CO-EXTOR
(Amlodipine + Valsartan + Hydrochlorothiazide)

(5 mg/160 mg/12.5 mg,10 mg/160mg/12.5mg & 5 mg/160mg/25mg)

Film coated Tablet

WARNING

FETAL TOXICITY

- When pregnancy is detected, discontinue Amlodipine + Valsartan + Hydrochlorothiazide as soon as possible.
- Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus.

COMPOSITION

Each film-coated tablet contains:
Amlodipine Besylate equivalent to Amlodipine…… 5mg
Valsartan ……160mg
Hydrochlorothiazide ……12.5mg

Each film-coated tablet contains:
Amlodipine Besylate equivalent to Amlodipine……10mg
Valsartan…….. 160mg
Hydrochlorothiazide ……..12.5mg

Each film-coated tablet contains:
Amlodipine Besylate equivalent to Amlodipine…… 5mg
Valsartan……160mg
Hydrochlorothiazide……25mg

THERAPEUTIC INDICATIONS

Treatment of essential hypertension as substitution therapy in adult patients whose blood pressure is adequately controlled on the combination of amlodipine, valsartan and hydrochlorothiazide (HCT), taken either as three single-component formulations or as a dual-component and a single-component formulation.

DOSAGE AND ADMINISTRATION

The recommended dose of Co Extor (Amlodipine, Valsartan & Hydrochlorothiazide combination) is one tablet per day, to be taken preferably in the morning.
Before switching to Amlodipine, Valsartan & Hydrochlorothiazide combination patients should be controlled on stable doses of the mono components taken at the same time. The dose of Amlodipine, Valsartan & Hydrochlorothiazide combination should be based on the doses of the individual components of the combination at the time of switching. The maximum recommended dose of Amlodipine, Valsartan & Hydrochlorothiazide combination is 10 mg/320 mg/25 mg.

Special populations

Renal impairment
Due to the hydrochlorothiazide component, Amlodipine, Valsartan & Hydrochlorothiazide combination is contraindicated for use in patients with anuria and in patients with severe renal impairment (glomerular filtration rate (GFR)
No adjustment of the initial dose is required for patients with mild to moderate renal impairment.

Hepatic impairment
Due to the valsartan component, Amlodipine, Valsartan & Hydrochlorothiazide combination is contraindicated in patients with severe hepatic impairment. In patients with mild to moderate hepatic impairment without cholestasis, the maximum recommended dose is 80 mg valsartan and therefore Amlodipine, Valsartan & Hydrochlorothiazide combination is not suitable in this group of patients. Amlodipine dose recommendations have not been established in patients with mild to moderate hepatic impairment. When switching eligible hypertensive patients with hepatic impairment to Amlodipine, Valsartan & Hydrochlorothiazide combination, the lowest available dose of the amlodipine component should be used.

Heart failure and coronary artery disease
There is limited experience with the use of Amlodipine, Valsartan & Hydrochlorothiazide combination, particularly at the maximum dose, in patients with heart failure and coronary artery disease. Caution is advised in patients with heart failure and coronary artery disease, particularly at the maximum dose of Amlodipine, Valsartan & Hydrochlorothiazide combination, 10 mg/320 mg/25 mg.

Elderly (age 65 years or over)
Caution, including more frequent monitoring of blood pressure, is recommended in elderly patients, particularly at the maximum dose of Amlodipine, Valsartan & Hydrochlorothiazide combination, 10 mg/320 mg/25 mg, since available data in this patient population are limited. When switching eligible elderly hypertensive patients
to Amlodipine, Valsartan & Hydrochlorothiazide combination, the lowest available dose of the amlodipine component should be used.

Paediatric population
There is no relevant use of Amlodipine, Valsartan & Hydrochlorothiazide combination in the pediatric population (patients below age 18 years) for the indication of essential hypertension. Method of administration Oral use. Amlodipine, Valsartan & Hydrochlorothiazide combination can be taken with or without food. The tablets should be swallowed whole with some water, at the same time of the day and preferably in the morning

CONTRAINDICATIONS

 Hypersensitivity to the active substances, to other sulphonamide derivatives, to dihydropyridine derivatives, or to any of the excipients

 Second and third trimesters of pregnancy

 Hepatic impairment, biliary cirrhosis or cholestasis.

 Severe renal impairment (GFR <30 ml/min/1.73 m^2), anuria and patients undergoing dialysis.

 Concomitant use of Amlodipine, Valsartan & Hydrochlorothiazide combination with aliskiren-containing products in patients with diabetes mellitus or renal impairment (GFR <60 ml/min/1.73 m^2)

 Refractory hypokalemia, hyponatremia, hypercalcemia, and symptomatic hyperuricaemia.

 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).

 Hemodynamically unstable heart failure after acute myocardial infarction.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Fetal Toxicity

Valsartan

Amlodipine, Valsartan & Hydrochlorothiazide combination can cause fetal harm when administered to a pregnant woman. 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 Amlodipine, Valsartan & Hydrochlorothiazide combination as soon as possible

Hydrochlorothiazide

Thiazides cross the placenta, and use of thiazides during pregnancy is associated with fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions that have occurred in adults.

Hypotension in Volume- or Salt-Depleted Patients

Excessive hypotension, including orthostatic hypotension, was seen in 1.7% of patients treated with the maximum dose of Amlodipine, Valsartan & Hydrochlorothiazide combination (10/320/25 mg) compared to 1.8% of valsartan/HCTZ (320/25 mg) patients, 0.4% of amlodipine/valsartan (10/320 mg) patients, and 0.2% of HCTZ/amlodipine (25/10 mg) patients in a controlled trial in patients with moderate to severe uncomplicated hypertension. In patients with an activated renin-angiotensin system, such as volume- or salt-depleted patients receiving high doses of diuretics,

symptomatic hypotension may occur in patients receiving angiotensin receptor blockers. Correct this condition prior to administration of Amlodipine, Valsartan & Hydrochlorothiazide combination.

Amlodipine, Valsartan & Hydrochlorothiazide combination has not been studied in patients with heart failure, recent myocardial infarction, or in patients undergoing surgery or dialysis. Patients with heart failure or post-myocardial infarction who were 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 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.

Since the vasodilation induced by amlodipine is gradual in onset, acute hypotension has rarely been reported after oral administration. Do not initiate treatment with Amlodipine, Valsartan & Hydrochlorothiazide combination in patients with aortic or mitral stenosis or obstructive hypertrophic cardiomyopathy.

If excessive hypotension occurs with Amlodipine, Valsartan & Hydrochlorothiazide combination, place the patient in a supine position and, if necessary, give intravenous normal saline. A transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty once the blood pressure has stabilized.

Increased Angina and/or Myocardial Infarction

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

Impaired Renal Function

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 renin-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 Amlodipine, Valsartan & Hydrochlorothiazide combination. Monitor renal function periodically in these patients. Consider withholding or discontinuing therapy in patients who develop a clinically significant decrease in renal function on Amlodipine, Valsartan & Hydrochlorothiazide combination.

Potassium Abnormalities

In the controlled trial of Amlodipine, Valsartan & Hydrochlorothiazide combination in moderate to severe hypertensive patients, the incidence of hypokalemia (serum potassium < 3.5 mEq/L) at any time post-baseline with the maximum dose of Amlodipine, Valsartan & Hydrochlorothiazide combination (10/320/25 mg) was 10% compared to 25% with HCTZ/amlodipine (25/10 mg), 7% with valsartan/HCTZ (320/25 mg), and 3% with amlodipine/valsartan (10/320 mg). One patient (0.2%) discontinued therapy due to an adverse event of hypokalemia in each of the Amlodipine, Valsartan & Hydrochlorothiazide combination and HCTZ/amlodipine groups. The incidence of hyperkalemia (serum potassium > 5.7 mEq/L) was 0.4% with Amlodipine, Valsartan & Hydrochlorothiazide combination compared to 0.2% to 0.7% with the dual therapies.

Some patients with heart failure have developed increases in potassium on valsartan. 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 the diuretic and/or valsartan may be required.

Hydrochlorothiazide can cause hypokalemia and hyponatremia. Hypomagnesemia can result in hypokalemia which appears difficult to treat despite potassium repletion. Drugs that inhibit the renin-angiotensin system can cause hyperkalemia. Monitor serum electrolytes periodically.

If hypokalemia is accompanied by clinical signs (e.g., muscular weakness, paresis, or ECG alterations), Amlodipine, Valsartan & Hydrochlorothiazide combination should be discontinued. Correction of hypokalemia and any coexisting hypomagnesemia is recommended prior to the initiation of thiazides.

Hypersensitivity Reaction

Hypersensitivity reactions to hydrochlorothiazide may occur in patients with or without a history of allergy or bronchial asthma, but are more likely in patients with such a history.

Systemic Lupus Erythematosus

Thiazide diuretics have been reported to cause exacerbation or activation of systemic lupus erythematosus.

Lithium Interaction

Increases in serum lithium concentrations and lithium toxicity have been reported with concomitant use of valsartan or thiazide diuretics. Monitor lithium levels in patients receiving Amlodipine, Valsartan & Hydrochlorothiazide combination and lithium

Metabolic Imbalances

Hydrochlorothiazide may alter glucose tolerance and raise serum levels of cholesterol and triglycerides.

Hydrochlorothiazide may raise the serum uric acid level due to reduced clearance of uric acid and may cause or exacerbate hyperuricemia and precipitate gout in susceptible patients.

Hydrochlorothiazide decreases urinary calcium excretion and may cause elevations of serum calcium. Monitor calcium levels in patients with hypercalcemia receiving Amlodipine, Valsartan & Hydrochlorothiazide combination.

Acute Myopia and Secondary Angle-Closure Glaucoma

Hydrochlorothiazide, a sulfonamide, can cause an idiosyncratic reaction, resulting in acute transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue hydrochlorothiazide as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy.

DRUG INTERACTIONS

No drug interaction studies have been conducted with Amlodipine, Valsartan & Hydrochlorothiazide combination and other drugs, although studies have been conducted with the individual components. A pharmacokinetic drug-drug interaction study has been conducted to address the potential for pharmacokinetic interaction between the triple combination, Amlodipine, Valsartan & Hydrochlorothiazide combination, and the corresponding 3 double combinations. No clinically relevant interaction was observed.

<u>Amlodipine</u>

Impact of Other Drugs on Amlodipine

CYP3A Inhibitors

Coadministration with CYP3A inhibitors (moderate and strong) results in increased systemic exposure to amlodipine and may require dose reduction. Monitor for symptoms of hypotension and edema when amlodipine is coadministered with CYP3A inhibitors to determine the need for dose adjustment.

CYP3A Inducers

No information is available on the quantitative effects of CYP3A inducers on amlodipine. Blood pressure should be closely monitored when amlodipine is coadministered with CYP3A inducers (e.g., rifampicin, St. John's Wort).

Sildenafil

Monitor for hypotension when sildenafil is coadministered with amlodipine.

Impact of Amlodipine on Other Drugs

Simvastatin

Coadministration of simvastatin with amlodipine increases the systemic exposure of simvastatin. Limit the dose of simvastatin in patients on amlodipine to 20 mg daily.

Immunosuppressants

Amlodipine may increase the systemic exposure of cyclosporine or tacrolimus when coadministered. Frequent monitoring of trough blood levels of cyclosporine and tacrolimus is recommended and adjust the dose when appropriate.

Valsartan

Agents Increasing Serum Potassium: Concomitant use of valsartan with other agents that block the renin-angiotensin system, potassium-sparing diuretics (e.g., spironolactone, triamterene, amiloride), potassium supplements, salt substitutes containing potassium or other drugs that may increase potassium levels (e.g., heparin) may lead to increases in serum potassium and in heart failure patients to increases in serum creatinine. If co-medication is considered necessary, monitoring of serum potassium is advisable.

Non-Steroidal Anti-Inflammatory (NSAID) Agents Including Selective Cyclooxygenase-2 Inhibitors (COX-2 Inhibitors): In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, coadministration 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. These effects are usually reversible. Monitor renal function periodically in patients receiving valsartan and NSAID therapy.

The antihypertensive effect of angiotensin II receptor antagonists, including valsartan, may be attenuated by NSAIDs including selective COX-2 inhibitors.

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. Most patients receiving the combination of two RAS inhibitors do not obtain any additional benefit compared to monotherapy. In general, avoid combined use of RAS inhibitors. Closely monitor blood pressure, renal function and electrolytes in patients on valsartan and other agents that affect the RAS.

Do not coadminister aliskiren with valsartan in patients with diabetes. Avoid use of aliskiren with valsartan in patients with renal impairment (GFR < 60 mL/min).

Valsartan – Hydrochlorothiazide

Lithium: Increases in serum lithium concentrations and lithium toxicity have been reported during concomitant administration of lithium with angiotensin II receptor antagonists or thiazides. Monitor lithium levels in patients taking Amlodipine, Valsartan & Hydrochlorothiazide combination.

Hydrochlorothiazide

When administered concurrently, the following drugs may interact with thiazide diuretics:

Antidiabetic Drugs (oral agents and insulin): Dosage adjustment of the antidiabetic drug may be required.

Non-Steroidal Anti-inflammatory Drugs (NSAIDs and COX-2 selective inhibitors): When Amlodipine, Valsartan & Hydrochlorothiazide combination and nonsteroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of diuretic is obtained.

Carbamazepine: May lead to symptomatic hyponatremia.

Ion Exchange Resins: Staggering the dosage of hydrochlorothiazide and ion exchange resins (e.g., cholestyramine, colestipol) such that hydrochlorothiazide is administered at least 4 hours before or 4 to 6 hours after the administration of resins, would potentially minimize the interaction.

Cyclosporine: Concomitant treatment with cyclosporine may increase the risk of hyperuricemia and gout-type complications.

FERTILITY, PREGNANCY AND LACTATION

Pregnancy

Amlodipine

The safety of amlodipine in human pregnancy has not been established. In animal studies, reproductive toxicity was observed at high doses. 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

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

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Whilst there is no controlled epidemiological data on the risk with Angiotensin II

Receptor Antagonists (AIIRAs), similar risks may exist for this class of drugs. Unless continued

AIIRA therapy is considered essential, patients planning pregnancy should be changed to alternative

antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with AIIRAs should be stopped immediately, and if appropriate, alternative therapy should be started.

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

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.

Hydrochlorothiazide

There is limited experience with hydrochlorothiazide during pregnancy, especially during the first trimester. Animal studies are insufficient.

Hydrochlorothiazide crosses the placenta. Based on the pharmacological mechanism of action of hydrochlorothiazide, its use during the second and third trimester may compromise foeto-placental perfusion and may cause foetal and neonatal effects like icterus, disturbance of electrolyte balance and thrombocytopenia.

Amlodipine/valsartan/hydrochlorothiazide

There is no experience on the use of Amlodipine, Valsartan & Hydrochlorothiazide combination in pregnant women. Based on the existing data with the components, the use of Amlodipine, Valsartan & Hydrochlorothiazide combination is not recommended during first trimester and contraindicated during the second and third trimester of pregnancy.

Breast-feeding

Amlodipine is excreted in human milk. The proportion of the maternal dose received by the infant has been estimated with an interquartile range of 3-7%, with a maximum of 15%. The effect of amlodipine on infants is unknown. No information is available regarding the use of valsartan during breastfeeding. Hydrochlorothiazide is excreted in human milk in small amounts. Thiazides in high doses causing intense diuresis can inhibit milk production. The use of Amlodipine, Valsartan & Hydrochlorothiazide during breast-feeding is not recommended. If Amlodipine, Valsartan & Hydrochlorothiazide is used during breast-feeding, doses should be kept as low as possible. Alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

Fertility

There are no clinical studies on fertility with Amlodipine, Valsartan & Hydrochlorothiazide.

Valsartan

Valsartan had no adverse effects on the reproductive performance of male or female rats at oral doses up to 200 mg/kg/day. This dose is 6 times the maximum recommended human dose on a mg/m2 basis (calculations assume an oral dose of 320 mg/day and a 60-kg patient).

Amlodipine

Reversible biochemical changes in the head of spermatozoa have been reported in some patients treated by calcium channel blockers. Clinical data are insufficient regarding the potential effect of amlodipine on fertility. In one rat study, adverse effects were found on male fertility

EFFECTS ON ABILITY TO DRIVE

Patients taking Amlodipine, Valsartan & Hydrochlorothiazide combination 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, Valsartan & Hydrochlorothiazide combination suffer from dizziness, headache, fatigue or nausea the ability to react may be impaired

ADVERSE DRUG REACTIONS

Clinical Trials Experience

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

In the controlled trial of Amlodipine, Valsartan & Hydrochlorothiazide combination, where only the maximum dose (10/320/25 mg) was evaluated, safety data were obtained in 582 patients with hypertension. Adverse reactions have generally been mild and transient in nature and have only infrequently required discontinuation of therapy.

The overall frequency of adverse reactions was similar between men and women, younger (< 65 years) and older (≥ 65 years) patients, and black and white patients. In the active controlled clinical trial, discontinuation because of adverse events occurred in 4.0% of patients treated with Amlodipine, Valsartan & Hydrochlorothiazide combination10/320/25 mg compared to 2.9% of patients treated with valsartan/HCTZ 320/25 mg, 1.6% of patients treated with amlodipine/valsartan 10/320 mg, and 3.4% of patients treated with HCTZ/amlodipine 25/10 mg. The most common reasons for discontinuation of therapy with Amlodipine, Valsartan & Hydrochlorothiazide combination were dizziness (1.0%) and hypotension (0.7%).

The most frequent adverse events that occurred in the active controlled clinical trial in at least 2% of patients treated with Amlodipine, Valsartan & Hydrochlorothiazide combination are presented in the following table.

Preferred Term	**Aml/Val/HCTZ 10/320/25 mg N=582 n (%)**	**Val/HCTZ 320/25 mg N=559 n (%)**	**Aml/Val 10/320 mg N=566 n (%)**	**HCTZ/Aml 25/10 mg N=561 n (%)**
Dizziness	48 (8.2)	40 (7.2)	14 (2.5)	23 (4.1)
Edema	38 (6.5)	8 (1.4)	65 (11.5)	63 (11.2)
Headache	30 (5.2)	31 (5.5)	30 (5.3)	40 (7.1)
Dyspepsia	13 (2.2)	5 (0.9)	6 (1.1)	2 (0.4)
Fatigue	13 (2.2)	15 (2.7)	12 (2.1)	8 (1.4)
Muscle spasms	13 (2.2)	7 (1.3)	7 (1.2)	5 (0.9)
Back pain	12 (2.1)	13 (2.3)	5 (0.9)	12 (2.1)
Nausea	**12 (2.1)**	**7 (1.3)**	**10 (1.8)**	**12 (2.1)**
Nasopharyngitis	**12 (2.1)**	**13 (2.3)**	**13 (2.3)**	**12 (2.1)**

Orthostatic events (orthostatic hypotension and postural dizziness) were seen in 0.5% of patients.

Valsartan

Valsartan has been evaluated for safety in more than 4000 hypertensive patients in clinical trials. In trials in which valsartan was compared to an ACE inhibitor with or without placebo, the incidence of dry cough was significantly greater in the ACE inhibitor group (7.9%) than in the groups who received valsartan (2.6%) or placebo (1.5%). In a 129-patient trial limited to patients who had dry cough when they had previously received ACE inhibitors, the incidences of cough in patients who received valsartan, HCTZ, or lisinopril were 20%, 19%, and 69%, respectively ($p < 0.001$).

Clinical Laboratory Test Findings

Clinical laboratory test findings for Amlodipine, Valsartan & Hydrochlorothiazide combination were obtained in a controlled trial of Amlodipine, Valsartan & Hydrochlorothiazide combination administered at the maximal dose of 10/320/25 mg compared to maximal doses of dual therapies, i.e., valsartan/HCTZ 320/25 mg, amlodipine/valsartan 10/320 mg, and HCTZ/amlodipine 25/10 mg. Findings for the components of Amlodipine, Valsartan & Hydrochlorothiazide combination were obtained from other trials.

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

Blood Urea Nitrogen (BUN): In hypertensive patients, greater than 50% increases in BUN were observed in 30% of Amlodipine, Valsartan & Hydrochlorothiazide combination-treated patients compared to 29% of valsartan/HCTZ patients, 15.8% of amlodipine/valsartan patients, and 18.5% of HCTZ/amlodipine patients. In heart failure patients, greater than 50% increases in BUN were observed in 17% of valsartan-treated patients compared to 6% of placebo-treated patients.

Neutropenia: Neutropenia (< 1500/L) was observed in 1.9% of patients treated with valsartan and 0.8% of patients treated with placebo.

Post marketing Experience

The following additional adverse reactions have been reported in post marketing experience. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Amlodipine

With amlodipine, gynecomastia has been reported infrequently and a causal relationship is uncertain. Jaundice and hepatic enzyme elevations (mostly consistent with cholestasis or hepatitis), in some cases severe enough to require hospitalization, have been reported in association with use of amlodipine.

Valsartan

The following additional adverse reactions have been reported in post marketing experience with valsartan or valsartan/hydrochlorothiazide:

Blood and Lymphatic: Decrease in hemoglobin, decrease in hematocrit, neutropenia

Hypersensitivity: Angioedema has been reported. Some of these patients previously experienced angioedema with other drugs, including ACE inhibitors. Amlodipine, Valsartan & Hydrochlorothiazide combination should not be re-administered to patients who have had angioedema.

Digestive: Elevated liver enzymes and reports of hepatitis

Musculoskeletal: Rhabdomyolysis

Renal: Impaired renal function, renal failure

Dermatologic: Alopecia, bullous dermatitis

Vascular: Vasculitis

Nervous System: Syncope

Hydrochlorothiazide

The following additional adverse reactions have been reported in post marketing experience with hydrochlorothiazide:

Acute renal failure, renal disorder, aplastic anemia, erythema multiforme, pyrexia, muscle spasm, asthenia, acute angle-closure glaucoma, bone marrow failure, worsening of diabetes control, hypokalemia, blood lipids increased, hyponatremia, hypomagnesemia, hypercalcemia, hypochloremic alkalosis, impotence, visual impairment.

Pathological changes in the parathyroid gland of patients with hypercalcemia and hypophosphatemia have been observed in a few patients on prolonged thiazide therapy. If hypercalcemia occurs, further diagnostic evaluation is necessary.

Non-melanoma Skin Cancer: Hydrochlorothiazide is associated with an increased risk of non-melanoma skin cancer. In a study conducted in the Sentinel System, increased risk was predominantly for squamous cell carcinoma (SCC) and in white patients taking large cumulative doses. The increased risk for SCC in the overall population was approximately 1 additional case per 16,000 patients per year, and for white patients taking a cumulative dose of ≥ 50,000 mg the risk increase was approximately 1 additional SCC case for every 6700 patients per year.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at pv@searlecompany.com

OVERDOSE

Limited data are available related to overdosage in humans. The most likely manifestations of overdosage would be hypotension and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, institute supportive treatment.

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 MRHD on a mg/m2 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, initiate cardiovascular support, including elevation of the extremities and the judicious administration of fluids. 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.

Valsartan

Depressed level of consciousness, circulatory collapse, and shock have been reported.

Valsartan is not removed from the plasma by hemodialysis.

Valsartan was without grossly observable adverse effects at single oral doses up to 2,000 mg/kg in rats and up to 1,000 mg/kg in marmosets, except for salivation and diarrhea in the rat and vomiting in the marmoset at the highest dose (60 and 31 times, respectively, the MRHD on a mg/m2 basis) (calculations assume an oral dose of 320 mg/day and a 60-kg patient).

Hydrochlorothiazide

The degree to which hydrochlorothiazide is removed by hemodialysis has not been established. The most common signs and symptoms observed in patients are those caused by electrolyte depletion (hypokalemia, hypochloremia, hyponatremia) and dehydration resulting from excessive diuresis. If digitalis has also been administered, hypokalemia may accentuate cardiac arrhythmias.

The oral LD50 of hydrochlorothiazide is greater than 10 g/kg in both mice and rats, 2000 and 4000 times, respectively, the MRHD on a mg/m2 basis (calculations assume an oral dose of 25 mg/day and a 60-kg patient).

Valsartan and Hydrochlorothiazide

In rats and marmosets, single oral doses of valsartan up to 1524 and 762 mg/kg in combination with hydrochlorothiazide at doses up to 476 and 238 mg/kg, respectively, were very well tolerated without any treatment-related effects. These no adverse effect doses in rats and marmosets, respectively, represent 46.5 and 23 times the MRHD of valsartan and 188 and 113 times the MRHD of hydrochlorothiazide on a mg/m2 basis (calculations assume an oral dose of 320 mg/day valsartan in combination with 25 mg/day hydrochlorothiazide and a 60 kg patient)

PHARMACOLOGICAL PROPERTIES

Mechanism of Action

The active ingredients of Amlodipine, Valsartan & Hydrochlorothiazide combination target 3 separate mechanisms involved in blood pressure regulation. Specifically, amlodipine blocks the contractile effects of calcium on cardiac and vascular smooth muscle cells; valsartan blocks the vasoconstriction and sodium retaining effects of angiotensin II on cardiac, vascular smooth muscle, adrenal and renal cells; and hydrochlorothiazide directly promotes the excretion of sodium and chloride in the kidney leading to reductions in intravascular volume. A more detailed description of the mechanism of action of each individual component follows.

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 AT1 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 AT2 receptor found in many tissues, but AT2 is not known to be associated with cardiovascular homeostasis. Valsartan has much greater affinity (about 20,000-fold) for the AT1 receptor than for the AT2 receptor. The increased plasma levels of angiotensin following AT1 receptor blockade with valsartan may stimulate the unblocked AT2 receptor. The primary metabolite of valsartan is essentially inactive with an affinity for the AT1 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.

Hydrochlorothiazide

Hydrochlorothiazide is a thiazide diuretic. Thiazides affect the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equivalent amounts. Indirectly, the diuretic action of hydrochlorothiazide reduces plasma volume, with consequent increases in plasma renin activity, increases in aldosterone secretion, increases in urinary potassium loss, and decreases in serum potassium. The renin-aldosterone link is mediated by angiotensin II, so coadministration of an angiotensin II receptor antagonist tends to reverse the potassium loss associated with these diuretics.

The mechanism of the antihypertensive effect of thiazides is unknown.

Pharmacodynamics

Amlodipine, Valsartan & Hydrochlorothiazide combination has been shown to be effective in lowering blood pressure. The 3 components of Amlodipine, Valsartan & Hydrochlorothiazide combination (amlodipine, valsartan, hydrochlorothiazide) lower the blood pressure through complementary mechanisms, each working at a separate site and blocking different effector pathways. The pharmacodynamics of each individual component are described below.

Amlodipine, Valsartan & Hydrochlorothiazide combination has not been studied in indications other than hypertension.

Amlodipine

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. Although the acute intravenous administration of amlodipine decreases arterial blood pressure and increases heart rate in hemodynamic studies of patients with chronic stable angina, chronic oral administration of amlodipine in clinical trials did not lead to clinically significant changes in heart rate or blood pressures in normotensive patients with angina.

With chronic, once-daily administration, antihypertensive effectiveness is maintained for at least 24 hours. Plasma concentrations correlate with effect in both young and elderly patients. The magnitude of reduction in blood pressure with amlodipine is also correlated with the height of pretreatment elevation; thus, individuals with moderate hypertension (diastolic pressure 105-114 mmHg) had about a 50% greater response than patients with mild hypertension (diastolic pressure 90-104 mmHg). Normotensive subjects experienced no clinically significant change in blood pressure (+1/-2 mmHg).

In hypertensive patients with normal renal function, therapeutic doses of amlodipine resulted in a decrease in renal vascular resistance and an increase in glomerular filtration rate and effective renal plasma flow without change in filtration fraction or proteinuria.

As with other calcium channel blockers, hemodynamic measurements of cardiac function at rest and during exercise (or pacing) in patients with normal ventricular function treated with amlodipine have generally demonstrated a small increase in cardiac index without significant influence on dP/dt or on left ventricular end diastolic pressure or volume. In hemodynamic studies, amlodipine has not been associated with a negative inotropic effect when administered in the therapeutic dose range to intact animals and man, even when coadministered with beta-blockers to man. Similar findings, however, have been observed in normal or well-compensated patients with heart failure with agents possessing significant negative inotropic effects.

Amlodipine does not change sinoatrial nodal function or atrioventricular conduction in intact animals or man. In patients with chronic stable angina, intravenous administration of 10 mg did not significantly alter A-H and H-V conduction and sinus node recovery time after pacing. Similar results were obtained in patients receiving amlodipine and concomitant beta-blockers. In clinical studies in which amlodipine was administered in combination with beta-blockers to patients with either hypertension or angina, no adverse effects of electrocardiographic (ECG) parameters were observed. In clinical trials with angina patients alone, amlodipine therapy did not alter ECG intervals or produce higher degrees of AV blocks.

Amlodipine has indications other than hypertension which are described in its full prescribing information.

Drug Interactions

Sildenafil

When amlodipine and sildenafil were used in combination, each agent independently exerted its own blood pressure lowering effect.

Valsartan

Valsartan inhibits the pressor effect of angiotensin II infusions. An oral dose of 80 mg inhibits the pressor effect by about 80% at peak with approximately 30% inhibition persisting for 24 hours. No information on the effect of larger doses is available.

Removal of the negative feedback of angiotensin II causes a 2- to 3-fold rise in plasma renin and consequent rise in angiotensin II plasma concentration in hypertensive patients. Minimal decreases in plasma aldosterone were observed after administration of valsartan; very little effect on serum potassium was observed.

Administration of valsartan to patients with essential hypertension results in a significant reduction of sitting, supine, and standing systolic blood pressure, usually with little or no orthostatic change.

Valsartan has indications other than hypertension which are described in its full prescribing information.

Hydrochlorothiazide

After oral administration of hydrochlorothiazide, diuresis begins within 2 hours, peaks in about 4 hours and lasts about 6 to 12 hours.

Pharmacokinetics

Amlodipine, Valsartan & Hydrochlorothiazide combination

Following oral administration of Amlodipine, Valsartan & Hydrochlorothiazide combination in normal healthy adults, peak plasma concentrations of amlodipine, valsartan, and HCTZ are reached in about 6 hours, 3 hours, and 2 hours, respectively. The rate and extent of absorption of amlodipine, valsartan, and HCTZ from Amlodipine, Valsartan & Hydrochlorothiazide combination are the same as when administered as individual dosage forms.

The bioavailability of amlodipine, valsartan, and HCTZ were not altered when Amlodipine, Valsartan & Hydrochlorothiazide combination was administered with food. Amlodipine, Valsartan & Hydrochlorothiazide combination may be administered with or without food.

Amlodipine

Peak plasma concentrations of amlodipine are reached 6 to 12 hours after administration of amlodipine alone. Absolute bioavailability has been estimated to be between 64% and 90%. The apparent volume of distribution of amlodipine is 21 L/kg. Approximately 93% of circulating amlodipine is bound to plasma proteins in hypertensive patients.

Amlodipine is extensively (about 90%) converted to inactive metabolites via hepatic metabolism with 10% of the parent compound and 60% of the metabolites excreted in the urine.

Elimination of amlodipine from the plasma is biphasic with a terminal elimination half-life of about 30 to 50 hours. Steady state plasma levels of amlodipine are reached after 7 to 8 days of consecutive daily dosing.

Valsartan

Following oral administration of valsartan alone, peak plasma concentrations of valsartan are reached in 2 to 4 hours. Absolute bioavailability is about 25% (range 10% to 35%).

The steady state volume of distribution of valsartan after intravenous administration is 17 L indicating that valsartan does not distribute into tissues extensively. Valsartan is highly bound to serum proteins (95%), mainly serum albumin.

Valsartan shows biexponential decay kinetics following intravenous administration with an average elimination half-life of about 6 hours. The recovery is mainly as unchanged drug, with only about 20% of dose recovered as metabolites. The primary metabolite, accounting for about 9% of dose, is valeryl 4-hydroxy valsartan. *In vitro* metabolism studies involving recombinant CYP450 enzymes indicated that the CYP2C9 isoenzyme is responsible for the formation of valeryl-4-hydroxy valsartan. Valsartan does not inhibit CYP450 isozymes at clinically relevant concentrations. CYP450 mediated drug interaction between valsartan and coadministered drugs are unlikely because of the low extent of metabolism.

Valsartan, when administered as an oral solution, is primarily recovered in feces (about 83% of dose) and urine (about 13% of dose). 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).

Hydrochlorothiazide

The estimated absolute bioavailability of hydrochlorothiazide after oral administration is about 70%. Peak plasma hydrochlorothiazide concentrations (Cmax) are reached within 2 to 5 hours after oral administration. There is no clinically significant effect of food on the bioavailability of hydrochlorothiazide.

Hydrochlorothiazide binds to albumin (40% to 70%) and distributes into erythrocytes. Following oral administration, plasma hydrochlorothiazide concentrations decline biexponentially, with a mean distribution half-life of about 2 hours and an elimination half-life of about 10 hours.

About 70% of an orally administered dose of hydrochlorothiazide is eliminated in the urine as unchanged drug.

Specific Populations

Geriatric: Elderly patients have decreased clearance of amlodipine with a resulting increase in peak plasma levels, elimination half-life, and AUC. Exposure (measured by AUC) to valsartan is higher by 70% and the half-life is longer by 35% in the elderly than in the young. Limited amount of data suggest that the systemic clearance of hydrochlorothiazide is reduced in both healthy and hypertensive elderly subjects compared to young healthy volunteers.

Gender: Pharmacokinetics of valsartan do not differ significantly between males and females.

Race: Pharmacokinetic differences due to race have not been studied.

Renal Insufficiency: The pharmacokinetics of amlodipine are not significantly influenced by renal impairment. There is no apparent correlation between renal function (measured by creatinine clearance) and exposure (measured by AUC) to valsartan in patients with different degrees of renal impairment. Valsartan has not been studied in patients with severe impairment of renal function (creatinine clearance <10 mL/min). Valsartan is not removed from the plasma by hemodialysis.

In a study in individuals with impaired renal function, the mean elimination half-life of hydrochlorothiazide was doubled in individuals with mild/moderate renal impairment (30 < CrCl < 90 mL/min) and tripled in severe renal impairment (CrCl ≤ 30 mL/min), compared to individuals with normal renal function (CrCl > 90 mL/min).

Hepatic Insufficiency: Patients with hepatic insufficiency have decreased clearance of amlodipine with resulting increase in AUC of approximately 40% to 60%. On average, patients with mild-to-moderate chronic liver disease have twice the exposure (measured by AUC values) to valsartan of healthy volunteers (matched by age, sex, and weight).

Drug Interactions

Amlodipine:

In vitro data in human plasma indicate that amlodipine has no effect on the protein binding of digoxin, phenytoin, warfarin, and indomethacin.

Impact of Other Drugs on Amlodipine

Coadministered cimetidine, magnesium-and aluminum hydroxide antacids, sildenafil, and grapefruit juice have no impact on the exposure to amlodipine.

CYP3A Inhibitors: Coadministration of a 180 mg daily dose of diltiazem with 5 mg amlodipine in elderly hypertensive patients resulted in a 60% increase in amlodipine systemic exposure. Erythromycin coadministration in healthy volunteers did not significantly change amlodipine systemic exposure. However, strong inhibitors of CYP3A (e.g., itraconazole, clarithromycin) may increase the plasma concentrations of amlodipine to a greater extent.

Impact of Amlodipine on Other Drugs

Coadministered amlodipine does not affect the exposure to atorvastatin, digoxin, ethanol and the warfarin prothrombin response time.

Simvastatin: Coadministration 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.

Cyclosporine: A prospective study in renal transplant patients (N = 11) showed on an average of 40% increase in trough cyclosporine levels when concomitantly treated with amlodipine.

Tacrolimus: A prospective study in healthy Chinese volunteers (N = 9) with CYP3A5 expressers showed a 2.5- to 4-fold increase in tacrolimus exposure when concomitantly administered with amlodipine compared to tacrolimus alone. This finding was not observed in CYP3A5 non-expressers (N = 6). However, a 3-fold increase in plasma exposure to tacrolimus in a renal transplant patient (CYP3A5 non-expresser) upon initiation of amlodipine for the treatment of post-transplant hypertension resulting in reduction of tacrolimus dose has been reported. Irrespective of the CYP3A5 genotype status, the possibility of an interaction cannot be excluded with these drugs.

Valsartan:

No clinically significant pharmacokinetic interactions were observed when Diovan (valsartan) was coadministered 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.

Coadministration of valsartan and warfarin did not change the pharmacokinetics of valsartan or the time-course of the anticoagulant properties of warfarin.

Transporters: The results from an *in vitro* study with human liver tissue indicate that valsartan is a substrate of the hepatic uptake transporter OATP1B1 and the hepatic efflux transporter MRP2. Coadministration of inhibitors of the uptake transporter (rifampin, cyclosporine) or efflux transporter (ritonavir) may increase the systemic exposure to valsartan.

Hydrochlorothiazide:

Drugs That Alter Gastrointestinal Motility: The bioavailability of thiazide-type diuretics may be increased by anticholinergic agents (e.g., atropine, biperiden), apparently due to a decrease in gastrointestinal motility and the stomach emptying rate. Conversely, pro-kinetic drugs may decrease the bioavailability of thiazide diuretics.

Cholestyramine: In a dedicated drug interaction study, administration of cholestyramine 2 hours before hydrochlorothiazide resulted in a 70% reduction in exposure to hydrochlorothiazide. Further, administration of hydrochlorothiazide 2 hours before cholestyramine resulted in 35% reduction in exposure to hydrochlorothiazide.

Antineoplastic Agents (e.g., cyclophosphamide, methotrexate): Concomitant use of thiazide diuretics may reduce renal excretion of cytotoxic agents and enhance their myelosuppressive effects.

Alcohol, Barbiturates, or Narcotics: Potentiation of orthostatic hypotension may occur.

Skeletal Muscle Relaxants: Possible increased responsiveness to muscle relaxants, such as curare derivatives.

Digitalis Glycosides: Thiazide-induced hypokalemia or hypomagnesemia may predispose the patient to digoxin toxicity.

PRECLINICAL SAFETY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies with Amlodipine/Valsartan/Hydrochlorothiazide: No carcinogenicity, mutagenicity, or fertility studies have been conducted with this combination. However, these studies have been conducted for amlodipine, valsartan, and hydrochlorothiazide alone. Based on the preclinical safety and human pharmacokinetic studies, there is no indication of any toxicologically significant adverse interaction between these components.

Studies with Amlodipine: Rats and mice treated with amlodipine maleate in the diet for up to two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 mg amlodipine/kg/day, showed no evidence of a carcinogenic effect of the drug. For the mouse, the highest dose was, on a mg/m2 basis, similar to the MRHD of 10 mg amlodipine/day. For the rat, the highest dose was, on a mg/m2 basis, about 2.5 times the MRHD (calculations based on a 60 kg patient).

Mutagenicity studies conducted with amlodipine maleate revealed no drug-related effects at either the gene or chromosome level.

There was no effect on the fertility of rats treated orally with amlodipine maleate (males for 64 days and females for 14 days prior to mating) at doses of up to 10 mg amlodipine/kg/day (about 10 times the MRHD of 10 mg/day on a mg/m2 basis).

Studies with Valsartan: There was no evidence of carcinogenicity when valsartan was administered in the diet to mice and rats for up to 2 years at concentrations calculated to provide doses of up to 160 and 200 mg/kg/day, respectively. These doses in mice and rats are about 2.4 and 6 times, respectively, the MRHD of 320 mg/day on a mg/m2 basis (calculations based on a 60 kg patient).

Mutagenicity assays did not reveal any valsartan-related effects at either the gene or chromosome level. These assays included bacterial mutagenicity tests with *Salmonella* and *E. coli*, a gene mutation test with Chinese hamster V79 cells, a cytogenetic test with Chinese hamster ovary cells, and a rat micronucleus test.

Valsartan had no adverse effects on the reproductive performance of male or female rats at oral doses of up to 200 mg/kg/day. This dose is about 6 times the MRHD on a mg/m2 basis.

Studies with Hydrochlorothiazide: Two-year feeding studies in mice and rats conducted under the auspices of the National Toxicology Program (NTP) uncovered no evidence of a carcinogenic potential of hydrochlorothiazide in female mice (at doses of up to approximately 600 mg/kg/day) or in male and female rats (at doses of up to approximately 100 mg/kg/day). The NTP, however, found equivocal evidence for hepatocarcinogenicity in male mice.

Hydrochlorothiazide was not genotoxic *in vitro* in the Ames mutagenicity assay of *Salmonella Typhimurium* strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 and in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations, or *in vivo* in assays using mouse germinal cell chromosomes, Chinese hamster bone marrow chromosomes, and the Drosophila sex-linked recessive lethal trait gene. Positive test results were obtained in the *in vitro* CHO Sister Chromatid Exchange (clastogenicity) and Mouse Lymphoma Cell (mutagenicity) assays and in the Aspergillus Nidulans non-disjunction assay.

Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed via diet at doses of up to 100 and 4 mg/kg, respectively, prior to mating and throughout gestation. These doses of hydrochlorothiazide in mice and rats are 19 and 1.5 times, respectively, the MRHD on a mg/m2 basis (calculations assume an oral dose of 25 mg/day and a 60-kg patient).

SUMMARY OF CLINICAL STUDIES

Amlodipine, Valsartan & Hydrochlorothiazide combination was studied in a double-blind, active controlled study in hypertensive patients. A total of 2271 patients with moderate to severe hypertension (mean baseline systolic/diastolic blood pressure was 170/107 mmHg) received treatments of amlodipine/valsartan/HCTZ 10/320/25 mg, valsartan/HCTZ 320/25 mg, amlodipine/valsartan 10/320 mg, or HCTZ/amlodipine 25/10 mg. At study initiation, patients assigned to the 2-component arms received lower doses of their treatment combination while patients assigned to the Amlodipine, Valsartan & Hydrochlorothiazide combination arm received 160/12.5 mg valsartan/hydrochlorothiazide. After 1 week, Amlodipine, Valsartan & Hydrochlorothiazide combination patients were titrated to 5/160/12.5 mg amlodipine/valsartan/hydrochlorothiazide, while all other patients continued receiving their initial doses. After 2 weeks, all patients were titrated to their full treatment dose. A total of 55% of patients were male, 14% were 65 years or older, 72% were Caucasian, and 17% were black.

At Week 8, the triple combination therapy produced greater reductions in blood pressure than each of the 3 dual combination treatments ($p < 0.0001$ for both diastolic and systolic blood pressures reductions). The reductions in systolic/diastolic blood pressure with Amlodipine, Valsartan & Hydrochlorothiazide combination were 7.6/5.0 mmHg greater than with valsartan/HCTZ, 6.2/3.3 mmHg greater than with amlodipine/valsartan, and 8.2/5.3 mmHg greater than with amlodipine/HCTZ. The full blood pressure lowering effect was achieved 2 weeks after being on the maximal dose of Amlodipine, Valsartan & Hydrochlorothiazide combination. As the pivotal study was an active-controlled trial, the treatment effects shown in Figures 1, 2, and 3 include a placebo effect of unknown size.

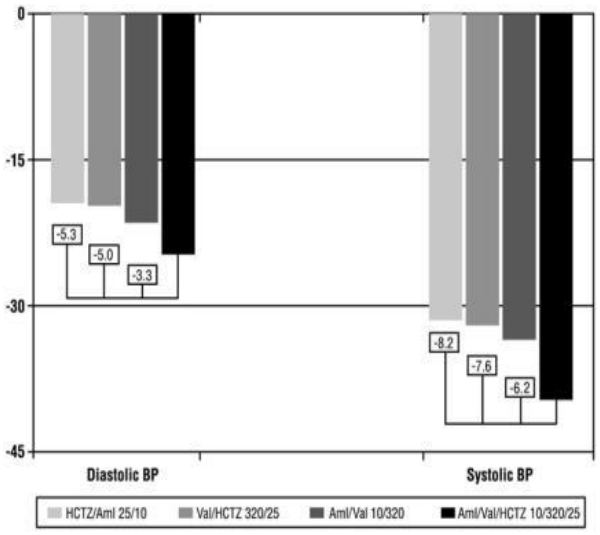

Figure 1: Reduction in Mean Blood Pressure at Endpoint

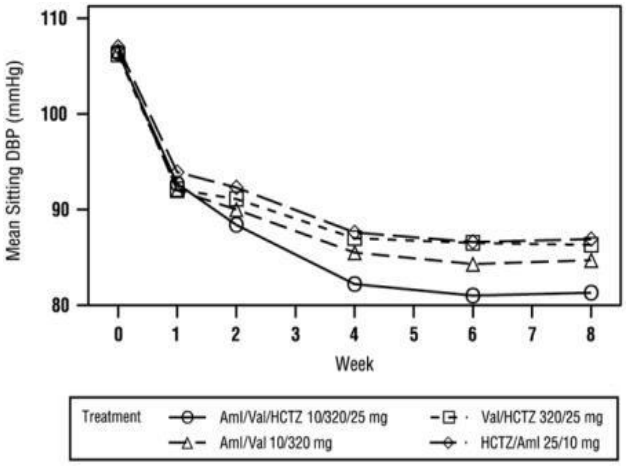

Figure 2: Mean Sitting Diastolic Blood Pressure by Treatment and Week

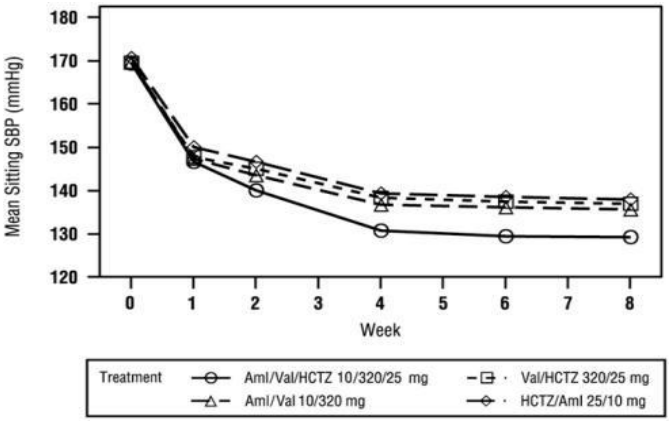

Figure 3: Mean Sitting Systolic Blood Pressure by Treatment and Week

A subgroup of 283 patients was studied with ambulatory blood pressure monitoring. The blood pressure lowering effect in the triple therapy group was maintained throughout the 24-hour period.

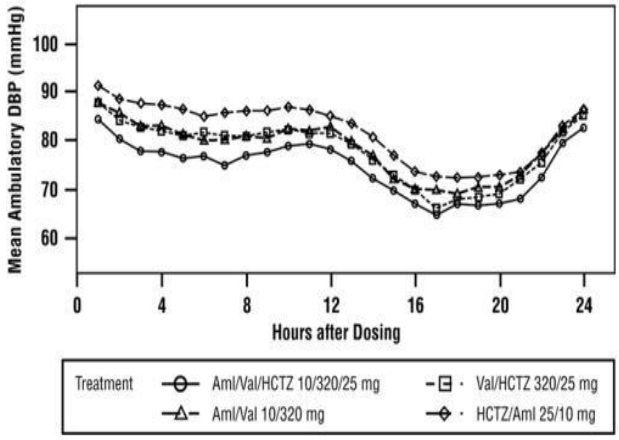

Figure 4: Mean Ambulatory Diastolic Blood Pressure at Endpoint by Treatment and Hour

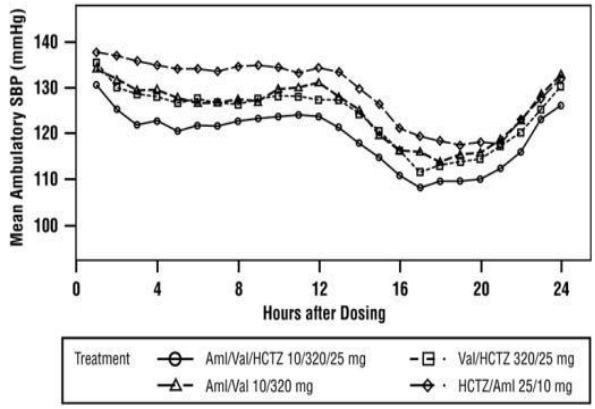

Figure 5: Mean Ambulatory Systolic Blood Pressure at Endpoint by Treatment and Hour

There are no trials of the Amlodipine, Valsartan & Hydrochlorothiazide combination tablet demonstrating reductions in cardiovascular risk in patients with hypertension, but both the amlodipine and hydrochlorothiazide components and several ARBs, which are the same pharmacological class as the valsartan component, have demonstrated such benefits.

PRESENTATION

Co-Extor 10mg+160mg+12.5mg film coated tablets are available in Alu Alu blister pack of 2 x 14's in carton.

Co-Extor 5mg+160mg+12.5mg film coated tablets are available in Alu Alu blister pack of 2 x 14's in carton.

Co-Extor 5mg+160mg+25mg film coated tablets are available in Alu Alu blister pack of 2 x 14's in carton

INSTRUCTIONS

- To be sold on the prescription of a registered medical practitioner only.

- Protect from sunlight, moisture and heat.

- Store below 30°C.

- Keep all medicines out of sight & reach of children

REGISTRATION NUMBER

Co-Extor 10mg + 160mg + 12.5mg tablet 071437

Co-Extor 5mg + 160mg + 12.5mg tablet 071438

Co-Extor 5mg + 160mg + 25mg tablet 071436

Manufacturing License Number: 000647

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION – As per registrations letter

Manufactured by:

The Searle Company Limited

32-Km, Multan Road, Lahore – Pakistan

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