ARBITEN® AM | Amlodipine + Valsartan

Composition

Arbiten AM 5 mg/80 mg : Film-coated caplets containing 5 mg amlodipine and 80 mg valsartan
Arbiten AM 5 mg/160 mg : Film-coated caplets containing 5 mg amlodipine and 160 mg valsartan
Arbiten AM 10 mg/160mg: Film-coated caplets containing 10 mg amlodipine and 160 mg valsartan

Indications / Potential uses

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

Dosage and Administration

Patients whose blood pressure is not adequately controlled by monotherapy may be switched to combination therapy of amlodipine and valsartan.
The recommended dose is one caplets per day (5 mg amlodipine and 80 mg valsartan, 5 mg amlodipine and 160 mg valsartan, or 10 mg amlodipine and 160 mg valsartan). When clinically appropriate, a direct switch from monotherapy to the fixed-dose combination may be considered. See Warnings and Precautions with regard to withdrawal of beta-blockers.
Patients receiving valsartan and amlodipine separately may be switched to the corresponding dose of **Arbiten AM**
Both amlodipine and valsartan monotherapy can be taken with or without food. It is recommended to take **Arbiten AM** with some water.

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

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

Renal and hepatic impairment
No dosage adjustment is required in patients with mild to moderate renal impairment. Caution is required if severe renal impairment occurs (see Contraindications). Caution is also required when administering Amlodipine/Valsartan combination to patients with hepatic impairment or biliary obstructive disorders (see Warnings and Precautions).

Contraindications

Hypersensitivity to either of the active substances.
Pregnancy, lactation (see Pregnancy and Lactation).
There are no data on patients with severe renal impairment (creatinine clearance <10 ml/minute). Amlodipine/Valsartan combination is contraindicated in patients with hereditary angioedema or in those in whom angioedema developed during earlier treatment with an ACE inhibitor or an angiotensin II receptor antagonist.

Warnings and Precautions

Sodium-and /or volume-depleted patients
Excessive hypotension was seen in 0.4% of patients with uncomplicated hypertension treated with Amlodipine/Valsartan combination in placebo-controlled studies. Symptomatic hypotension may occur in patients with an activated renin-angiotensin system (such as volume- and/or salt- depleted patients receiving high doses of diuretics) who are given angiotensin II antagonists. Correction of this condition prior to administration of Amlodipine/Valsartan combination, or close medical supervision at the start of treatment, is recommended.
If hypotension occurs with Amlodipine/Valsartan combination, 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.

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.

Beta-blocker withdrawal
Amlodipine is not a beta-blocker and therefore provides no protection against the risks of abrupt beta-blocker withdrawal. Any such withdrawal should be by gradual reduction of the dose of the beta-blocker.

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

Kidney transplantation
No data are currently available on the safe use of Amlodipine/Valsartan combination in patients who have recently undergone kidney transplantation.

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

Renal impairment
No dosage adjustment of Amlodipine/Valsartan combination is required in patients with mild to moderate renal impairment. However, no data are available on severe renal impairment (creatinine clearance <10 ml/minute) and caution is therefore required.

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

Interactions

Amlodipine
Amlodipine may be concomitantly administered with thiazide diuretics, alpha-blockers, beta-blockers, ACE inhibitors, long action nitrates, sublingual glyceryl trinitrate (nitroglycerin), NSAIDs, antibiotics and oral antidiabetics.
Calcium channel blockers may interfere with the cytochrome P450- dependent metabolism of theophylline and ergotamine. Neither in vitro nor in vivo interaction studies are thus far available for amlodipine in combination with theophylline or ergotamine, and regular monitoring of theophylline or ergotamine blood levels is therefore recommended at the start of concomitant administration with amlodipine.
In vitro studies with human plasma show that amlodipine does not affect the protein binding of digoxin, phenytoin, coumarin, warfarin or indomethacin.

Special studies: Effects or other active substances on amlodipine
Cimetidine: concomitant administration of amlodipine and cimetidine does not alter the pharmacokinetics of amlodipine.
Grapefruit juice: studies in 20 healthy volunteers have shown that concomitant administration of 240 ml grapefruit juice and a single dose of amlodipine (5 mg or 10 mg) results in a slight increase in the Cmax and AUC of amlodipine.
Aluminium/magnesium (antacids): concomitant administration of aluminium/magnesium antacids and a single dose of amlodipine had no significant effect on the pharmacokinetics of amlodipine.
Sildenafil: In patients with essential hypertension, a single dose of sildenafil (100 mg) had no effect on the pharmacokinetic parameters of amlodipine. When amlodipine and sildenafil were co-administrated, each active substance independently exerted its own antihypertensive effect.

Special studies: Effects of amlodipine on other active substances
Atorvastatin: concomitant administration of several doses of amlodipine (10 mg) with atorvastatin (80 mg) did not result in any significant changes in the steady-state pharmacokinetic parameters of atorvastatin.
Digoxin: studies in healthy volunteers have shown that concomitant administration of amlodipine and digoxin does not result in any changes in digoxin plasma levels or renal digoxin clearance.
Ethanol (alcohol): single and multiple doses of amlodipine (10 mg) had no significant effect on the pharmacokinetics of ethanol.
Warfarin: concomitant administration of amlodipine did not significantly alter the effect of warfarin on prothrombin time in healthy male volunteers.
Ciclosporin: pharmacokinetic studies with ciclosporin have shown that amlodipine does not significantly alter the pharmacokinetics of ciclosporin.

Valsartan
No clinically relevant interactions with the following substances have been found: cimetidine, warfarin, furosemide, digoxin, atenolol, indomethacin, hydrochlorothiazide, amlodipine and glibenclamide.
Valsartan is only metabolized to a slight extent, so no clinically relevant drug interactions - in the form of metabolic induction or inhibition of the cytochrome P450 system - are to be expected. Although valsartan is extensively bound to plasma proteins, in vitro studies have not shown any interaction at this level with a range of other substances that are extensively bound to plasma proteins (e.g. diclofenac, furosemide and warfrain).
There is no experience with concomitant use of valsartan and lithium. Regular monitoring of serum lithium levels is therefore recommended in the event of concomitant administration of lithium and valsartan.
Concomitant administration of potassium-sparing diuretics (e.g. spironolactone, triamterene, amiloride), potassium supplements or salt substitutes containing potassium may lead to increase in serum potassium and, in heart failure patients, to increase in serum creatinine. Caution is therefore indicated when such co-medication is given.

Pregnancy and Lactation

Pregnancy
Due to the mechanism of action of angiotensin II antagonists, a risk to the fetus cannot be ruled out. Fetal injury and death have been reported during the second and third trimesters in pregnant women using ACE inhibitors (a specific class of drugs that acts on the renin-angiotensin-aldosterone system [RAAS]). 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 renal dysfunction in neonates when pregnant women have inadvertently taken valsartan. As with any substances that act directly on the RAAS, Amlodipine/Valsartan combination must not be used during pregnancy or in women planning to become pregnant (see Contraindications). Healthcare professionals prescribing any medical products that act on the RAAS should inform women of childbearing potential about the potential risk of these products during pregnancy. Amlodipine/Valsartan combination must be discontinued immediately if pregnancy is confirmed during therapy.

Lactation
It is not known whether valsartan and/or amlodipine are excreted in human milk. Valsartan was excreted in the milk of lactating rats. Use is therefore contraindicated in women who are breast feeding.

Effects on ability to drive and use machines

Due to possible adverse effects, caution is required when using machines or driving.

Adverse effects

The safety of Amlodipine/Valsartan combination has been evaluated in five controlled studies in 5175 patients, 2613 of whom received valsartan in combination with amlodipine.

Adverse effects are listed according to their frequency
Frequency
Very common (>1/10), common (>1/100 to<1/10), uncommon (>1/1000 to<1/100), rare (>1/10000 to <1/1000), very rare (<1/10000).
Within each frequency grouping, adverse effects are listed in the order of decreasing severity.
Infections: Common: Nasopharyngitis, influenza.
Immune system disorders: Rare: Hypersensitivity.
Psychiatric disorders: Rare: Anxiety states.
Nervous system disorders: Common: Headache. Uncommon: Dizziness, drowsiness, postural dizziness, paraesthesia.
Eye disorders: Rare: Disturbed vision.
Ear and inner ear: Uncommon: Vertigo. Rare: Tinnitus.
Cardiac disorders: Uncommon: Tachycardia, palpitations. Rare: Syncope.
Vascular disorders: Uncommon: Orthostatic hypotension. Rare: Hypotension.
Respiratory tract: Uncommon: Cough, laryngeal pain.
Gastrointestinal disorders: Uncommon: Diarrhoea, nausea, abdominal pain, constipation, dry mouth.
Skin: Uncommon: Rash, erythema. Rare: Hyperhidrosis, exanthema, pruritus.
Musculoskeletal system: Uncommon: Joint swelling, back pain, arthralgia. Rare: Muscle spasm, sensation of heaviness.
Renal and urinary disorders: Rare: Pollakiuria, polyuria.
Reproductive system and breast disorders: Rare: Erectile dysfunction.
General disorders: Common: Oedema, pitting oedema, facial oedema, peripheral oedema, fatigue, flushing, asthenia, hot flushes.
Additional information on combination therapy
In double-blind, active-or placebo-controlled completed studies, the incidence of peripheral oedema was statistically lower in patients treated with the combination (5.8%) than in patients treated with amlodipine monotherapy (9%).
Laboratory data
Very few hypertensive patients treated with valsartan/ amlodipine showed notable changes from baseline in laboratory test results. There was a slight higher incidence of elevated blood urea nitrogen (BUN) in the amlodipine/valsartan (5.5%) and valsartan monotherapy (5.5%) groups than in the placebo group (4.5%).
Additional information on the individual components
An adverse effect caused by one of the two components may occur with Amlodipine/Valsartan combination even if it has not been observed in clinical trials.

Amlodipine
Other adverse effects that occurred during amlodipine monotherapy, irrespective of their causal association with the study medication, were as follows:
Adverse effects that were uncommon, or rarely reported, were insomnia, mood disorder, mood changes, tremor, dysgeusia, syncope, hypoaesthesia, dyspnoea, rhinitis,vomiting, dyspepsia, altered bowel habits, dry mouth, alopecia, purpura, skin discoloration, increased sweating, rash, photosensitization, myalgia, disturbances of micturition, nocturia, increased urinary frequency, impotence, gynaecomastia, asthenia, pain, malaise, weight gain, weight loss.
Adverse effects that were very rarely reported were leucopenia, thrombocytopenia, allergic reactions, hyperglycaemia, peripheral neuropathy, vasculities, pancreatitis, gastritis, gingival hyperplasia, hepatitis, jaundice, elevated liver enzyme counts (usually consistent with cholestasis), vascular oedema, erythema multiforme, urticaria, muscle stiffness or muscle tension.
In a long-term, placebo-controlled study of amlodipine (PRAISE-2) in patients with NYHA class III and IV heart failure of non-ischaemic etiology, amlodipine was associated with increased pulmonary oedema despite the absence of any significant difference in the incidence of worsening heart failure as compared with placebo.

Valsartan
Other additional adverse effects that occurred in clinical studies with valsartan monotherapy in the indication hypertension, irrespective of their causal association with the study medication, were as follows:
Adverse effects that were frequently reported were viral infections, elevated blood levels of creatinine and urea.
Adverse effects that were uncommon, or rarely reported, were upper respiratory tract infections, impaired renal function, fatigue. Adverse effects that were very rarely reported were neutropenia, thrombocytopenia, insomnia, reduced libido, light-headedness, arrhythmia, rhinitis, sinusitis, pharyngitis, vomiting, angioedema, vascultitis, rash, myalgia, fetal complications, elevated levels of bilirubin, reduced blood levels of haemoglobin/ haematocrit, abnormal liver function values.
In patients with heart failure, increases in creatinine of over 50% were reported in 3.9% of those treated with valsartan

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as compared with 0.9% in the placebo group. In patients with status post myocardial infarction, serum creatinine doubled in 4.2% of the patients treated with vaslartan, as compared with 3.4% of patients treated with captopril. In patients with heart failure, increases in serum potassium levels of over 20% were reported in 10% of the patients treated with valsartan, as compared with 5.1% of patients given placebo. In patients with heart failure, increases in BUN of over 50% were reported in 16.6% of the patients treated with valsartan, as compared with 6.3% of patients given placebo.

Overdose

There is no experience to date of overdose with Amlodipine/Valsartan combination. The major symptom of overdose with valsartan is probably 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. 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 Amlodipine/Valsartan combination overdose calls for active cardiovascular support, including close 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, provide 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.

Properties and Actions

ATC code: C09DB01

Amlodipine/Valsartan combination combines two antihypertensive active substances with complementary mechanisms to control blood pressure in patients with hypertension: amlodipine belongs to the calcium channel blocker 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 inhibits the transmembrane entry of calcium ions into cardiac and vascular smooth muscle cells. The mechanism of the antihypertensive action of amlodipine is due to a direct relaxant effect on vascular smooth muscle, causing reductions in peripheral vascular resistance and 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 pressure. This decrease in blood pressure is 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 a 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 healthy animals and humans, or even when co-administered with beta-blockers in 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 in patients with either hypertension or angina, no adverse effects on electrocardiographic parameters were observed.

Valsartan

Valsartan is an orally active, potent and specific angiotensin (AT) II receptor antagonist. It acts selectively on the AT_1 receptor subtype, 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 AT_2 receptor, 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 20000 times) 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 comparing valsartan 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 the ACE inhibitor (2.6% versus 7.9%). In a clinical trial involving patients with a known history of dry cough during ACE inhibitor therapy, 19.5% of those receiving valsartan and 19.0% of those receiving a thiazide diuretic experienced coughing, compared with 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 that play a role in cardiovascular regulation.

Administration of valsartan to patients with hypertension results in a drop in blood pressure without affecting heart rate.

In most patients, onset of antihypertensive activity occurs within 2 hours of administration of a single oral dose, 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 in 2-4 weeks and is sustained during long-term therapy. Abrupt withdrawal of valsartan has not been associated with rebound hypertension or other adverse clinical events.

Valsartan/ amlodipine

Over 1400 hypertensive patients received Amlodipine/Valsartan combination once daily in two placebo-controlled trails. The antihypertensive effect of a single dose of the combination persisted for 24 hours. Amlodipine/Valsartan combination was studied in 2 placebo-controlled trails in hypertensive patients with a diastolic blood pressure ≥ 95 mmHg and < 110 mmHg. In the first study (baseline blood pressure 153/99 mmHg), Amlodipine/Valsartan combination at doses of 5/80 mg, 5/160 mg and 5/320 mg reduced blood pressure by 20-23/14-16 mmHg, compared with 7/7 mmHg with placebo. In the second study (baseline blood pressure 157/99 mmHg), Amlodipine/Valsartan combination-at doses of 10/160 mg and 10/320 mg-reduced blood pressure by 28/18-19 mmHg, compared with 13/9 mmHg with placebo.

A randomized, double-blind, active-controlled, multicentre, parallel-group trial in patients not adequately controlled on 160 mg valsartan showed normalization of blood pressure (sitting diastolic blood pressure <90 mmHg at the end of the trail) in 75% of patients treated with 10mg/160 mg amlodipine/valsartan and 62% of patients treated with 5 mg/160 mg amlodipine/valsartan, compared with 53% of patients remaining on 160 mg valsartan only. The addition of 10 mg and 5 mg amlodipine produced an additional reduction in systolic /diastolic blood pressure of 6.0/4.8 mmHg and 3.9/ 2.9 mmHg, respectively, compared with patients who remained on 160 mg valsartan only.

A randomized, double-blind, active-controlled, multicentre, parallel-group trial in patients not adequately controlled on 10 mg amlodipine showed normalization of blood pressure (sitting diastolic blood pressure < 90 mmHg at the end of the trail) in 78% of patients treated with 10mg/160 mg amlodipine/valsartan, compared with 67% of patients remaining on 10 mg amlodipine only. The addition of 160 mg valsartan produced an additional reduction in systolic/diastolic blood pressure of 2.9/2.1 mmHg, compared with patients who remained on 10 mg amlodipine only. Amlodipine/Valsartan combination was also studied in an active-controlled trail involving 130 hypertensive patients with diastolic blood pressure ≥ 110 mmHg and < 120 mmHg. In this study (baseline blood pressure 171/113 mmHg), an Amlodipine/Valsartan combination regimen of 5 mg/160 mg titrated to 10 mg/160 mg reduced sitting blood pressure by 36/29 mmHg as compared with 32/28 mmHg with a regimen of 10 mg/12.5 mg lisinopril/hydrochlorothiazide titrated to 20 mg/12.5 mg. In two long-term studies, the effect of Amlodipine/Valsartan combination was maintained for over one year. In patients whose blood pressure was adequately controlled with amlodipine but who experience unacceptable oedema, Amlodipine/Valsartan combination may achieve similar blood pressure control with less oedema. The patient's age, sex and race do not influence his or her response to Amlodipine/Valsartan combination.

Pharmacokinetics

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 is between 64% and 80%. Amlodipine bioavailability is unaffected by food ingestion.

Distribution: The volume of distribution is approximately 21 liters/kg. In vitro studies with amlodipine have shown that approximately 97.5% of circulating drug is bound to plasma proteins in hypertensive patients.

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

Elimination: Amlodipine elimination from the 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. 10% of original amlodipine and 60% of amlodipine metabolites are excreted in the urine.

Valsartan

Absorption: Absorption of valsartan following oral administration is rapid, although the amount absorbed varies considerably. The mean absolute bioavailability of valsartan is 23% (range 23 ± 7). Its pharmacokinetics is linear in the dose range studied. When given once daily, valsartan shows little accumulation. Plasma concentrations were found to be similar in males and females. Ingestion with food reduces the area under the valsartan plasma concentration curve (AUC) by 48%, and Cmax by 59%. However, plasma concentrations are similar from 8 hours onwards for ingestion with or without food. The reductions in AUC and Cmax do not result in a clinically significant reduction in therapeutic effect, and valsartan can therefore be given either with or without food.

Distribution: Valsartan is extensively (94-97%) bound to serum proteins, primarily albumin. Steady state is reached within 1 week. The volume of distribution at steady state is approx.17 liters. Plasma clearance is relatively slow (about 2 liters/hour) compared with hepatic blood flow (about 30 liters/hour).

Elimination: Valsartan displays multiexponential decay kinetics (primary, alpha half-life < 1 hour; terminal, beta half-life approx. 9 hours). Approx.70% of absorbed valsartan is excreted in the faeces and 30% in the urine, mainly as unchanged compound.

Valsartan/ amlodipine

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

Pharmacokinetics in special patient populations

Children: No pharmacokinetic data are available in children.

Elderly patients: Time to peak plasma amlodipine concentrations is similar in young and elderly patients. In elderly patients, amlodipine clearance tends to decline, causing increases in AUC and elimination half-life. Systemic exposure to valsartan is slightly higher in the elderly than in the young, but this has not been shown to have any clinical significance. Since the two components are equally well tolerated in younger and elderly patients, normal dose regimens are recommended (see Dosage and Administration).

Renal impairment: The pharmacokinetics of amlodipine are not significantly affected by renal impairment. There is no apparent correlation between renal function (measured by creatinine clearance) and exposure to valsartan (measured by AUC) in patients with different degrees of renal impairment. Patients with mild to moderate renal impairment may therefore receive the usual initial dose (see dosage and Administration and Warnings and Precaution).

Caution is required if severe renal impairment occurs.

Hepatic impairment: Patients with hepatic impairment have decreased clearance of amlodipine, with a resulting increase in AUC of approximately 40-60%. On average, in patients with mild to moderate chronic liver impairment, exposure to valsartan (measured by AUC) is twice that found in healthy volunteers (matched by age, sex and weight). Caution is therefore required in patients with liver impairment (see Dosage and administration and Warnings and Precautions).

Preclinical data

Animal studies lasting 13 weeks have been conducted with the fixed combination product in rats and marmosets, and studies have been carried out in rats to investigate embryofetal toxicity. There were no toxicological findings that might be relevant to human therapeutic use.

Amlodipine

Carcinogenicity: No signs of carcinogenicity were observed in rats and mice given amlodipine for two years in feed at concentrations providing daily doses of 0.5, 1.25 and 2.5 mg/kg. The highest dose (in mice similar to, and in rats double* the maximum recommended clinical dose of 10 mg on a mg/m^2 basis) was close to the maximum tolerated dose in mice but not in rats.

Mutagenicity: Mutagenicity studies showed no substance-related effects at the gene or chromosome level.

Disturbances of fertility: There was no effects on the fertility of rats following administration of amlodipine (in males for 64 days and in females for 14 days prior to mating) at doses of up to 10 mg/kg/day (8 times* the maximum recommended human dose of 10 mg on a mg/m^2 basis).

*based on a patients weight of 50 kg.

Valsartan

In a variety of preclinical safety studies conducted in several animal species, there was no evidence of systemic or target organ toxicity, apart from fetotoxicity. Offspring of rats given 600 mg/kg during the last trimester and during lactation showed a slightly reduced survival rate and a slight developmental delay (see Pregnancy and Lactation). The main preclinical safety findings are attributed to the pharmacological action of the compound and have not been demonstrated to have any clinical significance.

There was no evidence of mutagenicity, clastogenicity or carcinogenicity.

In Active Ingredients

Microcrystalline cellulose, Povidone, Crospovidone, Sodium lauryl sulphate (SLS), Colloidal silicone dioxide, Magnesium stearate, HPMC (Hydroxy propyl methyl cellulose), Titanium dioxide, Polyethylene glycol, Arbiten AM 5/160:Yellow iron oxide & Arbiten AM 10/160:Yellow iron oxide& Red iron oxide.

Storage Conditions

Store below 30°C

Presentation

Arbiten AM 5 mg/80 mg : Each pack contains 30 film-coated caplets.
Arbiten AM 5 mg/160 mg : Each pack contains 30 film-coated caplets.
Arbiten AM 10 mg/160 mg: Each pack contains 30 film-coated caplets.

- A medicament is a product that affects your health, and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who dispensed the medicament.
- The doctor and the pharmacist are experts in medicine.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.
- Keep medicaments out of the reach of children.

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UNION OF ARAB PHARMACISTS

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