1. Name of the medicinal product

VALSAR-HT 160/25 (Valsartan and Hydrochlorothiazide Tablets USP 160/25 mg)

2. Qualitative and quantitative composition

Each film coated tablet contains 160 mg of Valsartan USP and 25 mg of Hydrochlorothiazide USP.

For excipients, see 6.1.

3. Pharmaceutical form

Film coated Tablet

Description: brown orange colored, oval, biconvex, film coated tablets debossed with H on one side and 'V8' on the other side.

4. Clinical particulars

4.1 Therapeutic indications

Treatment of Hypertension:

Valsartan and hydrochlorothiazide Tablet USP 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 hydrochlorothiazide and the ARB class to which valsartan principally belongs. There are no controlled trials demonstrating risk reduction with Valsartan and hydrochlorothiazide Tablet USP.

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 have also 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.

Add-On Therapy

Valsartan and hydrochlorothiazide Tablet USP may be used in patients whose blood pressure is not adequately controlled on monotherapy.

Replacement Therapy

Valsartan and hydrochlorothiazide Tablet USP may be substituted for the titrated components.

Initial Therapy

Valsartan and hydrochlorothiazide Tablet USP may be used as initial therapy in patients who are likely to need multiple drugs to achieve blood pressure goals.

The choice of Valsartan and hydrochlorothiazide Tablet USP as initial therapy for hypertension should be based on an assessment of potential benefits and risks.

Patients with stage 2 hypertension are at a relatively high risk for cardiovascular events (such as strokes, heart attacks, and heart failure), kidney failure, and vision problems, so prompt treatment is clinically relevant. The decision to use a combination as initial therapy should be individualized and should be shaped by considerations such as baseline blood pressure, the target goal, and the incremental likelihood of achieving goal with a combination compared to monotherapy. Individual blood pressure goals may vary based upon the patient's risk.

Data from the high dose multifactorial trial [see Clinical Studies] provides estimates of the probability of reaching a target blood pressure with Valsartan and hydrochlorothiazide Tablet USP compared to valsartan or hydrochlorothiazide monotherapy. The figures below provide estimates of the likelihood of achieving systolic or diastolic blood pressure control with Valsartan

and hydrochlorothiazide Tablet USP 320/25 mg, based upon baseline systolic or diastolic blood pressure. The curve of each treatment group was estimated by logistic regression modeling. The estimated likelihood at the right tail of each curve is less reliable due to small numbers of subjects with high baseline blood pressures.

Figure 1: Probability of Achieving Systolic Blood Pressure < 140 mmHg at Week 8

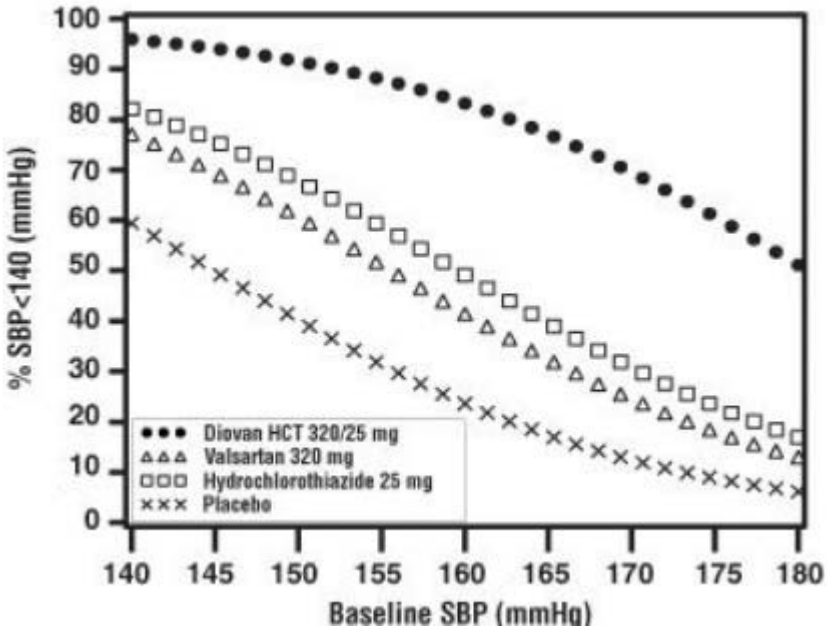


Figure 2: Probability of Achieving Diastolic Blood Pressure < 90 mmHg at Week 8

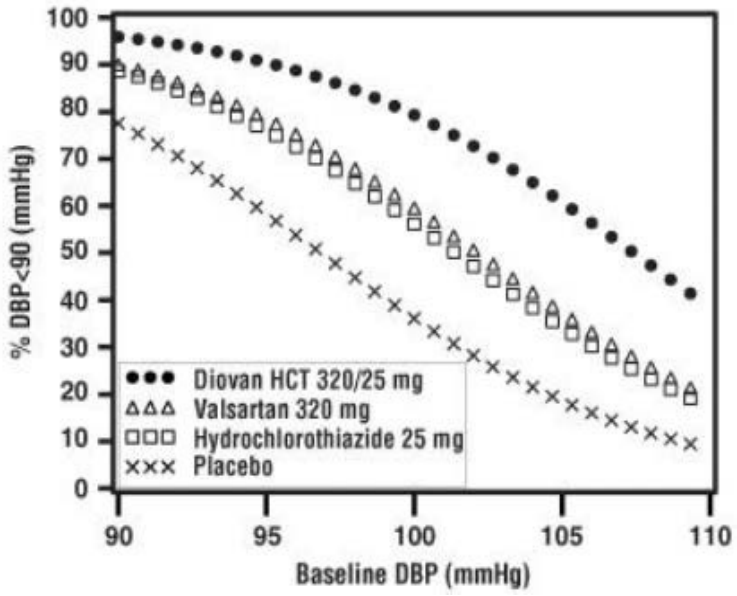


Figure 3: Probability of Achieving Systolic Blood Pressure < 130 mmHg at Week 8

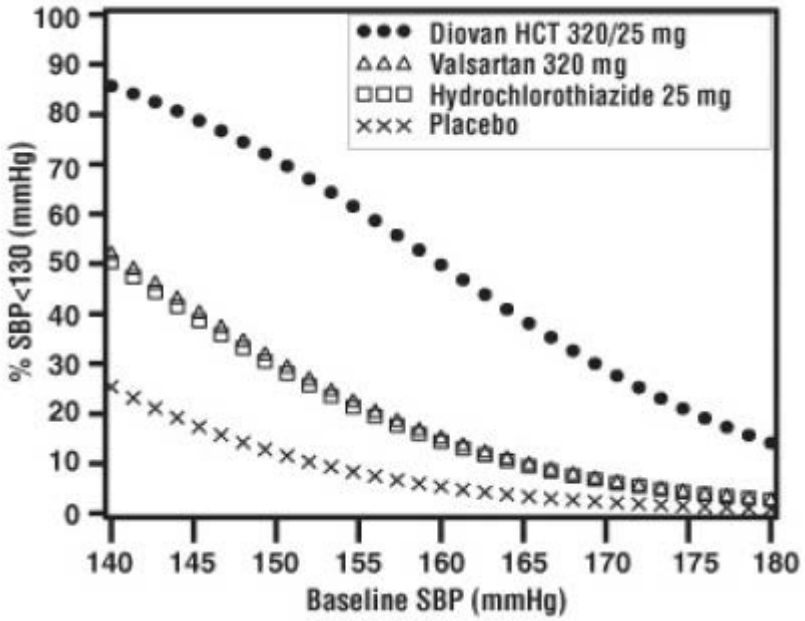
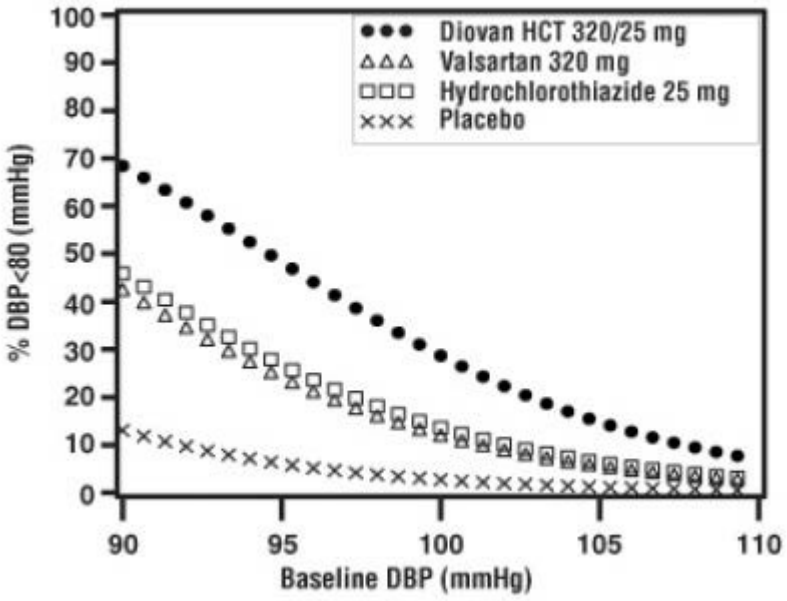


Figure 4: Probability of Achieving Diastolic Blood Pressure < 80 mmHg at Week 8



For example, a patient with a baseline blood pressure of 160/100 mmHg has about a 41% likelihood of achieving a goal of <140 mmHg (systolic) and 60% likelihood of achieving <90 mmHg (diastolic) on valsartan alone and the likelihood of achieving these goals on HCTZ alone is about 50% (systolic) or 57% (diastolic). The likelihood of achieving these goals on Diovan HCT rises to about 84% (systolic) or 80% (diastolic). The likelihood of achieving these goals on placebo is about 23% (systolic) or 36% (diastolic).

4.2 Posology and method of administration

General Considerations

The usual starting dose is Valsartan and hydrochlorothiazide Tablet USP 160/12.5 mg once daily. The dosage can be increased after 1 to 2 weeks of therapy to a maximum of one 320/25 tablet once daily as needed to control blood pressure [see Clinical Studies]. Maximum antihypertensive effects are attained within 2 to 4 weeks after a change in dose.

Add-On Therapy

A patient whose blood pressure is not adequately controlled with valsartan (or another ARB) alone or hydrochlorothiazide alone may be switched to combination therapy with Valsartan and hydrochlorothiazide Tablet USP.

A patient who experiences dose-limiting adverse reactions on either component alone may be

switched to Valsartan and hydrochlorothiazide Tablet USP containing a lower dose of that component in combination with the other to achieve similar blood pressure reductions. The clinical response to Valsartan and hydrochlorothiazide Tablet USP should be subsequently evaluated and if blood pressure remains uncontrolled after 3 to 4 weeks of therapy, the dose may be titrated up to a maximum of 320/25 mg.

Replacement Therapy

Valsartan and hydrochlorothiazide Tablet USP may be substituted for the titrated components.

Initial Therapy

Valsartan and hydrochlorothiazide Tablet USP is not recommended as initial therapy in patients with intravascular volume depletion [see Warnings and Precautions]

Use with Other Antihypertensive Drugs

Valsartan and hydrochlorothiazide Tablet USP may be administered with other antihypertensive agents.

4.3 Contraindications

Valsartan and hydrochlorothiazide Tablet USP is contraindicated in patients who are hypersensitive to any component of this product.

Because of the hydrochlorothiazide component, this product is contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs.

Do not coadminister aliskiren with Valsartan and hydrochlorothiazide Tablet USP in patients with diabetes [see Drug Interactions].

a. Special warnings and precautions for use

Fetal Toxicity

Pregnancy Category D

Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. When pregnancy is detected, discontinue Valsartan and hydrochlorothiazide Tablet USP as soon as possible [see Use in Specific Populations].

Hypotension in Volume- and/or Salt-Depleted Patients

Excessive reduction of blood pressure was rarely seen (0.7%) in patients with uncomplicated hypertension treated with Valsartan and hydrochlorothiazide Tablet USP in controlled trials. In patients with an activated renin-angiotensin system, such as volume- and/or salt-depleted patients receiving high doses of diuretics, symptomatic hypotension may occur. This condition should be corrected prior to administration of Valsartan and hydrochlorothiazide Tablet USP, or the treatment should start under close medical supervision.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, given an intravenous infusion of 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.

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 Valsartan and hydrochlorothiazide Tablet USP. Monitor renal function periodically in these patients. Consider withholding or discontinuing therapy in patients who develop a clinically significant decrease in renal function on Valsartan and hydrochlorothiazide Tablet USP [see Drug Interactions].

Hypersensitivity Reaction

Hydrochlorothiazide: 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

Hydrochlorothiazide: 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 Valsartan and hydrochlorothiazide Tablet USP and lithium [see Drug Interactions].

Potassium Abnormalities

Valsartan–Hydrochlorothiazide: In the controlled trials of various doses of Valsartan and hydrochlorothiazide Tablet USP the incidence of hypertensive patients who developed hypokalemia (serum potassium <3.5 mEq/L) was 3.0%; the incidence of hyperkalemia (serum potassium >5.7 mEq/L) was 0.4%.

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), Valsartan and hydrochlorothiazide Tablet USP should be discontinued. Correction of hypokalemia and any coexisting hypomagnesemia is recommended prior to the initiation of thiazides.

Some patients with heart failure have developed increases in potassium with Valsartan and hydrochlorothiazide Tablet USP therapy. These effects are usually minor and transient, and they are more likely to occur in patients with pre-existing renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or Valsartan and hydrochlorothiazide Tablet USP may be required [see Adverse Reactions].

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.

Metabolic Disturbances

Hydrochlorothiazide

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 Valsartan and hydrochlorothiazide Tablet USP.

4.5 Interaction with other medicinal products and other forms of interaction

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 Valsartan and hydrochlorothiazide Tablet USP.

Valsartan: No clinically significant pharmacokinetic interactions were observed when 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.

CYP 450 Interactions: In vitro metabolism studies indicate that CYP 450 mediated drug interactions between valsartan and coadministered drugs are unlikely because of the low extent of metabolism [see Clinical Pharmacology].

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.

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, 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.

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 comedication is considered necessary, monitoring of serum potassium is advisable.

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 hydrochlorothiazide Tablet USP and other agents that affect the RAS.

Do not coadminister aliskiren with Valsartan and hydrochlorothiazide Tablet USP in patients with diabetes. Avoid use of aliskiren with Valsartan and hydrochlorothiazide Tablet USP in patients with renal impairment (GFR <60 mL/min).

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.

Nonsteroidal Anti-inflammatory Drugs (NSAIDs and COX-2 selective inhibitors) - When Valsartan and hydrochlorothiazide Tablet USP and nonsteroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of the 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 [see Clinical Pharmacology].

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

4.6 Fertility, pregnancy and lactation

4.6.1Pregnancy

Pregnancy Category D

Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. When pregnancy is detected, discontinue Valsartan and hydrochlorothiazide as soon as possible. These adverse outcomes are usually associated with use of these drugs in the second and third trimester of pregnancy. Most epidemiologic studies examining fetal abnormalities after exposure to antihypertensive use in the first trimester have not distinguished drugs affecting the renin-angiotensin system from other antihypertensive agents. Appropriate management of maternal hypertension during pregnancy is important to optimize outcomes for both mother and fetus.

In the unusual case that there is no appropriate alternative to therapy with drugs affecting the renin-angiotensin system for a particular patient, apprise the mother of the potential risk to the fetus. Perform serial ultrasound examinations to assess the intra-amniotic environment. If oligohydramnios is observed, discontinue Valsartan and hydrochlorothiazide, unless it is considered lifesaving for the mother. Fetal testing may be appropriate, based on the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury. Closely observe infants with histories of in utero exposure to Valsartan and hydrochlorothiazide for hypotension, oliguria, and hyperkalemia [see Use in Specific Populations (8.4)].

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 reported 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 or 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 hydrochlorothiazide for other indications (e.g., heart disease) in pregnancy should be avoided.

Nursing Mothers

It is not known whether valsartan is excreted in human milk. Valsartan was excreted into the milk of lactating rats; however, animal breast milk drug levels may not accurately reflect human breast milk levels. Hydrochlorothiazide is excreted in human breast milk. Because many drugs are excreted into human milk and because of the potential for adverse reactions in nursing infants from Valsartan and hydrochlorothiazide, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness of Valsartan and hydrochlorothiazide in pediatric patients have not been established.

Neonates with a history of in utero exposure to Valsartan and hydrochlorothiazide:

If oliguria or hypotension occurs, direct attention toward support of blood pressure and renal perfusion. Exchange transfusions or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal function.

4.7 Undesirable effects

Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reactions 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 practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates

Hypertension

Valsartan and hydrochlorothiazide Tablet USP has been evaluated for safety in more than 5700 patients, including over 990 treated for over 6 months, and over 370 for over 1 year. Adverse experiences have generally been mild and transient in nature and have only infrequently required discontinuation of therapy. The overall incidence of adverse reactions with Valsartan and hydrochlorothiazide Tablet USP was comparable to placebo.

The overall frequency of adverse reactions was neither dose-related nor related to gender, age, or race. In controlled clinical trials, discontinuation of therapy due to side effects was required in 2.3% of valsartan-hydrochlorothiazide patients and 3.1% of placebo patients. The most common reasons for discontinuation of therapy with Valsartan and hydrochlorothiazide Tablet USP were headache and dizziness.

The only adverse reaction that occurred in controlled clinical trials in at least 2% of patients

treated with Valsartan and hydrochlorothiazide Tablet USP and at a higher incidence in valsartan-hydrochlorothiazide (n=4372) than placebo (n=262) patients was nasopharyngitis (2.4% vs. 1.9%).

Dose-related orthostatic effects were seen in fewer than 1% of patients. In individual trials, a dose-related increase in the incidence of dizziness was observed in patients treated with Valsartan and hydrochlorothiazide Tablet USP.

Other adverse reactions that have been reported with valsartan-hydrochlorothiazide (>0.2% of valsartan-hydrochlorothiazide patients in controlled clinical trials) without regard to causality, are listed below:

Cardiovascular: Palpitations and tachycardia

Ear and Labyrinth: Tinnitus and vertigo

Gastrointestinal: Dyspepsia, diarrhea, flatulence, dry mouth, nausea, abdominal pain, abdominal pain upper, and vomiting

General and Administration Site Conditions: Asthenia, chest pain, fatigue, peripheral edema and pyrexia

Infections and Infestations: Bronchitis, bronchitis acute, influenza, gastroenteritis, sinusitis, upper respiratory tract infection, and urinary tract infection

Investigations: Blood urea increased

Musculoskeletal: Arthralgia, back pain, muscle cramps, myalgia, and pain in extremity

Nervous System: Dizziness postural, paresthesia, and somnolence

Psychiatric: Anxiety and insomnia

Renal and Urinary: Pollakiuria

Reproductive System: Erectile dysfunction

Respiratory, Thoracic and Mediastinal: Dyspnea, cough, nasal congestion, pharyngolaryngeal pain, and sinus congestion

Skin and Subcutaneous Tissue: Hyperhidrosis and rash

Vascular: Hypotension

Other reported reactions seen less frequently in clinical trials included abnormal vision, anaphylaxis, bronchospasm, constipation, depression, dehydration, decreased libido, dysuria, epistaxis, flushing, gout, increased appetite, muscle weakness, pharyngitis, pruritus, sunburn, syncope, and viral infection.

Initial Therapy-Hypertension

In a clinical study in patients with severe hypertension (diastolic blood pressure ≥110 mmHg and systolic blood pressure ≥140 mmHg), the overall pattern of adverse reactions reported through 6 weeks of follow-up was similar in patients treated with Valsartan and hydrochlorothiazide Tablet USP as initial therapy and in patients treated with valsartan as initial therapy. Comparing the groups treated with Valsartan and hydrochlorothiazide Tablet USP (force-titrated to 320/25 mg) and valsartan (force-titrated to 320 mg), dizziness was observed in 6% and 2% of patients, respectively. Hypotension was observed in 1% of those patients receiving Valsartan and hydrochlorothiazide Tablet USP and 0% of patients receiving valsartan. There were no reported cases of syncope in either treatment group. Laboratory changes with Valsartan and hydrochlorothiazide Tablet USP as initial therapy in patients with severe hypertension were similar to those reported with Valsartan and hydrochlorothiazide Tablet USP in patients with less severe hypertension [see Clinical Studies and Drug Interactions].

Valsartan: 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 had dry cough when they had previously received ACE inhibitors, the incidences of cough in patients who received valsartan, hydrochlorothiazide, or lisinopril were 20%, 19%, 69% respectively ($p < 0.001$).

Other reported reactions seen less frequently in clinical trials included chest pain, syncope, anorexia, vomiting, and angioedema.

Hydrochlorothiazide: Other adverse reactions not listed above that have been reported with hydrochlorothiazide, without regard to causality, are listed below:

Body As A Whole: weakness

Digestive: pancreatitis, jaundice (intrahepatic cholestatic jaundice), sialadenitis, cramping, gastric irritation

Hematologic: aplastic anemia, agranulocytosis, leukopenia, hemolytic anemia, thrombocytopenia

Hypersensitivity: purpura, photosensitivity, urticaria, necrotizing angiitis (vasculitis and cutaneous vasculitis), fever, respiratory distress including pneumonitis and pulmonary edema, anaphylactic reactions

Metabolic: hyperglycemia, glycosuria, hyperuricemia

Musculoskeletal: muscle spasm

Nervous System/Psychiatric: restlessness

Renal: renal failure, renal dysfunction, interstitial nephritis

Skin: erythema multiforme including Stevens-Johnson syndrome, exfoliative dermatitis including toxic epidermal necrolysis

Special Senses: transient blurred vision, xanthopsia

Clinical Laboratory Test Findings

In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with administration of Valsartan and hydrochlorothiazide Tablet USP.

Creatinine/Blood Urea Nitrogen (BUN): Minor elevations in creatinine and BUN occurred in 2% and 15% respectively, of patients taking Valsartan and hydrochlorothiazide Tablet USP and 0.4% and 6% respectively, given placebo in controlled clinical trials

Hemoglobin and Hematocrit: Greater than 20% decreases in hemoglobin and hematocrit were observed in less than 0.1% of Valsartan and hydrochlorothiazide Tablet USP patients, compared with 0% in placebo-treated patients

Liver Function Tests: Occasional elevations (greater than 150%) of liver chemistries occurred in Valsartan and hydrochlorothiazide Tablet USP treated patients

Neutropenia: Neutropenia was observed in 0.1% of patients treated with Valsartan and hydrochlorothiazide Tablet USP and 0.4% of patients treated with placebo.

Postmarketing Experience

The following additional adverse reactions have been reported in valsartan or valsartan/hydrochlorothiazide postmarketing 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.

Hypersensitivity: There are rare reports of angioedema. Some of these patients previously experienced angioedema with other drugs including ACE inhibitors. Valsartan and hydrochlorothiazide Tablet USP should not be re-administered to patients who have had angioedema.

Digestive: Elevated liver enzymes and very rare reports of hepatitis

Renal: Impaired renal function

Clinical Laboratory Tests: Hyperkalemia

Dermatologic: Alopecia, bullous dermatitis

Vascular: Vasculitis

Nervous System: Syncope

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

Hydrochlorothiazide:

The following additional adverse reactions have been reported in postmarketing 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, and 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.

4.8 Overdose

Valsartan-Hydrochlorothiazide: 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. Depressed level of consciousness, circulatory collapse and shock have been reported. If symptomatic hypotension should occur, supportive treatment should be instituted.

Valsartan is not removed from the plasma by dialysis.

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.

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 maximum recommended human dose (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.)

Valsartan: 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 oral LD50 of hydrochlorothiazide is greater than 10 g/kg in both mice and rats, which represents 2027 and 4054 times, respectively, the MRHD on a mg/m2 basis. (Calculations assume an oral dose of 25 mg/day and a 60-kg patient.)

5.0 Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antihypertensive

ATC code: C09D A03

Mechanism of action

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 20000-fold) for the AT1 receptor than for the 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 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.

5.1 Pharmacodynamics

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.

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

Drug Interactions

Hydrochlorothiazide:

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.

5.2 Pharmacokinetics

Valsartan: Valsartan peak plasma concentration is reached 2 to 4 hours after dosing. Valsartan shows bi-exponential decay kinetics following intravenous administration, with an average

elimination half-life of about 6 hours. Absolute bioavailability for the capsule formulation is about 25% (range 10% to 35%). Food decreases the exposure (as measured by AUC) to valsartan by about 40% and peak plasma concentration (Cmax) by about 50%. AUC and Cmax values of valsartan increase approximately linearly with increasing dose over the clinical dosing range. Valsartan does not accumulate appreciably in plasma following repeated administration.

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 bi-exponentially, with a mean distribution half-life of about 2 hours and an elimination half-life of about 10 hours.

Valsartan and hydrochlorothiazide Tablet USP: Valsartan and hydrochlorothiazide Tablet USP may be administered with or without food.

Distribution

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

Metabolism

Valsartan: The primary metabolite, accounting for about 9% of dose, is valeryl 4-hydroxy valsartan. In vitro metabolism studies involving recombinant CYP 450 enzymes indicated that the CYP 2C9 isoenzyme is responsible for the formation of valeryl-4-hydroxy valsartan. Valsartan does not inhibit CYP 450 isozymes at clinically relevant concentrations. CYP 450 mediated drug interaction between valsartan and coadministered drugs are unlikely because of the low extent of metabolism.

Hydrochlorothiazide: Is not metabolized.

Excretion

Valsartan: Valsartan, when administered as an oral solution, is primarily recovered in feces (about 83% of dose) and urine (about 13% of dose). The recovery is mainly as unchanged drug, with only about 20% of dose recovered as metabolites.

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

Special Populations

Geriatric: 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. A 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: 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) [see Use in Specific Populations].

Hepatic Insufficiency: 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) [see Use in Specific Populations].

Drug Interactions

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.

6. Pharmaceutical particulars

6.1 List of excipients

Tablet core

Excipients: The excipients such as Microcrystalline Cellulose (Vivapur 102) , Crospovidone (Kollidon CL), Magnesium Stearate, Colloidal Silicon Dioxide (Aerosil 200), Opadry Brown 02F565015 and Purified water.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months (2 years).

6.4 Special precautions for storage

Store below 30°C and protect from moisture.

6.5 Nature and contents of container

Blisters: 10's Alu-Alu blisters.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Marketing authorization holder

7.1 Name and Address of Manufacturer

Name:	**Hetero Labs Limited (Unit-V)**
Business Address:	TSIIC Formulation SEZ, Survey No. 411, 425, 435 & 458, Polepally village, Jadcherla Mandal, Mahaboob Nagar (Dist) – 509301, Telangana. India
Country:	INDIA
Phone:	+91 08542-238400
Fax:	+ 91 08542 238404

7.2 Name and Address of Principal

Name : Hetero Labs Limited

Business Address : 7-2-A2, Hetero Corporate,
Industrial Estates, Sanath Nagar,
Hyderabad-500 018
Telangana.

Country : INDIA

Telephone : 0091-040-23704923/24

8. REGISTRATION NUMBER

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9. DATE OF PUBLICATION OF THIS PACKAGE INSERT
