

VALSARTAN AND HYDROCHLOROTHIAZIDE- valsartan and hydrochlorothiazide tablet, film coated
Mylan Pharmaceuticals Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use valsartan and hydrochlorothiazide tablets safely and effectively. See full prescribing information for valsartan and hydrochlorothiazide tablets.

VALSARTAN and HYDROCHLOROTHIAZIDE tablets USP, for oral use
Initial U.S. Approval: 1998

WARNING: FETAL TOXICITY

See full prescribing information for complete boxed warning.

- **When pregnancy is detected, discontinue valsartan and hydrochlorothiazide tablets as soon as possible. (5.1)**
- **Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus. (5.1)**

----- **INDICATIONS AND USAGE** -----

Valsartan and hydrochlorothiazide is the combination tablet of valsartan, an angiotensin II receptor blocker (ARB) and hydrochlorothiazide (HCTZ), a diuretic. Valsartan and hydrochlorothiazide tablets are indicated for the treatment of hypertension, to lower blood pressure:

- In patients not adequately controlled with monotherapy (1)
- As initial therapy in patients likely to need multiple drugs to achieve their blood pressure goals (1)

Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions.

----- **DOSAGE AND ADMINISTRATION** -----

- Dose once daily. Titrate as needed to a maximum dose of 320 mg/25 mg (2)
- May be used as add-on/switch therapy for patients not adequately controlled on any of the components (valsartan or HCTZ) (2)
- May be substituted for titrated components (2.3)

----- **DOSAGE FORMS AND STRENGTHS** -----

Tablets (valsartan and HCTZ): 80 mg/12.5 mg, 160 mg/12.5 mg, 160 mg/25 mg, 320 mg/12.5 mg, 320 mg/25 mg (3)

----- **CONTRAINDICATIONS** -----

Anuria; Hypersensitivity to any sulfonamide-derived drugs or any component; Do not coadminister aliskiren with valsartan and hydrochlorothiazide tablets in patients with diabetes. (4)

----- **WARNINGS AND PRECAUTIONS** -----

- Hypotension: Correct volume depletion prior to initiation (5.2)
- Observe for signs of fluid or electrolyte imbalance (5.9)
- Monitor renal function and potassium in susceptible patients (5.3, 5.7)
- Exacerbation or activation of systemic lupus erythematosus (5.5)
- Acute angle-closure glaucoma (5.8)

----- **ADVERSE REACTIONS** -----

The most common reasons for discontinuation of therapy with valsartan and hydrochlorothiazide were headache and dizziness. The only adverse experience that occurred in $\geq 2\%$ of patients treated with valsartan and hydrochlorothiazide and at a higher incidence than placebo was nasopharyngitis (2.4% vs. 1.9%). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Mylan Pharmaceuticals Inc. at 1-877-446-3679 (1-877-4-INFO-RX) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----- **DRUG INTERACTIONS** -----

- Antidiabetic drugs: Dosage adjustment of antidiabetic may be required. (7)
- Cholestyramine and colestipol: Reduced absorption of thiazides. (12.3)
- Lithium: Increased risk of lithium toxicity. Monitor serum lithium concentrations during concurrent use. (7)
- Non-Steroidal Anti-Inflammatory Drugs (NSAIDs): May increase risk of renal impairment. Can reduce diuretic, natriuretic and antihypertensive effects of diuretics. (7)
- Dual inhibition of the renin-angiotensin system: Increased risk of renal impairment, hypotension and hyperkalemia. (7)

----- **USE IN SPECIFIC POPULATIONS** -----

Nursing Mothers: Nursing or drug should be discontinued (8.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 12/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: FETAL TOXICITY

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

- 2.1 General Considerations
- 2.2 Add-On Therapy
- 2.3 Replacement Therapy
- 2.4 Initial Therapy
- 2.5 Use with Other Antihypertensive Drugs

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Fetal Toxicity
- 5.2 Hypotension in Volume- and/or Salt-Depleted Patients
- 5.3 Impaired Renal Function
- 5.4 Hypersensitivity Reaction
- 5.5 Systemic Lupus Erythematosus
- 5.6 Lithium Interaction
- 5.7 Potassium Abnormalities
- 5.8 Acute Myopia and Secondary Angle-Closure Glaucoma
- 5.9 Metabolic Disturbances

6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience
- 6.2 Post-Marketing Experience

7 DRUG INTERACTIONS

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Renal Impairment
- 8.7 Hepatic Impairment

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.3 Developmental Toxicity Studies

14 CLINICAL STUDIES

14.1 Hypertension

14.2 Initial Therapy - Hypertension

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: FETAL TOXICITY

- **When pregnancy is detected, discontinue valsartan and hydrochlorothiazide tablets as soon as possible. (5.1)**
- **Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus. (5.1)**

1 INDICATIONS AND USAGE

Valsartan and hydrochlorothiazide tablets are 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 tablets.

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 one 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 (for example, 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 tablets may be used in patients whose blood pressure is not adequately controlled on monotherapy.

Replacement Therapy: Valsartan and hydrochlorothiazide tablets may be substituted for the titrated components.

Initial Therapy: Valsartan and hydrochlorothiazide tablets 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 tablets 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 (14.1)*] provides estimates of the probability of reaching a target blood pressure with valsartan and hydrochlorothiazide tablets 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 tablets 320 mg/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.

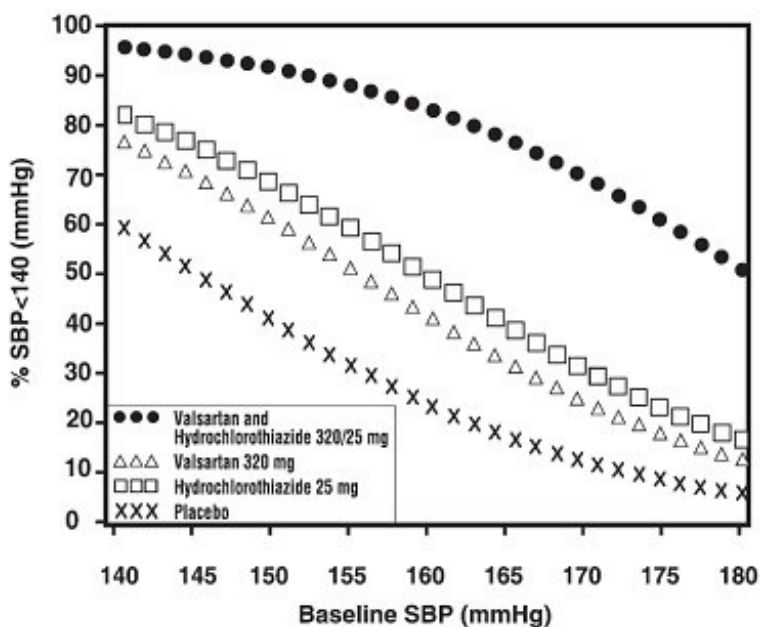


Figure 1. Probability of Achieving Systolic Blood Pressure < 140 mm/Hg at Week 8

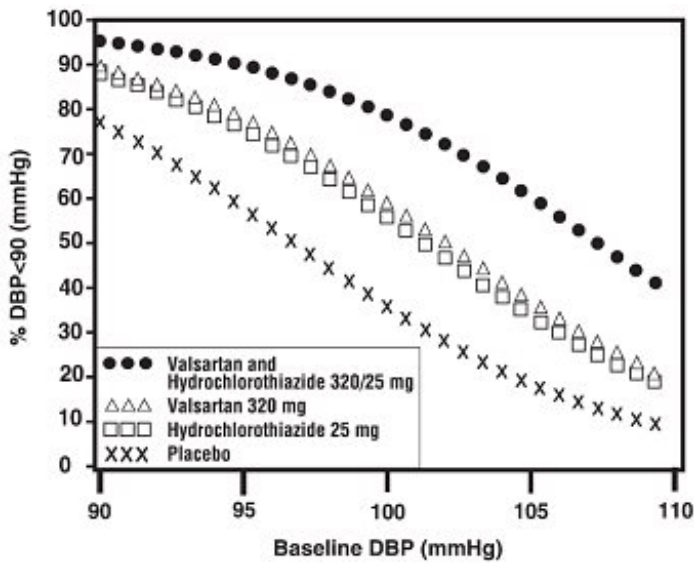


Figure 2. Probability of Achieving Diastolic Blood Pressure < 90 mm/Hg at Week 8

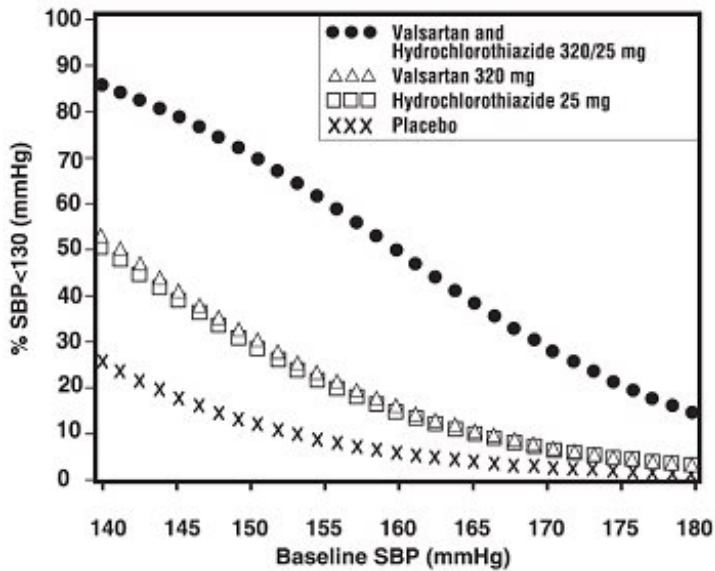


Figure 3. Probability of Achieving Systolic Blood Pressure < 130 mm/Hg at Week 8

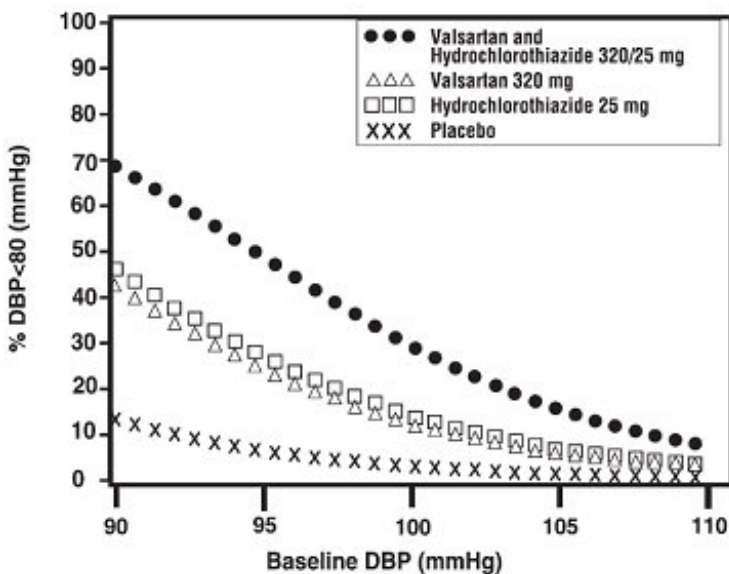


Figure 4. Probability of Achieving Diastolic Blood Pressure < 80 mm/Hg at Week 8

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 valsartan and hydrochlorothiazide tablets rises to about 84% (systolic) or 80% (diastolic). The likelihood of achieving these goals on placebo is about 23% (systolic) or 36% (diastolic).

2 DOSAGE AND ADMINISTRATION

2.1 General Considerations

The usual starting dose is valsartan and hydrochlorothiazide tablets 160 mg/12.5 mg once daily. The dosage can be increased after 1 to 2 weeks of therapy to a maximum of one 320 mg/25 mg tablet once daily as needed to control blood pressure [see *Clinical Studies (14.2)*]. Maximum antihypertensive effects are attained within 2 to 4 weeks after a change in dose.

2.2 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 tablets.

A patient who experiences dose-limiting adverse reactions on either component alone may be switched to valsartan and hydrochlorothiazide tablets 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 tablets 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 mg/25 mg.

2.3 Replacement Therapy

Valsartan and hydrochlorothiazide tablets may be substituted for the titrated components.

2.4 Initial Therapy

Valsartan and hydrochlorothiazide tablets are not recommended as initial therapy in patients with intravascular volume depletion [see *Warnings and Precautions (5.2)*].

2.5 Use with Other Antihypertensive Drugs

Valsartan and hydrochlorothiazide tablets may be administered with other antihypertensive agents.

3 DOSAGE FORMS AND STRENGTHS

80 mg/12.5 mg tablets, debossed with **M** on one side of the tablet and **V21** on the other side.

160 mg/12.5 mg tablets, debossed with **M** on one side of the tablet and **V22** on the other side.

160 mg/25 mg tablets, debossed with **M** on one side of the tablet and **V23** on the other side.

320 mg/12.5 mg tablets, debossed with **M** on one side of the tablet and **V24** on the other side.

320 mg/25 mg tablets, debossed with **M** on one side of the tablet and **V25** on the other side.

4 CONTRAINDICATIONS

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

Do not coadminister aliskiren with valsartan and hydrochlorothiazide in patients with diabetes [see *Drug Interactions (7)*].

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

5 WARNINGS AND PRECAUTIONS

5.1 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 as soon as possible [see *Use in Specific Populations (8.1)*].

Intrauterine exposure to thiazide diuretics is associated with fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions that have occurred in adults.

5.2 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 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, 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.

5.3 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. 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 [see *Drug Interactions (7)*].

5.4 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.

5.5 Systemic Lupus Erythematosus

Hydrochlorothiazide

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

erythematosis.

5.6 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 and lithium [see *Drug Interactions (7)*].

5.7 Potassium Abnormalities

Valsartan and Hydrochlorothiazide

In the controlled trials of various doses of valsartan and hydrochlorothiazide the incidence of hypertensive patients who developed hypokalemia (serum potassium < 3.5 mEq/L) was 3%; 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 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 therapy. These effects are usually minor and transient, and they are more likely to occur in patients with preexisting renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or valsartan may be required [see *Adverse Reactions (6.1)*].

5.8 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.

5.9 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.

6 ADVERSE REACTIONS

6.1 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 has been evaluated for safety in more than 5,700 patients, including over 990 treated for over 6 months, and over 370 for over one 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 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 and hydrochlorothiazide patients and 3.1% of placebo patients. The most common reasons for discontinuation of therapy with valsartan and hydrochlorothiazide 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 and at a higher incidence in valsartan and hydrochlorothiazide (n = 4,372) 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.

Other adverse reactions that have been reported with valsartan and hydrochlorothiazide (> 0.2% of valsartan and 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 \geq 110 mmHg and systolic blood pressure \geq 140 mmHg), the overall pattern of adverse reactions reported through 6 weeks of follow-up was similar in patients treated with valsartan and hydrochlorothiazide as initial therapy and in patients treated with valsartan as initial therapy. Comparing the groups treated with valsartan and hydrochlorothiazide (force-titrated to 320 mg/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 and 0% of patients receiving valsartan. There were no reported cases of syncope in either treatment group. Laboratory changes with valsartan and hydrochlorothiazide as initial therapy in patients with severe hypertension were similar to those reported with valsartan and hydrochlorothiazide in patients with less severe hypertension [see *Clinical Studies (14.2) and Drug Interactions (7)*].

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 angitis (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.

Creatinine/Blood Urea Nitrogen (BUN)

Minor elevations in creatinine and BUN occurred in 2% and 15% respectively, of patients taking valsartan and hydrochlorothiazide 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 patients, compared with 0% in placebo-treated patients.

Liver Function Tests

Occasional elevations (greater than 150%) of liver chemistries occurred in valsartan and hydrochlorothiazide-treated patients.

Neutropenia

Neutropenia was observed in 0.1% of patients treated with valsartan and hydrochlorothiazide and 0.4% of patients treated with placebo.

6.2 Post-Marketing Experience

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

Hypersensitivity: There are rare reports of angioedema. Some of these patients previously experienced angioedema with other drugs including ACE inhibitors. Valsartan and hydrochlorothiazide 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 post-marketing experience with hydrochlorothiazide:

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

7 DRUG INTERACTIONS

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.

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* (12.3)].

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, or salt substitutes containing potassium 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.

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 and other agents that affect the RAS.

Do not coadminister aliskiren with valsartan and hydrochlorothiazide in patients with diabetes. Avoid use of aliskiren with valsartan and hydrochlorothiazide 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 and non-steroidal 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* (12.3)].

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

type complications.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects. 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.

8.3 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.

8.4 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.

8.5 Geriatric Use

In the controlled clinical trials of valsartan and hydrochlorothiazide, 764 (17.5%) patients treated with valsartan and hydrochlorothiazide were ≥ 65 years and 118 (2.7%) were ≥ 75 years. No overall difference in the efficacy or safety of valsartan and hydrochlorothiazide was observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Renal Impairment

Safety and effectiveness of valsartan and hydrochlorothiazide in patients with severe renal impairment ($\text{CrCl} \leq 30$ mL/min) have not been established. No dose adjustment is required in patients with mild (CrCl 60 to 90 mL/min) or moderate (CrCl 30 to 60 mL/min) renal impairment.

8.7 Hepatic Impairment

Valsartan

No dose adjustment is necessary for patients with mild to moderate liver disease. No dosing recommendations can be provided for patients with severe liver disease.

Hydrochlorothiazide

Minor alterations of fluid and electrolyte balance may precipitate hepatic coma in patients with impaired hepatic function or progressive liver disease.

10 OVERDOSAGE

Valsartan and 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/m^2 basis. (Calculations assume an oral dose of 320 mg/day valsartan in combination with 25 mg/day hydrochlorothiazide and a 60 kg patient.)

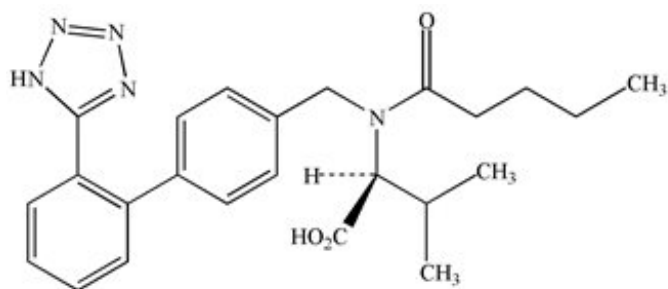
Valsartan: Valsartan was without grossly observable adverse effects at single oral doses up to 2000 mg/kg in rats and up to 1000 mg/kg in marmosets, except for salivation and diarrhea in the rat and vomiting in the marmoset at the highest dose (60 and 31 times, respectively, the MRHD on a mg/m^2 basis). (Calculations assume an oral dose of 320 mg/day and a 60 kg patient.)

Hydrochlorothiazide: The oral LD_{50} of hydrochlorothiazide is greater than 10 g/kg in both mice and rats, which represents 2,027 and 4,054 times, respectively, the MRHD on a mg/m^2 basis. (Calculations assume an oral dose of 25 mg/day and a 60 kg patient.)

11 DESCRIPTION

Valsartan and hydrochlorothiazide tablets, USP is a combination of valsartan, an orally active, specific angiotensin II receptor blocker (ARB) acting on the AT₁ receptor subtype, and hydrochlorothiazide, a diuretic.

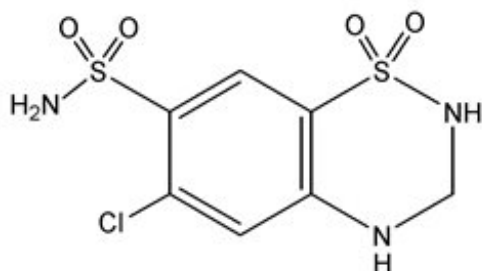
Valsartan, a nonpeptide molecule, is chemically described as *N*-[p-(*o*-1*H*-Tetrazol-5-ylphenyl)benzyl-*N*-Valeryl-L-valine. Its molecular formula is C₂₄H₂₉N₅O₃, its molecular weight is 435.5, and its structural formula is



Valsartan, USP is a white to practically white fine powder. It is soluble in ethanol and methanol and slightly soluble in water.

Hydrochlorothiazide, USP is a white, or practically white, practically odorless, crystalline powder. It is slightly soluble in water; freely soluble in sodium hydroxide solution, in *n*-butylamine, and in dimethylformamide; sparingly soluble in methanol; and insoluble in ether, in chloroform, and in dilute mineral acids. Hydrochlorothiazide is chemically described as 6-chloro-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide.

Hydrochlorothiazide is a thiazide diuretic. Its molecular formula is C₇H₈ClN₃O₄S₂, its molecular weight is 297.73, and its structural formula is



Valsartan and hydrochlorothiazide tablets are formulated for oral administration to contain valsartan and hydrochlorothiazide 80 mg/12.5 mg, 160 mg/12.5 mg, 160 mg/25 mg, 320 mg/12.5 mg and 320 mg/25 mg. The inactive ingredients of the tablets are colloidal silicon dioxide, crospovidone, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polydextrose, polyethylene glycol, povidone, pregelatinized starch (corn), sodium lauryl sulfate, titanium dioxide and triacetin. The 80 mg/12.5 mg, 160 mg/12.5 mg, 160 mg/25 mg and 320 mg/12.5 mg tablets also contain red iron oxide and yellow iron oxide. The 320 mg/25 mg tablet also contains FD&C Blue No. 2 Aluminum Lake and FD&C Yellow No. 6 Aluminum Lake.

12 CLINICAL PHARMACOLOGY

12.1 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 20,000-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.

12.2 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

Potential 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.

12.3 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 (C_{max}) by about 50%. AUC and C_{max} 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 (C_{max}) 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

Valsartan and hydrochlorothiazide 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 ($30 < \text{CrCl} < 90$ mL/min) and tripled in severe renal impairment ($\text{CrCl} \leq 30$ mL/min), compared to individuals with normal renal function ($\text{CrCl} > 90$ mL/min) [see *Use in Specific Populations (8.6)*].

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 (8.7)*].

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.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Valsartan and Hydrochlorothiazide

No carcinogenicity, mutagenicity or fertility studies have been conducted with the combination of valsartan and hydrochlorothiazide. However, these studies have been conducted for valsartan as well as hydrochlorothiazide alone. Based on the preclinical safety and human pharmacokinetic studies, there is no indication of any adverse interaction between valsartan and hydrochlorothiazide.

Valsartan

There was no evidence of carcinogenicity when valsartan was administered in the diet to mice and rats for up to 2 years at doses up to 160 and 200 mg/kg/day, respectively. These doses in mice and rats are about 2.6 and 6 times, respectively, the MRHD on a mg/m² basis. (Calculations assume an oral dose of 320 mg/day and a 60 kg patient.)

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

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

Hydrochlorothiazide

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

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

hydrochlorothiazide from 43 to 1300 mcgm/mL, and in the *Aspergillus Nidulans* non-disjunction assay at an unspecified concentration.

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

13.3 Developmental Toxicity Studies

Valsartan and Hydrochlorothiazide

There was no evidence of teratogenicity in mice, rats or rabbits treated orally with valsartan at doses up to 600, 100 and 10 mg/kg/day, respectively, in combination with hydrochlorothiazide at doses up to 188, 31 and 3 mg/kg/day. These non-teratogenic doses in mice, rats and rabbits, respectively, represent 9, 3.5 and 0.5 times the MRHD of valsartan and 38, 13 and 2 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.)

Fetotoxicity was observed in association with maternal toxicity in rats and rabbits at valsartan doses of \geq 200 and 10 mg/kg/day, respectively, in combination with hydrochlorothiazide doses of \geq 63 and 3 mg/kg/day. Fetotoxicity in rats was considered to be related to decreased fetal weights and included fetal variations of sternbrae, vertebrae, ribs and/or renal papillae. Fetotoxicity in rabbits included increased numbers of late resorptions with resultant increases in total resorptions, postimplantation losses and decreased number of live fetuses. The no observed adverse effect doses in mice, rats and rabbits for valsartan were 600, 100 and 3 mg/kg/day, respectively, in combination with hydrochlorothiazide doses of 188, 31 and 1 mg/kg/day. These no adverse effect doses in mice, rats and rabbits, respectively, represent 9, 3 and 0.18 times the MRHD of valsartan and 38, 13 and 0.5 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

No teratogenic effects were observed when valsartan was administered to pregnant mice and rats at oral doses up to 600 mg/kg/day and to pregnant rabbits at oral doses up to 10 mg/kg/day. However, significant decreases in fetal weight, pup birth weight, pup survival rate, and slight delays in developmental milestones were observed in studies in which parental rats were treated with valsartan at oral, maternally toxic (reduction in body weight gain and food consumption) doses of 600 mg/kg/day during organogenesis or late gestation and lactation. In rabbits, fetotoxicity (i.e., resorptions, litter loss, abortions and low body weight) associated with maternal toxicity (mortality) was observed at doses of 5 and 10 mg/kg/day. The no observed adverse effect doses of 600, 200 and 2 mg/kg/day in mice, rats and rabbits represent 9, 6 and 0.1 times, respectively, the MRHD on a mg/m² basis. (Calculations assume an oral dose of 320 mg/day and a 60 kg patient.)

Hydrochlorothiazide

Under the auspices of the National Toxicology Program, pregnant mice and rats that received hydrochlorothiazide via gavage at doses up to 3000 and 1000 mg/kg/day, respectively, on gestation days 6 through 15 showed no evidence of teratogenicity. These doses of hydrochlorothiazide in mice and rats represent 608 and 405 times, respectively, the MRHD dose on a mg/m² basis. (Calculations assume an oral dose of 25 mg/day and a 60 kg patient.)

14 CLINICAL STUDIES

14.1 Hypertension

Valsartan and Hydrochlorothiazide

In controlled clinical trials including over 7,600 patients, 4,372 patients were exposed to valsartan (80 mg, 160 mg and 320 mg) and concomitant hydrochlorothiazide (12.5 mg and 25 mg). Two factorial trials compared various combinations of 80 mg/12.5 mg, 80 mg/25 mg, 160 mg/12.5 mg, 160 mg/25 mg, 320 mg/12.5 mg and 320 mg/25 mg with their respective components and placebo. The combination of valsartan and hydrochlorothiazide resulted in additive placebo-adjusted decreases in systolic and diastolic blood pressure at trough of 14 to 21/8 to 11 mmHg at 80 mg/12.5 mg to 320 mg/25 mg, compared to 7 to 10/4 to 5 mmHg for valsartan 80 mg to 320 mg and 5 to 11/2 to 5 mmHg for hydrochlorothiazide 12.5 mg to 25 mg, alone.

Three other controlled trials investigated the addition of hydrochlorothiazide to patients who did not respond adequately to valsartan 80 mg to valsartan 320 mg, resulted in the additional lowering of systolic and diastolic blood pressure by approximately 4 to 12/2 to 5 mmHg.

The maximal antihypertensive effect was attained 4 weeks after the initiation of therapy, the first time point at which blood pressure was measured in these trials.

In long-term follow-up studies (without placebo control) the effect of the combination of valsartan and hydrochlorothiazide appeared to be maintained for up to 2 years. The antihypertensive effect is independent of age or gender. The overall response to the combination was similar for Black and non-Black patients.

There was essentially no change in heart rate in patients treated with the combination of valsartan and hydrochlorothiazide in controlled trials. There are no trials of the valsartan and hydrochlorothiazide combination tablet demonstrating reductions in cardiovascular risk in patients with hypertension, but the hydrochlorothiazide component and several ARBs, which are the same pharmacological class as the valsartan component, have demonstrated such benefits.

Valsartan

The antihypertensive effects of valsartan were demonstrated principally in seven placebo-controlled, 4- to 12-week trials (one in patients over 65 years) of dosages from 10 to 320 mg/day in patients with baseline diastolic blood pressures of 95 to 115 mmHg. The studies allowed comparison of once daily and twice daily regimens of 160 mg/day; comparison of peak and trough effects; comparison (in pooled data) of response by gender, age and race; and evaluation of incremental effects of hydrochlorothiazide.

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

In most patients, after administration of a single oral dose, onset of antihypertensive activity occurs at approximately 2 hours, and maximum reduction of blood pressure is achieved within 6 hours. The antihypertensive effect persists for 24 hours after dosing, but there is a decrease from peak effect at lower doses (40 mg) presumably reflecting loss of inhibition of angiotensin II. At higher doses, however (160 mg), there is little difference in peak and trough effect. During repeated dosing, the reduction in blood pressure with any dose is substantially present within 2 weeks, and maximal reduction is generally attained after 4 weeks. In long-term follow-up studies (without placebo control) the effect of valsartan appeared to be maintained for up to 2 years. The antihypertensive effect is independent of age, gender or race. The latter finding regarding race is based on pooled data and should be viewed with caution, because antihypertensive drugs that affect the renin-angiotensin system (that is, ACE inhibitors and angiotensin II blockers) have generally been found to be less effective in low-renin hypertensives (frequently Blacks) than in high-renin hypertensives (frequently Whites). In pooled, randomized, controlled trials of valsartan that included a total of 140 Blacks and 830 Whites, valsartan and an ACE-inhibitor control were generally at least as effective in Blacks as Whites. The explanation for this difference from previous findings is unclear.

Abrupt withdrawal of valsartan has not been associated with a rapid increase in blood pressure.

The seven studies of valsartan monotherapy included over 2,000 patients randomized to various doses of valsartan and about 800 patients randomized to placebo. Doses below 80 mg were not consistently distinguished from those of placebo at trough, but doses of 80 mg, 160 mg and 320 mg produced dose related decreases in systolic and diastolic blood pressure, with the difference from placebo of approximately 6 to 9/3 to 5 mmHg at 80 mg to 160 mg and 9/6 mmHg at 320 mg.

Patients with an inadequate response to 80 mg once daily were titrated to either 160 mg once daily or 80 mg twice daily, which resulted in a comparable response in both groups.

In another 4-week study, 1,876 patients randomized to valsartan 320 mg once daily had an incremental blood pressure reduction 3/1 mmHg lower than did 1,900 patients randomized to valsartan 160 mg once daily.

In controlled trials, the antihypertensive effect of once daily valsartan 80 mg was similar to that of once daily enalapril 20 mg or once daily lisinopril 10 mg.

There was essentially no change in heart rate in valsartan-treated patients in controlled trials.

14.2 Initial Therapy - Hypertension

The safety and efficacy of valsartan and hydrochlorothiazide as initial therapy for patients with severe hypertension (defined as a sitting diastolic blood pressure \geq 110 mmHg and systolic blood pressure \geq 140 mmHg off all antihypertensive therapy) was studied in a 6-week multicenter, randomized, double-blind study. Patients were randomized to either valsartan and hydrochlorothiazide 160 mg/12.5 mg once daily or to valsartan (160 mg once daily) and followed for blood pressure response. Patients were force-titrated at 2 week intervals. Patients on combination therapy were subsequently titrated to 160 mg/25 mg followed by 320 mg/25 mg valsartan and hydrochlorothiazide. Patients on monotherapy were subsequently titrated to 320 mg valsartan followed by a titration to 320 mg valsartan to maintain the blind.

The study randomized 608 patients, including 261 (43%) females, 147 (24%) Blacks and 75 (12%) \geq 65 years of age. The mean blood pressure at baseline for the total population was 168/112 mmHg. The mean age was 52 years. After 4 weeks of therapy, reductions in systolic and diastolic blood pressure were 9/5 mmHg greater in the group treated with valsartan and hydrochlorothiazide compared to valsartan. Similar trends were seen when the patients were grouped according to gender, race or age.

16 HOW SUPPLIED/STORAGE AND HANDLING

Valsartan and Hydrochlorothiazide Tablets, USP are available containing 80 mg/12.5 mg, 160 mg/12.5 mg, 160 mg/25 mg, 320 mg/12.5 mg or 320 mg/25 mg of valsartan, USP and hydrochlorothiazide, USP

The 80 mg/12.5 mg tablets are an orange film-coated, round, unscored tablets, debossed with **M** on one side of the tablet and **V21** on the other side. They are available as follows:

NDC 0378-6321-77
bottles of 90 tablets

NDC 0378-6321-05
bottles of 500 tablets

The 160 mg/12.5 mg tablets are an orange film-coated, round, unscored tablets, debossed with **M** on one side of the tablet and **V22** on the other side. They are available as follows:

NDC 0378-6322-77
bottles of 90 tablets

NDC 0378-6322-05
bottles of 500 tablets

The 160 mg/25 mg tablets are an orange film-coated, oval, unscored tablets, debossed with **M** on one

side of the tablet and **V23** on the other side. They are available as follows:

NDC 0378-6323-77

bottles of 90 tablets

NDC 0378-6323-05

bottles of 500 tablets

The 320 mg/12.5 mg tablets are an orange film-coated, oval, unscored tablets debossed with **M** on one side of the tablet and **V24** on the other side. They are available as follows:

NDC 0378-6324-77

bottles of 90 tablets

NDC 0378-6324-05

bottles of 500 tablets

The 320 mg/25 mg tablets are beige film-coated, oval, unscored tablets debossed with **M** on one side of the tablet and **V25** on the other side. They are available as follows:

NDC 0378-6325-77

bottles of 90 tablets

NDC 0378-6325-05

bottles of 500 tablets

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]

Protect from moisture and heat.

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

PHARMACIST: Dispense the Patient Information Leaflet with each prescription.

17 PATIENT COUNSELING INFORMATION

Information for Patients:*Pregnancy:* Female patients of childbearing age should be told about the consequences of exposure to valsartan and hydrochlorothiazide during pregnancy. Discuss treatment options with women planning to become pregnant. Patients should be asked to report pregnancies to their physicians as soon as possible.

Symptomatic Hypotension: A patient receiving valsartan and hydrochlorothiazide should be cautioned that lightheadedness can occur, especially during the first days of therapy, and that it should be reported to the prescribing physician. The patients should be told that if syncope occurs, valsartan and hydrochlorothiazide should be discontinued until the physician has been consulted.

All patients should be cautioned that inadequate fluid intake, excessive perspiration, diarrhea or vomiting can lead to an excessive fall in blood pressure, with the same consequences of lightheadedness and possible syncope.

Potassium Supplements: A patient receiving valsartan and hydrochlorothiazide should be told not to use potassium supplements or salt substitutes containing potassium without consulting the prescribing physician.

FDA-Approved Patient Labeling

PATIENT INFORMATION LEAFLET

VALSARTAN AND HYDROCHLOROTHIAZIDE TABLETS, USP

(val sar' tan) (hye" droe klor" oh thye' a zide)

80 mg/12.5 mg, 160 mg/12.5 mg, 160 mg/25 mg, 320 mg/12.5 mg and 320 mg/25 mg

Read the Patient Information that comes with valsartan and hydrochlorothiazide tablets before you start taking it and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your doctor about your condition and treatment. If you have any questions about valsartan and hydrochlorothiazide tablets, ask your doctor or pharmacist.

What is the most important information I should know about valsartan and hydrochlorothiazide tablets?

Valsartan and hydrochlorothiazide tablets can cause harm or death to an unborn baby. Talk to your doctor about other ways to lower your blood pressure if you plan to become pregnant. If you get pregnant while taking valsartan and hydrochlorothiazide tablets, tell your doctor right away.

What are valsartan and hydrochlorothiazide tablets?

Valsartan and hydrochlorothiazide tablets contains two prescription medicines:

1. valsartan, an angiotensin receptor blocker (ARB)
2. hydrochlorothiazide (HCTZ), a water pill (diuretic)

Valsartan and hydrochlorothiazide tablets may be used to lower high blood pressure (hypertension) in adults-

- when one medicine to lower your high blood pressure is not enough
- as the first medicine to lower high blood pressure if your doctor decides you are likely to need more than one medicine.

Valsartan and hydrochlorothiazide tablets has not been studied in children under 18 years of age.

Who should not take valsartan and hydrochlorothiazide tablets?

Do not take valsartan and hydrochlorothiazide tablets if you:

- **are allergic to any of the ingredients in valsartan and hydrochlorothiazide tablets.** See the end of this leaflet for a complete list of ingredients in valsartan and hydrochlorothiazide tablets.
- make less urine due to kidney problems
- are allergic to medicines that contain sulfonamides.

What should I tell my doctor before taking valsartan and hydrochlorothiazide tablets?

Tell your doctor about all your medical conditions including if you:

- **are pregnant or plan to become pregnant.** See “What is the most important information I should know about valsartan and hydrochlorothiazide tablets?”
- **are breast-feeding.** Valsartan and hydrochlorothiazide passes into breast milk. You should choose either to take valsartan and hydrochlorothiazide tablets or breast-feed, but not both.
- **have liver problems**
- **have kidney problems**
- **have or had gallstones**
- **have Lupus**
- **have low levels of potassium** (with or without symptoms such as muscle weakness, muscle spasms, abnormal heart rhythm) or magnesium in your blood
- **have high levels of calcium in your blood** (with or without symptoms such as nausea, vomiting, constipation, stomach pain, frequent urination, thirst, muscle weakness and twitching).

- **have high levels of uric acid in the blood.**
- **have ever had a reaction called angioedema to another blood pressure medication. Angioedema causes swelling of the face, lips, tongue, throat, and may cause difficulty breathing.**

Tell your doctor about all the medicines you take including prescription and non-prescription medicines, vitamins and herbal supplements. Some of your other medicines and valsartan and hydrochlorothiazide tablets could affect each other, causing serious side effects. Especially, tell your doctor if you take:

- other medicines for high blood pressure or a heart problem
- water pills (diuretics)
- potassium supplements. Your doctor may check the amount of potassium in your blood periodically.
- a salt substitute. Your doctor may check the amount of potassium in your blood periodically.
- antidiabetic medicines including insulin
- narcotic pain medicines
- sleeping pills
- lithium, a medicine used in some types of depression (Eskalith^{®*}, Lithobid^{®*}, Lithium Carbonate, Lithium Citrate)
- aspirin or other medicines called Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), like ibuprofen or naproxen
- digoxin or other digitalis glycosides (a heart medicine)
- muscle relaxants (medicines used during operations)
- certain cancer medicines, like cyclophosphamide or methotrexate
- certain antibiotics (rifamycin group), a drug used to protect against transplant rejection (cyclosporin) or an antiretroviral drug used to treat HIV/AIDS infection (ritonavir). These drugs may increase the effect of valsartan.

Ask your doctor if you are not sure if you are taking one of these medicines.

Know the medicines you take. Keep a list of your medicines with you to show to your doctor and pharmacist when a new medicine is prescribed. Talk to your doctor or pharmacist before you start taking any new medicine. Your doctor or pharmacist will know what medicines are safe to take together.

How should I take valsartan and hydrochlorothiazide tablets?

- Take valsartan and hydrochlorothiazide tablets exactly as prescribed by your doctor. Your doctor may change your dose if needed.
- Take valsartan and hydrochlorothiazide tablets once each day.
- Valsartan and hydrochlorothiazide tablets can be taken with or without food.
- If you miss a dose, take it as soon as you remember. If it is close to your next dose, do not take the missed dose. Just take the next dose at your regular time.
- If you take too much valsartan and hydrochlorothiazide, call your doctor or Poison Control Center, or go to the nearest hospital emergency room.

What should I avoid while taking valsartan and hydrochlorothiazide tablets?

You should not take valsartan and hydrochlorothiazide tablets during pregnancy. See “What is the most important information I should know about valsartan and hydrochlorothiazide tablets?”

What are the possible side effects of valsartan and hydrochlorothiazide tablets?

Valsartan and hydrochlorothiazide tablets may cause serious side effects including:

- **Harm to an unborn baby causing injury and even death.** See “What is the most important information I should know about valsartan and hydrochlorothiazide tablets?”
- **Low blood pressure (hypotension).** Low blood pressure is most likely to happen if you:
 - take water pills
 - are on a low salt diet
 - get dialysis treatments
 - have heart problems
 - get sick with vomiting or diarrhea
 - drink alcohol

Lie down if you feel faint or dizzy. Call your doctor right away.

- **Allergic reactions.** People with and without allergy problems or asthma who take valsartan and hydrochlorothiazide tablets may get allergic reactions.
- **Worsening of Lupus.** Hydrochlorothiazide, one of the medicines in valsartan and hydrochlorothiazide tablets may cause Lupus to become active or worse.
- **Fluid and electrolyte (salt) problems.** Tell your doctor about any of the following signs and symptoms of fluid and electrolyte problems:

-
- | | | |
|------------------------------|-------------------------|-------------------------|
| • dry mouth | • drowsiness | • muscle fatigue |
| • thirst | • restlessness | • very low urine output |
| • lack of energy (lethargic) | • confusion | • fast heartbeat |
| • weakness | • seizures | • nausea and vomiting |
| | • muscle pain or cramps | |
-

- **Kidney problems.** Kidney problems may become worse in people that already have kidney disease. Some people will have changes on blood tests for kidney function and may need a lower dose of valsartan and hydrochlorothiazide tablets. Call your doctor if you get swelling in your feet, ankles, or hands, or unexplained weight gain. If you have heart failure, your doctor should check your kidney function before prescribing valsartan and hydrochlorothiazide tablets.
- **Skin rash.** Call your doctor right away if you have an unusual skin rash.
- **Eye Problems.** One of the medicines in valsartan and hydrochlorothiazide tablets can cause eye problems that may lead to vision loss. Symptoms of eye problems can happen within hours to weeks of starting valsartan and hydrochlorothiazide tablets. Tell your doctor right away if you have:
 - decrease in vision
 - eye pain

Other side effects were generally mild and brief. They generally have not caused patients to stop taking valsartan and hydrochlorothiazide tablets.

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of valsartan and hydrochlorothiazide tablets. For a complete list, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How do I store valsartan and hydrochlorothiazide tablets?

- Store valsartan and hydrochlorothiazide tablets at 20° to 25°C (68° to 77°F). Protect from moisture and heat.
- Keep valsartan and hydrochlorothiazide tablets in a closed container in a dry place.

Keep valsartan and hydrochlorothiazide tablets and all medicines out of the reach of children.

General information about valsartan and hydrochlorothiazide tablets

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use valsartan and hydrochlorothiazide tablets for a condition for which it was not prescribed. Do not give valsartan and hydrochlorothiazide tablets to other people, even if they have the same symptoms you have. It may harm them.

This leaflet summarizes the most important information about valsartan and hydrochlorothiazide tablets. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about valsartan and hydrochlorothiazide tablets that is written for health professionals. For more information about valsartan and hydrochlorothiazide tablets, call Mylan Pharmaceuticals Inc. at 1-877-446-3679 (1-877-4-INFO-RX).

What are the ingredients in valsartan and hydrochlorothiazide tablets?

Active ingredients: Valsartan and hydrochlorothiazide

Inactive ingredients: colloidal silicon dioxide, crospovidone, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polydextrose, polyethylene glycol, povidone, pregelatinized starch (corn), sodium lauryl sulfate, titanium dioxide and triacetin. The 80 mg/12.5 mg, 160 mg/12.5 mg, 160 mg/25 mg and 320 mg/12.5 mg tablets also contain red iron oxide and yellow iron oxide. The 320 mg/25 mg tablet also contains FD&C Blue No. 2 Aluminum Lake and FD&C Yellow No. 6 Aluminum Lake.

What is high blood pressure (hypertension)?

Blood pressure is the force in your blood vessels when your heart beats and when your heart rests. You have high blood pressure when the force is too much. Valsartan and hydrochlorothiazide tablets can help your blood vessels relax and reduce the amount of water in your body so your blood pressure is lower. Medicines that lower blood pressure lower your risk of having a stroke or heart attack.

High blood pressure makes the heart work harder to pump blood throughout the body and causes damage to the blood vessels. If high blood pressure is not treated, it can lead to stroke, heart attack, heart failure, kidney failure, and vision problems.

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Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.

REVISED DECEMBER 2014
VATZ:R5ppt

PRINCIPAL DISPLAY PANEL - 80 mg/ 12.5 mg

NDC 0378-6321-77

**Valsartan and
Hydrochlorothiazide
Tablets, USP
80 mg/12.5 mg**

**PHARMACIST: Dispense the accompanying
Patient Information Leaflet to each patient.**

Rx only 90 Tablets

Each film-coated tablet contains:
Valsartan, USP 80 mg
Hydrochlorothiazide, USP 12.5 mg

Dispense in a tight, light-resistant
container as defined in the USP
using a child-resistant closure.

Keep container tightly closed.

**Keep this and all medication
out of the reach of children.**

**Store at 20° to 25°C (68° to 77°F).
[See USP Controlled Room
Temperature.]**

Protect from moisture and heat.

Usual Dosage: See accompanying
prescribing information.

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Morgantown, WV 26505 U.S.A.

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Each film-coated tablet contains:
Valsartan, USP 80 mg
Hydrochlorothiazide, USP 12.5 mg

NDC 0378-6321-77

**Valsartan and
Hydrochlorothiazide**
Tablets, USP

80 mg/12.5 mg

PHARMACIST: Dispense the accompanying
Patient Information Leaflet to each patient.

Mylan®

Rx only 90 Tablets

Dispense in a tight, light-resistant
container as defined in the USP
using a child-resistant closure.
Keep container tightly closed.
**Keep this and all medication
out of the reach of children.**
Store at 20° to 25°C (68° to 77°F).
[See USP Controlled Room
Temperature.]
Protect from moisture and heat.
Usual Dosage: See accompanying
prescribing information.
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RM6321MM2

PRINCIPAL DISPLAY PANEL - 160 mg/ 12.5 mg

NDC 0378-6322-77

**Valsartan and
Hydrochlorothiazide
Tablets, USP
160 mg/12.5 mg**

**PHARMACIST: Dispense the accompanying
Patient Information Leaflet to each patient.**

Rx only 90 Tablets

Each film-coated tablet contains:
Valsartan, USP 160 mg
Hydrochlorothiazide, USP 12.5 mg

Dispense in a tight, light-resistant
container as defined in the USP
using a child-resistant closure.

Keep container tightly closed.

**Keep this and all medication
out of the reach of children.**

**Store at 20° to 25°C (68° to 77°F).
[See USP Controlled Room
Temperature.]**

Protect from moisture and heat.

Usual Dosage: See accompanying
prescribing information.

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Each film-coated tablet contains:
Valsartan, USP 160 mg
Hydrochlorothiazide, USP 12.5 mg

NDC 0378-6322-77

**Valsartan and
Hydrochlorothiazide**
Tablets, USP

160 mg/12.5 mg

PHARMACIST: Dispense the accompanying
Patient Information Leaflet to each patient.

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Rx only 90 Tablets

Dispense in a tight, light-resistant
container as defined in the USP
using a child-resistant closure.
Keep container tightly closed.
**Keep this and all medication
out of the reach of children.**
Store at 20° to 25°C (68° to 77°F).
[See USP Controlled Room
Temperature.]
Protect from moisture and heat.
Usual Dosage: See accompanying
prescribing information.
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PRINCIPAL DISPLAY PANEL - 160 mg/ 25 mg

NDC 0378-6323-77

**Valsartan and
Hydrochlorothiazide
Tablets, USP
160 mg/25 mg**

**PHARMACIST: Dispense the accompanying
Patient Information Leaflet to each patient.**

Rx only 90 Tablets

Each film-coated tablet contains:
Valsartan, USP 160 mg
Hydrochlorothiazide, USP 25 mg

Dispense in a tight, light-resistant
container as defined in the USP
using a child-resistant closure.

Keep container tightly closed.

**Keep this and all medication
out of the reach of children.**

**Store at 20° to 25°C (68° to 77°F).
[See USP Controlled Room
Temperature.]**

Protect from moisture and heat.

Usual Dosage: See accompanying
prescribing information.

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RM6323MM2

Each film-coated tablet contains:
Valsartan, USP 160 mg
Hydrochlorothiazide, USP 25 mg

NDC 0378-6323-77

**Valsartan and
Hydrochlorothiazide**
Tablets, USP

160 mg/25 mg

PHARMACIST: Dispense the accompanying
Patient Information Leaflet to each patient.

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Rx only 90 Tablets

Dispense in a tight, light-resistant
container as defined in the USP
using a child-resistant closure.
Keep container tightly closed.
**Keep this and all medication
out of the reach of children.**
Store at 20° to 25°C (68° to 77°F).
[See USP Controlled Room
Temperature.]
Protect from moisture and heat.
Usual Dosage: See accompanying
prescribing information.
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RM6323MM2

PRINCIPAL DISPLAY PANEL - 320 mg/ 12.5 mg

NDC 0378-6324-77

Valsartan and

Hydrochlorothiazide

Tablets, USP

320 mg/12.5 mg

PHARMACIST: Dispense the accompanying Patient Information Leaflet to each patient.

Rx only 90 Tablets

Each film-coated tablet contains:

Valsartan, USP 320 mg

Hydrochlorothiazide, USP 12.5 mg

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

Keep container tightly closed.

Keep this and all medication out of the reach of children.

Store at 20° to 25°C (68° to 77°F).

[See USP Controlled Room Temperature.]

Protect from moisture and heat.

Usual Dosage: See accompanying prescribing information.

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RM6324MM3

Each film-coated tablet contains:
Valsartan, USP 320 mg
Hydrochlorothiazide, USP 12.5 mg

NDC 0378-6324-77

Valsartan and Hydrochlorothiazide
Tablets, USP

320 mg/12.5 mg

PHARMACIST: Dispense the accompanying Patient Information Leaflet to each patient.

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Rx only 90 Tablets

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.
Keep container tightly closed.
Keep this and all medication out of the reach of children.
Store at 20° to 25°C (68° to 77°F).
[See USP Controlled Room Temperature.]
Protect from moisture and heat.
Usual Dosage: See accompanying prescribing information.
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RM6324MM3

PRINCIPAL DISPLAY PANEL - 320 mg/ 25 mg

NDC 0378-6325-77

Valsartan and Hydrochlorothiazide

Tablets, USP
320 mg/25 mg

PHARMACIST: Dispense the accompanying Patient Information Leaflet to each patient.

Rx only 90 Tablets

Each film-coated tablet contains:
Valsartan, USP 320 mg
Hydrochlorothiazide, USP 25 mg

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

Keep container tightly closed.

Keep this and all medication out of the reach of children.

Store at 20° to 25°C (68° to 77°F).
[See USP Controlled Room Temperature.]

Protect from moisture and heat.

Usual Dosage: See accompanying prescribing information.

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RM6325MM3

Each film-coated tablet contains:
Valsartan, USP 320 mg
Hydrochlorothiazide, USP 25 mg

NDC 0378-6325-77

Valsartan and Hydrochlorothiazide
Tablets, USP
320 mg/25 mg

PHARMACIST: Dispense the accompanying Patient Information Leaflet to each patient.

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Rx only 90 Tablets

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.
Keep container tightly closed.
Keep this and all medication out of the reach of children.
Store at 20° to 25°C (68° to 77°F).
[See USP Controlled Room Temperature.]
Protect from moisture and heat.
Usual Dosage: See accompanying prescribing information.
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RM6325MM3

VALSARTAN AND HYDROCHLOROTHIAZIDE

valsartan and hydrochlorothiazide tablet, film coated

Product Information

Product Type	HUMAN PRESCRIPTION DRUG LABEL	Item Code (Source)	NDC:0378-6321
Route of Administration	ORAL	DEA Schedule	

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
VALSARTAN (VALSARTAN)	VALSARTAN	80 mg
HYDROCHLOROTHIAZIDE (HYDROCHLOROTHIAZIDE)	HYDROCHLOROTHIAZIDE	12.5 mg

Inactive Ingredients

Ingredient Name	Strength
SILICON DIOXIDE	
CROSPVIDONE	
HYPROMELLOSES	
FERRIC OXIDE RED	
LACTOSE MONOHYDRATE	
MAGNESIUM STEARATE	
FERRIC OXIDE YELLOW	
CELLULOSE, MICROCRYSTALLINE	
POLYDEXTROSE	
POLYETHYLENE GLYCOLS	
POVIDONES	
STARCH, CORN	
SODIUM LAURYL SULFATE	
TITANIUM DIOXIDE	
TRACETIN	

Product Characteristics

Color	ORANGE	Score	no score
Shape	ROUND	Size	9mm
Flavor		Imprint Code	M;V21
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0378-6321-77	90 in 1 BOTTLE, PLASTIC; Combination Product Type = C112160		
2	NDC:0378-6321-05	500 in 1 BOTTLE, PLASTIC; Combination Product Type = C112160		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA078020	09/21/2012	

VALSARTAN AND HYDROCHLOROTHIAZIDE

valsartan and hydrochlorothiazide tablet, film coated

Product Information

Product Type	HUMAN PRESCRIPTION DRUG LABEL	Item Code (Source)	NDC:0378-6322
Route of Administration	ORAL	DEA Schedule	

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
VALSARTAN (VALSARTAN)	VALSARTAN	160 mg
HYDROCHLOROTHIAZIDE (HYDROCHLOROTHIAZIDE)	HYDROCHLOROTHIAZIDE	12.5 mg

Inactive Ingredients

Ingredient Name	Strength
SILICON DIOXIDE	
CROSPVIDONE	
HYPROMELLOSES	
FERRIC OXIDE RED	
LACTOSE MONOHYDRATE	
MAGNESIUM STEARATE	
FERRIC OXIDE YELLOW	
CELLULOSE, MICROCRYSTALLINE	
POLYDEXTROSE	
POLYETHYLENE GLYCOLS	
POVIDONES	
STARCH, CORN	
SODIUM LAURYL SULFATE	
TITANIUM DIOXIDE	
TRIACETIN	

Product Characteristics

Color	ORANGE	Score	no score
Shape	ROUND	Size	10mm
Flavor		Imprint Code	M;V22
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0378-6322-77	90 in 1 BOTTLE, PLASTIC; Combination Product Type = C112160		

2	NDC:0378-6322-05	500 in 1 BOTTLE, PLASTIC; Combination Product Type = C112160
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Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA078020	09/21/2012	

VALSARTAN AND HYDROCHLOROTHIAZIDE

valsartan and hydrochlorothiazide tablet, film coated

Product Information

Product Type	HUMAN PRESCRIPTION DRUG LABEL	Item Code (Source)	NDC:0378-6323
Route of Administration	ORAL	DEA Schedule	

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
VALSARTAN (VALSARTAN)	VALSARTAN	160 mg
HYDROCHLOROTHIAZIDE (HYDROCHLOROTHIAZIDE)	HYDROCHLOROTHIAZIDE	25 mg

Inactive Ingredients

Ingredient Name	Strength
SILICON DIOXIDE	
CROSPVIDONE	
HYPROMELLOSES	
FERRIC OXIDE RED	
LACTOSE MONOHYDRATE	
MAGNESIUM STEARATE	
FERRIC OXIDE YELLOW	
CELLULOSE, MICROCRYSTALLINE	
POLYDEXTROSE	
POLYETHYLENE GLYCOLS	
POVIDONES	
STARCH, CORN	
SODIUM LAURYL SULFATE	
TRIACETIN	
TITANIUM DIOXIDE	

Product Characteristics

Color	ORANGE	Score	no score
Shape	OVAL	Size	15mm
Flavor		Imprint Code	M;V23
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0378-6323-77	90 in 1 BOTTLE, PLASTIC; Combination Product Type = C112160		
2	NDC:0378-6323-05	500 in 1 BOTTLE, PLASTIC; Combination Product Type = C112160		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA078020	09/21/2012	

VALSARTAN AND HYDROCHLOROTHIAZIDE

valsartan and hydrochlorothiazide tablet, film coated

Product Information

Product Type	HUMAN PRESCRIPTION DRUG LABEL	Item Code (Source)	NDC:0378-6324
Route of Administration	ORAL	DEA Schedule	

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
VALSARTAN (VALSARTAN)	VALSARTAN	320 mg
HYDROCHLOROTHIAZIDE (HYDROCHLOROTHIAZIDE)	HYDROCHLOROTHIAZIDE	12.5 mg

Inactive Ingredients

Ingredient Name	Strength
SILICON DIOXIDE	
CROSPVIDONE	
HYPROMELLOSES	
FERRIC OXIDE RED	
LACTOSE MONOHYDRATE	
MAGNESIUM STEARATE	
FERRIC OXIDE YELLOW	
CELLULOSE, MICROCRYSTALLINE	
POLYDEXTROSE	
POLYETHYLENE GLYCOLS	
POVIDONES	
STARCH, CORN	
SODIUM LAURYL SULFATE	
TITANIUM DIOXIDE	
TRACETIN	

Product Characteristics

Color	ORANGE	Score	no score
Shape	OVAL	Size	21mm
Flavor		Imprint Code	M;V24
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0378-6324-77	90 in 1 BOTTLE, PLASTIC; Combination Product Type = C112160		
2	NDC:0378-6324-05	500 in 1 BOTTLE, PLASTIC; Combination Product Type = C112160		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA078020	09/21/2012	

VALSARTAN AND HYDROCHLOROTHIAZIDE

valsartan and hydrochlorothiazide tablet, film coated

Product Information

Product Type	HUMAN PRESCRIPTION DRUG LABEL	Item Code (Source)	NDC:0378-6325
Route of Administration	ORAL	DEA Schedule	

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
VALSARTAN (VALSARTAN)	VALSARTAN	320 mg
HYDROCHLOROTHIAZIDE (HYDROCHLOROTHIAZIDE)	HYDROCHLOROTHIAZIDE	25 mg

Inactive Ingredients

Ingredient Name	Strength
SILICON DIOXIDE	
CROSPVIDONE	
HYPROMELLOSES	
LACTOSE MONOHYDRATE	
FD&C BLUE NO. 2	
MAGNESIUM STEARATE	
CELLULOSE, MICROCRYSTALLINE	
FD&C YELLOW NO. 6	

POLYDEXTROSE
POLYETHYLENE GLYCOLS
POVIDONES
STARCH, CORN
SODIUM LAURYL SULFATE
TITANIUM DIOXIDE
TRIACETIN

Product Characteristics

Color	ORANGE (beige)	Score	no score
Shape	OVAL	Size	21mm
Flavor		Imprint Code	M;V25
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0378-6325-77	90 in 1 BOTTLE, PLASTIC; Combination Product Type = C112160		
2	NDC:0378-6325-05	500 in 1 BOTTLE, PLASTIC; Combination Product Type = C112160		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA078020	09/21/2012	

Labeler - Mylan Pharmaceuticals Inc. (059295980)