyrinth disorders	Tinnitus	Rare	Uncommon	-
	Vertigo	Uncommon	-	Uncommon
Cardiac disorders	Palpitations	Uncommon	Common	-
	Syncope	Rare	-	-
	Tachycardia	Uncommon	-	-
	Arrhythmias (including bradycardia, ventricular tachycardia, and atrial fibrillation)	-	Very rare	-
	Myocardial infarction	-	Very rare	-
Vascular disorders	Flushing	-	Common	-
	Hypotension	Rare	Uncommon	-
	Orthostatic hypotension	Uncommon	-	-
	Vasculitis	-	Very rare	Not known
Respiratory, thoracic and mediastinal disorders	Cough	Uncommon	Very rare	Uncommon
	Dyspnoea	-	Uncommon	-
	Pharyngolaryngeal pain	Uncommon	-	-
	Rhinitis	-	Uncommon	-
Gastrointestinal disorders	Abdominal discomfort, abdominal pain upper	Uncommon	Common	Uncommon
	Change of bowel habit	-	Uncommon	-
	Constipation	Uncommon	-	-
	Diarrhoea	Uncommon	Uncommon	-
	Dry mouth	Uncommon	Uncommon	-
	Dyspepsia	-	Uncommon	-
	Gastritis	-	Very rare	-
	Gingival hyperplasia	-	Very rare	-
	Nausea	Uncommon	Common	-
	Pancreatitis	-	Very rare	-
	Vomiting	-	Uncommon	-
Hepatobiliary disorders	Hepatic enzyme elevation, including increase of serum bilirubin	-	Very rare*	Not known
	Hepatitis	-	Very rare	-
	Intrahepatic cholestasis, jaundice	-	Very rare	-
Skin and subcutaneous tissue disorders	Alopecia	-	Uncommon	-
	Angioedema	-	Very rare	Not known
	Erythema	Uncommon	-	-
	Erythema multiforme	-	Very rare	-
	Exanthema	Rare	Uncommon	-
	Hyperhidrosis	Rare	Uncommon	-
	Photosensitivity reaction	-	Uncommon	-
	Pruritus	Rare	Uncommon	Not known
	Purpura	-	Uncommon	-
	Rash	Uncommon	Uncommon	Not known
	Skin discolouration	-	Uncommon	-
	Urticaria and other forms of rash	-	Very rare	-
	Exfoliative dermatitis	-	Very rare	-
	Stevens-Johnson syndrome	-	Very rare	-
	Quincke oedema	-	Very rare	-
Musculoskeletal and connective tissue disorders	Arthralgia	Uncommon	Uncommon	-
	Back pain	Uncommon	Uncommon	-
	Joint swelling	Uncommon	-	-
	Muscle spasm	Rare	Uncommon	-
	Myalgia	-	Uncommon	Not known
	Ankle swelling	-	Common	-
	Sensation of heaviness	Rare	-	-
Renal and urinary disorders	Elevation of serum creatinine	-	-	Not known
	Micturition disorder	-	Uncommon	-
	Nocturia	-	Uncommon	-
	Pollakiuria	Rare	Uncommon	-
	Polyuria	Rare	-	-
	Renal failure and impairment	-	-	Not known
Reproductive system and breast disorders	Impotence	-	Uncommon	--
	Erectile dysfunction	Rare	-	-
	Gynaecomastia	-	Uncommon	-
General disorders and administration site conditions	Asthenia	Common	Uncommon	-
	Discomfort, malaise	-	Uncommon	-
	Fatigue	Common	Common	Uncommon
	Facial oedema	Common	-	-
	Flushing, hot flush	Common	-	-
	Non cardiac chest pain	-	Uncommon	-
	Oedema	Common	Common	-
	Oedema peripheral	Common	-	-
	Pain	-	Uncommon	-
	Pitting oedema	Common	-	-
Investigations	Serum potassium increased	-	-	Not known
	Weight increase	-	Uncommon	-
	Weight decrease	-	Uncommon	-

* Mostly consistent with cholestasis

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 reported double-blind, controlled clinical trials, the incidence of peripheral oedema by dose was as follows:

% of patients who experienced peripheral oedema		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.

Other reported adverse effects are: Lymphadenopathy, ear pain, dyspepsia, abdominal distention, colitis, pyrexia, seasonal allergies, sinusitis, bronchitis, pharyngitis, gastroenteritis, pharyngotonsillitis, bronchitis acute, tonsillitis, epicondylitis, joint sprain, limb injury, gout, non-insulin-dependent diabetes mellitus, hypercholesterolemia, pain in extremity, osteoarthritis, musculoskeletal chest pain, sciatica, cervicobrachial syndrome, carpal tunnel syndrome, sinus headache, depression, hematuria, nephrolithiasis, sinus congestion, epistaxis, productive cough, dysphonia, nasal congestion, eczema.

Additional information on the individual components
Adverse drug reactions previously reported with one of the individual components (amlodipine or valsartan) may be potential undesirable effects with fixed dose combination of amlodipine and valsartan as well, even if not observed in clinical trials or during the post-marketing period.
<u>***Amlodipine***</u>

Common	Somnolence, dizziness, palpitations, abdominal pain, nausea, ankle swelling.
Uncommon	Insomnia, mood changes (including anxiety), depression, tremor, dysgeusia, syncope, hypoesthesia, visual disturbance (including diplopia), tinnitus, hypotension, dyspnoea, rhinitis, vomiting, dyspepsia, alopecia, purpura, skin discolouration, hyperhidrosis, pruritus, exanthema, myalgia, muscle cramps, pain, micturition disorder, increased urinary frequency, impotence, gynaecomastia, chest pain, malaise, weight increase, weight decrease.
Rare	Confusion.
Very rare	Leukocytopenia, thrombocytopenia, allergic reactions, hyperglycaemia, hypertonia, peripheral neuropathy, myocardial infarction, arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation), vasculitis, pancreatitis, gastritis, gingival hyperplasia, hepatitis, jaundice, hepatic enzymes increased*, angioedema, erythema multiforme, urticaria, exfoliative dermatitis, Stevens-Johnson syndrome, Quincke oedema, photosensitivity.

* mostly consistent with cholestasis

Exceptional cases of extrapyramidal syndrome have been reported.
Other reported adverse effects are: Othoperipheral ischemia, dysphagia, rigors, sexual dysfunction (male and female), nervousness, abnormal dreams, depersonalization, abnormal vision, conjunctivitis, eye pain, thirst, cardiac failure, pulse irregularity, extrasystoles, skin dryness, dermatitis, muscle weakness, twitching, ataxia, migraine, cold and clammy skin, apathy, agitation, amnesia, increased appetite, dysuria, parosmia, taste perversion, abnormal visual accommodation, xerophthalmia, and angina.
<u>***Valsartan***</u>

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.

Other reported adverse effects are: Sinusitis, pharyngitis, hepatitis, hyperkalemia.

Rare cases of rhabdomyolysis have been reported in patients receiving angiotensin II receptor blockers.

OVERDOSE [1,2]
Symptoms
There is no experience of overdose with fixed dose combination of amlodipine and valsartan. 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 fixed dose combination of amlodipine and valsartan 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
Information on Amlodipine
Single oral doses of amlodipine maleate equivalent to 40 mg/kg and 100 mg/kg amlodipine in mice and rats, respectively, caused deaths. Single oral doses equivalent to 4 or more mg/kg amlodipine in dogs (11 or more times the maximum recommended human dose on a mg/m^2 basis) caused a marked peripheral vasodilation and hypotension.
Overdosage might be expected to cause excessive peripheral vasodilation with marked hypotension. In humans, experience with intentional overdosage of amlodipine is limited. Marked and potentially prolonged systemic hypotension up to and including shock with fatal outcome have been reported.
If massive overdose should occur, initiate active cardiac and respiratory monitoring. Frequent blood pressure measurements are essential. Should hypotension occur, cardiovascular support including elevation of the extremities and the judicious administration of fluids should be initiated. If hypotension remains unresponsive to these conservative measures, consider administration of vasopressors (such as phenylephrine) with attention to circulating volume and urine output. As amlodipine is highly protein bound, hemodialysis is not likely to be of benefit. 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.
Information on Valsartan
Limited data are available related to overdosage in humans. The most likely effect of overdose with valsartan would be peripheral vasodilation, hypotension, and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. Depressed levels of consciousness, circulatory collapse, and shock have been reported. If symptomatic hypotension should occur, supportive treatment should be instituted.
Valsartan was without grossly observable adverse effects at single oral doses up to 2000 mg/kg in rats and up to 1000 mg/kg in marmosets, except for the salivation and diarrhea in the rat and vomiting in the marmoset at the highest dose (60 and 37 times, respectively, the maximum recommended human dose (MRHD) on a mg/m^2 basis). (Calculations assume an oral dose of 320 mg/day and a 60-kg patient.)

PHARMACODYNAMIC AND PHARMACOKINETIC PROPERTIES [1,2]
- **Mechanism of Action**

Pharmacotherapeutic group: Agents acting on the renin-angiotensin system; angiotensin II antagonists, combinations; angiotensin II antagonists and calcium channel blockers.
Fixed dose combination of amlodipine and valsartan 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
Amlodipine is a dihydropyridine calcium channel blocker that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. Experimental data suggest that amlodipine binds to both dihydropyridine and nondihydropyridine binding sites. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. Amlodipine inhibits calcium ion influx across cell membranes selectively, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells. Negative inotropic effects can be detected *in vitro* but such effects have not been seen in intact animals at therapeutic doses. Serum calcium concentration is not affected by amlodipine. Within the physiologic pH range, amlodipine is an ionized compound (pKa=8.6), and its kinetic interaction with the calcium channel receptor is characterized by a gradual rate of association and dissociation with the receptor binding site, resulting in a gradual onset of effect.
Amlodipine is a peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and reduction in blood pressure.
Valsartan
Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzyme (ACE, kininase II). Angiotensin II is the principal pressor agent of the renin-angiotensin system, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation, and renal reabsorption of sodium. Valsartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT_1 receptor in many tissues, such as vascular smooth muscle and the adrenal gland. Its action is therefore independent of the pathways for angiotensin II synthesis.
There is also an AT_2 receptor found in many tissues, but AT_2 is not known to be associated with cardiovascular homeostasis. Valsartan has much greater affinity (about 20,000-fold) for the AT_1 receptor than for the AT_2 receptor. The increased plasma levels of angiotensin following AT_1 receptor blockade with valsartan may stimulate the unblocked AT_2 receptor. The primary metabolite of valsartan is essentially inactive with an affinity for the AT_1 receptor about one-200th that of valsartan itself.
Blockade of the renin-angiotensin system with ACE inhibitors, which inhibit the biosynthesis of angiotensin II from angiotensin I, is widely used in the treatment of hypertension. ACE inhibitors also inhibit the degradation of bradykinin, a reaction also catalyzed by ACE. Because valsartan does not inhibit ACE (kininase II), it does not affect the response to bradykinin. Whether this difference has clinical relevance is not yet known. Valsartan does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.
Blockade of the angiotensin II receptor inhibits the negative regulatory feedback of angiotensin II on renin secretion, but the resulting increased plasma renin activity and angiotensin II circulating levels do not overcome the effect of valsartan on blood pressure.
- **Pharmacodynamics**

Amlodipine/Valsartan
The combination of amlodipine and valsartan produces dose-related additive reduction in blood pressure by reducing peripheral resistance, but calcium influx blockade and reduction of angiotensin II vasoconstriction are complementary mechanisms 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 fixed dose combination of amlodipine and valsartan once daily in two reported 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 reported 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 reported 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.
Fixed dose combination of amlodipine and valsartan was also studied in a reported 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 Fixed dose combination of amlodipine and valsartan 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 reported long-term follow-up studies the effect of Fixed dose combination of amlodipine and valsartan was maintained for over one year. Abrupt withdrawal of Fixed dose combination of amlodipine and valsartan has not been associated with a rapid increase in blood pressure.
Age, gender, race or body mass index (≥30 kg/m2, <30 kg/m^2) did not influence the response to fixed dose combination of amlodipine and valsartan.
Fixed dose combination of amlodipine and valsartan 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 fixed dose combination of amlodipine and valsartan 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.
Use in patients with hypertension
A reported randomised double-blind morbidity-mortality study called the Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT) was performed to compare newer therapies: amlodipine 2.5-10 mg/day (calcium channel blocker) or lisinopril 10-40 mg/day (ACE-inhibitor) as first-line therapies to that of the thiazide-diuretic, chlorthalidone 12.5-25 mg/day in mild to moderate hypertension.
A total of 33,357 hypertensive patients aged 55 or older were randomised and followed for a mean of 4.9 years. The patients had at least one additional coronary heart disease risk factor, including: previous myocardial infarction or stroke (>6 months prior to enrollment) or documentation of other atherosclerotic cardiovascular disease (overall 51.5%), type 2 diabetes (36.1%), high density lipoprotein - cholesterol <35 mg/dl or <0.906 mmol/l (11.6%), left ventricular hypertrophy diagnosed by electrocardiogram or echocardiography (20.9%), current cigarette smoking (21.9%).
The primary endpoint was a composite of fatal coronary heart disease or non-fatal myocardial infarction. There was no significant difference in the primary endpoint between amlodipine-based therapy and chlorthalidone-based therapy: risk ratio (RR) 0.98 95% CI (0.90-1.07) p=0.65. Among secondary endpoints, the incidence of heart failure (component of a composite combined cardiovascular endpoint) was significantly higher in the amlodipine group as compared to the chlorthalidone group (10.2% versus 7.7%, RR 1.38, 95% CI [1.25-1.52] p<0.001). However, there was no significant difference in all-cause mortality between amlodipine-based therapy and chlorthalidone-based therapy RR 0.96 95% CI [0.89-1.02] p=0.20.
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.
- **Pharmacokinetics**

Linearity
Amlodipine and valsartan exhibit linear pharmacokinetics.
Amlodipine/Valsartan
Following oral administration of fixed dose combination of amlodipine and valsartan, peak plasma concentrations of valsartan and amlodipine are reached in 3 and 6–8 hours, respectively. The rate and extent of absorption of fixed dose combination of amlodipine and valsartan are equivalent to the bioavailability of valsartan and amlodipine when administered as individual tablets. The bioavailabilities of amlodipine and valsartan are not altered by the co-administration of food.
Amlodipine
Absorption
After oral administration of therapeutic doses of amlodipine alone, peak plasma concentrations of amlodipine are reached in 6–12 hours. Absolute bioavailability has been calculated as between 64% and 80%. Amlodipine bioavailability is unaffected by food ingestion.
Distribution
Volume of distribution is approximately 21 l/kg. *In vitro* studies with amlodipine have shown that approximately 97.5% of circulating drug is bound to plasma proteins.
Biotransformation:
Amlodipine is extensively (approximately 90%) 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 (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 shows multiexponential decay kinetics ($t_{½α}$ <1 h and $t_{½β}$ 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.
Special populations
Paediatric population (age below 18 years)
No pharmacokinetic data are available in the paediatric population.
Gender
Studies with Valsartan: Pharmacokinetics of valsartan does not differ significantly between males and females.
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. Consequently, dose adjustment is not required in patients with mild-to-moderate renal dysfunction. No studies have been performed in patients with severe impairment of renal function (creatinine clearance <10 mL/min). Valsartan is not removed from the plasma by hemodialysis. In the case of severe renal disease, exercise care with dosing of valsartan.
Hepatic impairment
Very limited clinical data are available regarding amlodipine administration in patients with hepatic impairment. Patients with hepatic impairment 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 **DOSE AND METHOD OF ADMINISTRATION**).
Drug Interactions
In vitro data in human plasma indicate that amlodipine has no effect on the protein binding of digoxin, phenytoin, warfarin and indomethacin.
Cimetidine: Co-administration of amlodipine with cimetidine did not alter the pharmacokinetics of amlodipine.
Grapefruit juice: 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.
Maalox® (antacid): Co-administration of the antacid Maalox with a single dose of amlodipine had no significant effect on the pharmacokinetics of amlodipine.
Sildenafil: A single 100 mg dose of sildenafil (Viagra®**) in subjects with essential hypertension had no effect on the pharmacokinetic parameters of amlodipine. When amlodipine and sildenafil were used in combination, each agent independently exerted its own blood pressure lowering effect.
Atorvastatin: Co-administration of multiple 10 mg doses of amlodipine with 80 mg of atorvastatin resulted in no significant change in the steady state pharmacokinetic parameters of atorvastatin.
Digoxin: Co-administration of amlodipine with digoxin did not change serum digoxin levels or digoxin renal clearance in normal volunteers.
Warfarin: Co-administration of amlodipine with warfarin did not change the warfarin prothrombin response time.
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. Limit the dose of simvastatin in patients on amlodipine to 20 mg daily.
CYP3A4 Inhibitors: Co-administration of a 180 mg daily dose of diltiazem with 5 mg amlodipine in elderly hypertensives patients resulted in a 60% increase in amlodipine systemic exposure. Erythromycin coadministration in healthy volunteers did not significantly change amlodipine systemic exposure. However, strong inhbitors of CYP3A4 (i.e., ketoconazole, itraconazole, ritonavir) may increase the plasma concentrations of amlodipine to a greater extent.

PRECLINICAL SAFETY [2]
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/m^2 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/m^2 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/m^2 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/m^2 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.

STORAGE AND HANDLING INSTRUCTIONS
Store below 30 ºC, protected from moisture.

Keep out of the reach of children

SUPPLY
Each carton contains 28 tablets packed in blister packs of 4x7 tablets.

Not all strengths mentioned in the Prescribing Information might be marketed.

REFERENCES
1. US Prescribing information of **Exforge**® (amlodipine and valsartan) Tablets Novartis Pharmaceuticals Corporation, USA; revised in November 2012.
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