1. NAME OF THE MEDICINAL PRODUCT

AMLODIPINE, VALSARTAN AND HYDROCHLOROTHIAZIDE TABLETS USP(10 MG/160 MG/12.5 MG)

2. QUALITATIVE AND QUANTITATIVECOMPOSITION

Each film coated tablet contains :
Amlodipine Besylate USP
Eq. to Amlodipine.....10 mg
Hydrochlorthiazide USP .....12.5 mg
Valsartan USP.....160 mg
Colour : Titanium Dioxide, Yellow oxide of Iron & Red oxide of Iron

3. PHARMACEUTICAL FORM

Oral Film coated Tablets

4. Clinical particulars

4.1 Therapeutic indications

Amlodipine/valsartan/hydrochlorothiazide is indicated for the treatment of hypertension, to lower blood pressure. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions. These benefits have been seen in controlled trials of antihypertensive drugs from a wide variety of pharmacologic classes, including amlodipine, hydrochlorothiazide, and the ARB class to which valsartan principally belongs. There are no controlled trials demonstrating risk reduction with amlodipine/valsartan/hydrochlorothiazide.

Control of high blood pressure should be part of comprehensive cardiovascular risk management, including, as appropriate, lipid control, diabetes management, antithrombotic therapy, smoking cessation, exercise, and limited sodium intake. Many patients will require more than 1 drug to achieve blood pressure goals. For specific advice on goals and management, see published guidelines, such as those of the National High Blood Pressure Education Program's Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC).

Numerous antihypertensive drugs, from a variety of pharmacologic classes and with different mechanisms of action, have been shown in randomized controlled trials to reduce cardiovascular morbidity and mortality, and it can be concluded that it is blood pressure reduction, and not some other pharmacologic property of the drugs, that is largely responsible for those benefits. The largest and most consistent cardiovascular outcome benefit has been a reduction in the risk of stroke, but reductions in myocardial infarction and cardiovascular mortality also have been seen regularly.

Elevated systolic or diastolic pressure causes increased cardiovascular risk, and the absolute risk increase per mmHg is greater at higher blood pressures, so that even modest reductions of severe hypertension can provide substantial benefit. Relative risk reduction from blood pressure reduction is similar across populations with varying absolute risk, so the absolute benefit is greater in patients who are at higher risk independent of their hypertension (e.g., patients with diabetes or hyperlipidemia), and such patients would be expected to benefit from more aggressive treatment to a lower blood pressure goal.

Some antihypertensive drugs have smaller blood pressure effects (as monotherapy) in black patients, and many antihypertensive drugs have additional approved indications and effects (e.g., on angina, heart failure, or diabetic kidney disease). These considerations may guide selection of therapy.

4.2 Contraindications

Do not use in patients with anuria, hypersensitivity to other sulfonamide-derived drugs, or hypersensitivity to any component of this product.
Do not co-administer aliskiren with amlodipine/valsartan/hydrochlorothiazide in patients with diabetes

4.3 Special warnings and precautions for use

Fetal Toxicity

Valsartan

Amlodipine/valsartan/hydrochlorothiazide 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 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 (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.

Amlodipine/valsartan/hydrochlorothiazide 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 patients given valsartan commonly have some reduction in blood pressure, but discontinuation of therapy because of continuing symptomatic hypotension usually is not necessary when dosing instructions are followed. In 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 in patients with aortic or mitral stenosis or obstructive hypertrophic cardiomyopathy.

If excessive hypotension occurs with amlodipine/valsartan/hydrochlorothiazide, the place 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. 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.

Potassium Abnormalities

In the controlled trial of amlodipine/valsartan/hydrochlorothiazide 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 (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 and HCTZ/amlodipine groups. The incidence of hyperkalemia (serum potassium >5.7 mEq/L) was 0.4% with amlodipine/valsartan/hydrochlorothiazide 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 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 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.

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.

4.4 Interaction with other medicinal products and other forms of interaction

No drug interaction studies have been conducted with amlodipine/valsartan/hydrochlorothiazide 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, and the corresponding 3 double combinations. No clinically relevant interaction was observed.

Amlodipine

Impact of other Drugs on Amlodipine

CYP3A Inhibitors

Co-administration 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 co-administered 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 co-administered with CYP3A inducers (e.g., rifampicin, St. John's Wort).

Sildenafil

Monitor for hypotension when sildenafil is co-administered with amlodipine.

Impact of Amlodipine on other Drugs

Simvastatin

Co-administration 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 co-administered. 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 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, co-administration of NSAIDs, including selective COX-2 inhibitors, with angiotensin II receptor antagonists, including valsartan, may result in deterioration of renal function, including possible acute renal failure. 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 co-administer 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.

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 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

4.5 Pregnancy and Lactation

Pregnancy:

Risk Summary

Amlodipine/valsartan/hydrochlorothiazide 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. Most epidemiologic studies examining fetal abnormalities after exposure to antihypertensive use in the first trimester have not distinguished drugs affecting the renin-angiotensin system from other antihypertensive agents. Published reports include cases of anhydramnios and oligohydramnios in pregnant women treated with valsartan (see Clinical Considerations). When pregnancy is detected, discontinue amlodipine/valsartan/hydrochlorothiazide as soon as possible.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Hypertension in pregnancy increases the maternal risk for preeclampsia, gestational diabetes, premature delivery, and delivery complications (e.g., need for cesarean section, and post-partum hemorrhage). Hypertension increases the fetal risk for intrauterine growth restriction and intrauterine death. Pregnant women with hypertension should be carefully monitored and managed accordingly.

Fetal/Neonatal Adverse Reactions

Valsartan:

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

Perform serial ultrasound examinations to assess the intra-amniotic environment. Fetal testing may be appropriate, based on the week of gestation. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury. If oligohydramnios is observed, consider alternative drug treatment. Closely observe neonates with histories of in utero exposure to amlodipine/valsartan/hydrochlorothiazide for hypotension, oliguria, and hyperkalemia. In neonates with a history of in utero exposure to Amlodipine/valsartan/hydrochlorothiazide, if oliguria or hypotension occurs, support blood pressure and renal perfusion. Exchange transfusions or dialysis may be required as a means of reversing hypotension and replacing renal function.

Hydrochlorothiazide

Thiazides can cross the placenta, and concentrations reached in the umbilical vein approach those in the maternal plasma. Hydrochlorothiazide, like other diuretics, can cause placental hypoperfusion. It accumulates in the amniotic fluid, with required concentrations up to 19 times higher than in umbilical vein plasma. Use of thiazides during pregnancy is associated with a risk of fetal or neonatal jaundice of thrombocytopenia. Since they do not prevent or alter the course of EPH (Edema, Proteinuria, Hypertension) gestosis (pre-eclampsia), these drugs should not be used to treat hypertension in pregnant women. The use of HCTZ for other indications (e.g., heart disease) in pregnancy should be avoided.

Data

Animal Data

Valsartan and Amlodipine:

In rats, administered 20 mg/kg/day amlodipine plus 320 mg/kg/day valsartan, treatment-related maternal and fetal effects (developmental delays and alterations noted in the presence of significant maternal toxicity) were noted with the high dose combination. This corresponds to dose multiples of 9 and 19.5 times, respectively, the maximum recommended human dose (MRHD) of 10 mg/day for amlodipine and 320 mg/day for valsartan (based on body surface area and considering a 60 kg patient).

Hydrochlorothiazide:

No teratogenic effects were observed when hydrochlorothiazide was administered to mice and rats via gavage at doses of up to 3000 and 1000 mg/kg/day (608 and 405 times the MRHD), on gestation days 6 through 15.

Lactation:

There is limited information regarding the presence of amlodipine/valsartan/hydrochlorothiazide in

human milk, the effects on the breastfed infant, or the effects on milk production. Hydrochlorothiazide is present in human milk and valsartan is present in rat milk. Limited published studies report that amlodipine is present in human milk. Because of the potential for serious adverse reactions in breastfed infants, advise a nursing woman that breastfeeding is not recommended during treatment with amlodipine/valsartan/hydrochlorothiazide.

4.6 Effects on ability to drive and use machines

Patients taking VAL AH 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 VAL AHsuffer from dizziness, headache, fatigue or nausea the ability to react may be impaired

4.7 Undesirable effects

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, 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 10/320/25 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 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 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 were obtained in a controlled trial of amlodipine/valsartan/hydrochlorothiazide 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 were obtained from other trials.

Creatinine: In heart 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 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.

4.8 Overdose

Amlodipine

Single oral doses of amlodipine maleate equivalent to 40 mg/kg and 100 mg/kg amlodipine in mice and rats, respectively, caused deaths. Single oral doses equivalent to 4 or more mg/kg amlodipine in dogs (11 or more times the maximum recommended human dose on a mg/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 2000 mg/kg in rats and up to 1000 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.)

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

Pharmacotherapeutic group: Angiotensin II receptor blockers , ATC code: C09DX01
Mechanism of Action
The active ingredients of amlodipine/valsartan/hydrochlorothiazide 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 co-administration of an angiotensin II receptor antagonist tends to reverse the potassium loss associated with these diuretics.

Pharmacodynamics

Amlodipine/valsartan/hydrochlorothiazide has been shown to be effective in lowering blood pressure. The 3 components of 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 is described below.

Amlodipine/valsartan/hydrochlorothiazide 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 to 114 mmHg) had about a 50% greater response than patients with mild hypertension (diastolic pressure 90 to 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 co-administered 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.

5.2 Pharmacokinetic properties

Absorption

Bioequivalence has been demonstrated between Vildagliptin and Metformin Tablets at three dose strengths (50 mg/500 mg, 50 mg/850 mg and 50 mg/1000 mg) versus free combination of vildagliptin and metformin hydrochloride tablets at the corresponding doses.

Food does not affect the extent and rate of absorption of vildagliptin from Vildagliptin and Metformin Tablets. The rate and extent of absorption of metformin from Vildagliptin and Metformin Tablets 50 mg/1000 mg were decreased when given with food as reflected by the decrease in Cmax by 26%, AUC by 7% and delayed Tmax (2.0 to 4.0 h).

The following statements reflect the pharmacokinetic properties of the individual active substances of Vildagliptin and Metformin Tablets.

Vildagliptin

Absorption

Following oral administration in the fasting state, vildagliptin is rapidly absorbed with peak plasma concentrations observed at 1.7 hours. Food slightly delays the time to peak plasma concentration to 2.5 hours, but does not alter the overall exposure (AUC). Administration of vildagliptin with food resulted in a decreased Cmax (19%) compared to dosing in the fasting state. However, the magnitude of change is not clinically significant, so that vildagliptin can be given with or without food. The absolute bioavailability is 85%.

Distribution

The plasma protein binding of vildagliptin is low (9.3%) and vildagliptin distributes equally between plasma and red blood cells. The mean volume of distribution of vildagliptin at steady-state after intravenous administration (Vss) is 71 litres, suggesting extravascular distribution.

Biotransformation

Metabolism is the major elimination pathway for vildagliptin in humans, accounting for 69% of the dose. The major metabolite (LAY 151) is pharmacologically inactive and is the hydrolysis product of the cyano moiety, accounting for 57% of the dose, followed by the amide hydrolysis product (4% of dose). DPP-4 contributes partially to the hydrolysis of vildagliptin based on an in vivo study using DPP-4 deficient rats. Vildagliptin is not metabolised by CYP 450 enzymes to any quantifiable extent,

and accordingly the metabolic clearance of vildagliptin is not anticipated to be affected by co-medications that are CYP 450 inhibitors and/or inducers. In vitro studies demonstrated that vildagliptin does not inhibit/induce CYP 450 enzymes. Therefore, vildagliptin is not likely to affect metabolic clearance of co-medications metabolised by CYP 1A2, CYP 2C8, CYP 2C9, CYP 2C19, CYP 2D6, CYP 2E1 or CYP 3A4/5.

Elimination

Following oral administration of [14C] vildagliptin, approximately 85% of the dose was excreted into the urine and 15% of the dose was recovered in the faeces. Renal excretion of the unchanged vildagliptin accounted for 23% of the dose after oral administration. After intravenous administration to healthy subjects, the total plasma and renal clearances of vildagliptin are 41 and 13 l/h, respectively. The mean elimination half-life after intravenous administration is approximately 2 hours. The elimination half-life after oral administration is approximately 3 hours.

Linearity/non-linearity

The Cmax for vildagliptin and the area under the plasma concentrations versus time curves (AUC) increased in an approximately dose proportional manner over the therapeutic dose range.

Characteristics in patients

Gender: No clinically relevant differences in the pharmacokinetics of vildagliptin were observed between male and female healthy subjects within a wide range of age and body mass index (BMI). DPP-4 inhibition by vildagliptin is not affected by gender.

Age: In healthy elderly subjects (≥ 70 years), the overall exposure of vildagliptin (100 mg once daily) was increased by 32%, with an 18% increase in peak plasma concentration as compared to young healthy subjects (18-40 years). These changes are not considered to be clinically relevant, however. DPP-4 inhibition by vildagliptin is not affected by age.

Hepatic impairment: In subjects with mild, moderate or severe hepatic impairment (Child-Pugh A-C) there were no clinically significant changes (maximum ~30%) in exposure to vildagliptin.

Renal impairment: In subjects with mild, moderate, or severe renal impairment, systemic exposure to vildagliptin was increased (Cmax 8-66%; AUC 32-134%) and total body clearance was reduced compared to subjects with normal renal function.

Ethnic group: Limited data suggest that race does not have any major influence on vildagliptin pharmacokinetics

Metformin

Absorption

After an oral dose of metformin, the maximum plasma concentration (Cmax) is achieved after about 2.5 h. Absolute bioavailability of a 500 mg metformin tablet is approximately 50-60% in healthy subjects. After an oral dose, the non-absorbed fraction recovered in faeces was 20-30%.

After oral administration, metformin absorption is saturable and incomplete. It is assumed that the pharmacokinetics of metformin absorption are non-linear. At the usual metformin doses and dosing schedules, steady state plasma concentrations are reached within 24-48 h and are generally less than 1 µg/ml. In controlled clinical trials, maximum metformin plasma levels (Cmax) did not exceed 4 µg/ml, even at maximum doses.

Food slightly delays and decreases the extent of the absorption of metformin. Following administration of a dose of 850 mg, the plasma peak concentration was 40% lower, AUC was decreased by 25% and time to peak plasma concentration was prolonged by 35 minutes. The clinical relevance of this decrease is unknown.

Distribution

Plasma protein binding is negligible. Metformin partitions into erythrocytes. The mean volume of distribution (Vd) ranged between 63-276 litres.

Biotransformation

Metformin is excreted unchanged in the urine. No metabolites have been identified in humans.

Elimination

Metformin is eliminated by renal excretion. Renal clearance of metformin is > 400 ml/min, indicating that metformin is eliminated by glomerular filtration and tubular secretion. Following an oral dose, the apparent terminal elimination half-life is approximately 6.5 h. When renal function is impaired, renal clearance is decreased in proportion to that of creatinine and thus the elimination half-life is prolonged, leading to increased levels of metformin in plasma.

5.3 Preclinical safety data

Amlodipine/Valsartan/Hydrochlorothiazide

In a variety of preclinical safety studies conducted in several animal species with amlodipine, valsartan, hydrochlorothiazide, valsartan/hydrochlorothiazide, amlodipine/valsartan and amlodipine/valsartan/hydrochlorothiazide (VAL AH), there was no evidence of systemic or target organ toxicity that would adversely affect the development of VAL AH for clinical use in humans.

Preclinical safety studies of up to 13 weeks in duration were conducted with amlodipine/valsartan/hydrochlorothiazide in rats. The combination resulted in expected reduction of red blood cell mass (erythrocytes, haemoglobin, haematocrit, and reticulocytes), increase in serum urea, increase in serum creatinine, increase in serum potassium, juxtaglomerular (JG) hyperplasia in the kidney and focal erosions in the glandular stomach in rats. All these changes were reversible after a 4-week recovery period and were considered to be exaggerated pharmacological effects.

The amlodipine/valsartan/hydrochlorothiazide combination was not tested for genotoxicity or carcinogenicity as there was no evidence of any interaction between these substances, which have been on the market for a long time. However, amlodipine, valsartan and hydrochlorothiazide have been tested individually for genotoxicity and carcinogenicity with negative results.

Amlodipine

Reproductive toxicology

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

Impairment of fertility

There was no effect on the fertility of rats treated with amlodipine (males for 64 days and females 14 days prior to mating) at doses up to 10 mg/kg/day (8 times* the maximum recommended human dose of 10 mg on a mg/m2 basis). In another rat study in which male rats were treated with amlodipine besilate for 30 days at a dose comparable with the human dose based on mg/kg, decreased plasma follicle-stimulating hormone and testosterone were found as well as decreases in sperm density and in the number of mature spermatids and Sertoli cells.

Carcinogenesis, mutagenesis

Rats and mice treated with amlodipine in the diet for two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 mg/kg/day showed no evidence of carcinogenicity. The highest dose (for mice, similar to, and for rats twice* the maximum recommended clinical dose of 10 mg on a mg/m2 basis) was close to the maximum tolerated dose for mice but not for rats. Mutagenicity studies revealed no drug related effects at either the gene or chromosome levels. * Based on patient weight of 50 kg

Valsartan

Non-clinical data

reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development. In rats, maternally toxic doses (600 mg/kg/day) during the last days of gestation and

lactation led to lower survival, lower weight gain and delayed development (pinna detachment and ear-canal opening) in the offspring (see section 4.6). These doses in rats (600 mg/kg/day) are approximately 18 times the maximum recommended human dose on a mg/m2 basis (calculations assume an oral dose of 320 mg/day and a 60-kg patient).

In non-clinical safety studies, high doses of valsartan (200 to 600 mg/kg body weight) caused in rats a reduction of red blood cell parameters (erythrocytes, haemoglobin, haematocrit) and evidence of changes in renal haemodynamics (slightly raised blood urea nitrogen, and renal tubular hyperplasia and basophilia in males). These doses in rats (200 and 600 mg/kg/day) are approximately 6 and 18 times the maximum recommended human dose on a mg/m2 basis (calculations assume an oral dose of 320 mg/day and a 60-kg patient).

In marmosets at comparable doses, the changes were similar though more severe, particularly in the kidney where the changes developed to a nephropathy including raised blood urea nitrogen and creatinine. Hypertrophy of the renal juxtaglomerular cells was also seen in both species. All changes were considered to be caused by the pharmacological action of valsartan which produces prolonged hypotension, particularly in marmosets. For therapeutic doses of valsartan in humans, the hypertrophy of the renal juxtaglomerular cells does not seem to have any relevance.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose(PH-112)
Crospovidone
Magnesium stearate
Colloidal anhydrous silica
Microcrystalline cellulose(PH-102)
Colorezy white
Red oxide of Iron
Isopropyl alcohol
Methylene chloride

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months from the date of manufacturing

6.4 Nature and contents of container<and special equipment for use, administration or implantation>

Packing: 3 X 10 Tablets Alu Alu blister pack
Primary Packing: Alu Alu Blister pack
Secondary Packing: Such 3 blisters packed in a carton with package insert.

6.5 Special precautions for disposal <and other handling>

None

7 <APPLICANT/MANUFACTURER>

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