

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use VALSARTAN TABLETS safely and effectively. See full prescribing information for VALSARTAN TABLETS.

VALSARTAN tablets, for oral use

Initial U.S. Approval: 1996

WARNING: FETAL TOXICITY	
<i>See full prescribing information for complete boxed warning.</i>	
• When pregnancy is detected, discontinue valsartan 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 tablets are angiotensin II receptor blocker (ARB) indicated for:

- Hypertension, to lower blood pressure in adults and children 6 years and older. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions (1, 11)
- Heart failure (NYHA class II-IV), to reduce hospitalization for heart failure in adults (1, 2)
- Post-myocardial infarction, for the reduction of cardiovascular mortality in clinically stable patients with left ventricular failure or left ventricular dysfunction following myocardial infarction in adults (1, 3)

DOSAGE AND ADMINISTRATION

Indication	Starting Dose	Dose Range*
Hypertension Adults (2, 2)	80-160 mg once daily	80-320 mg once daily
6-16 years (2, 2)	1 mg/kg once daily Up to 40 mg daily	14 mg/kg once daily Up to 160 mg daily
Heart Failure (2, 4)	40 mg twice daily	40-160 mg twice daily
Post-Myocardial Infarction (2, 5)	20 mg twice daily	20-160 mg twice daily

*As tolerated by patient

DOSAGE FORMS AND STRENGTHS

Tablets (mg): 40 (scored), 80, 160, 320 (3)

CONTRAINDICATIONS

Known hypersensitivity to any component. Do not coadminister aliskiren with valsartan in patients with diabetes (4)

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FULL PRESCRIBING INFORMATION**WARNING: FETAL TOXICITY**

- When pregnancy is detected, discontinue valsartan 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**1.1 Hypertension**

Valsartan tablets are indicated for the treatment of hypertension, to lower blood pressure in adults and pediatric patients six years of age and older. 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 the class to which valsartan principally belongs. There are no controlled trials in hypertensive patients demonstrating risk reduction with valsartan 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 also have been seen regularly.

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

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

Valsartan tablets may be used alone or in combination with other antihypertensive agents.

Additional pediatric use information is approved for Novartis Pharmaceuticals Corporation's Diovan (valsartan) tablets. However, due to Novartis Pharmaceuticals Corporation's marketing exclusivity rights, this drug product is not labeled with that information.

1.2 Heart Failure

Valsartan tablets are indicated to reduce the risk of hospitalization for heart failure in adult patients with heart failure (NYHA class II-IV). There is no evidence that valsartan tablets provide added benefits when it is used with an adequate dose of an angiotensin converting enzyme (ACE) inhibitor [see *Clinical Studies* (14.2)].

1.3 Post-Myocardial Infarction

In clinically stable adult patients with left ventricular failure or left ventricular dysfunction following myocardial infarction, Valsartan tablets is indicated to reduce the risk of cardiovascular mortality [see *Clinical Studies* (14.3)].

2 DOSAGE AND ADMINISTRATION**2.1 Important Dosage and Preparation Information**

Valsartan tablets and oral suspension are not substitutable on a milligram-per-milligram basis. Do not combine two dosage forms to achieve the total dose. The systemic exposure to valsartan (AUC) is 60% higher with the suspension compared to tablets [see *Clinical Pharmacology* (12.3)].

Use of the oral suspension is recommended:

- in patients ≥ 6 years of age who cannot swallow tablets and
- in pediatric patients for whom the calculated dose (mg/kg) does not correspond to the available tablet strengths of valsartan tablets.

When switching between suspension and tablets, the dose of valsartan may need to be adjusted.

Preparation of Suspension (for 160 mL of a 4 mg/mL suspension)

- Add 80 mL of Ora-Plus™ oral suspending vehicle to an amber glass bottle containing 8 valsartan 80 mg tablets and shake for a minimum of 2 minutes.
- Allow the suspension to stand for a minimum of 1 hour.
- After the standing time, shake the suspension for a minimum of 1 additional minute.
- Add 80 mL of Ora-Sweet SF™ oral sweetening vehicle to the bottle and shake the suspension for at least 10 seconds to disperse the ingredients.
- The suspension is homogeneous and can be stored for either up to 30 days at room temperature (below 30°C/86°F) or up to 75 days at refrigerated conditions (2°C to 8°C/35°F to 46°F) in the glass bottle with a child-resistant screw cap closure.
- Shake the bottle well (at least 10 seconds) prior to dispensing the suspension.

*Ora-Sweet SF® and Ora-Plus® are registered trademarks of Paddock Laboratories, Inc.

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2.2 Adult Hypertension

The recommended starting dose of valsartan tablets is 80 mg or 160 mg once daily when used as monotherapy in patients who are not volume-depleted. Patients requiring greater reductions may be started at the higher dose. Valsartan tablets may be used over a dose range of 80 mg to 320 mg daily, administered once a day. The antihypertensive effect is substantially present within 2 weeks and maximal reduction is generally attained after 4 weeks. If additional antihypertensive effect is required over the starting dose range, the dose may be increased to a maximum of 320 mg or a diuretic may be added. Addition of a diuretic has a greater effect than dose increases beyond 80 mg.

Valsartan tablets may be administered with other antihypertensive agents.

WARNINGS AND PRECAUTIONS

- Observe for signs and symptoms of hypotension (5.2)
- Monitor renal function and potassium in susceptible patients (5.3, 5.4)

ADVERSE REACTIONS

Hypertension: Most common adverse reactions are headache, dizziness, viral infection, fatigue and abdominal pain (6.1)
Heart Failure: Most common adverse reactions are dizziness, hypotension, diarrhea, arthralgia, back pain, fatigue and hyperkalemia (6.1)

Post-Myocardial Infarction: Most common adverse reactions which caused patients to discontinue therapy are hypotension, cough and increased blood creatinine (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact **Jubilant Cadista Pharmaceuticals Inc. at 1-800-313-4623 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**

DRUG INTERACTIONS

- Potassium-sparing diuretics, potassium supplements or salt substitutes may lead to increases in serum potassium, and in heart failure patients, increases in serum creatinine (7.1)
- Non-Steroidal Anti-Inflammatory Drug (NSAID) use may lead to increased risk of renal impairment and loss of antihypertensive effect (7.2)
- Dual inhibition of the Renin-Angiotensin System (RAS): Increased risk of renal impairment, hypotension, and hyperkalemia (7.3)
- Lithium: Increases in serum lithium level and lithium toxicity (7.4)

USE IN SPECIFIC POPULATIONS

Lactation: Breastfeeding is not recommended (8.2)

Pediatrics: Use of valsartan tablets is not recommended in children less than 1 year of age (6.1, 8.4, 13.2)

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

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7 DRUG INTERACTIONS

- Agents Increasing Serum Potassium
- Non-Steroidal Anti-Inflammatory Agents Including Selective Cyclooxygenase-2 Inhibitors (COX-2 Inhibitors)
- Dual Blockade of the Renin-Angiotensin System (RAS)
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2.3 Pediatric Hypertension 6 to 16 Years of Age

The usual recommended starting dose is 1 mg/kg once daily (up to 40 mg total). A higher starting dose of 2 mg/kg may be considered in selected cases when a greater reduction of blood pressure is needed. The dosage should be adjusted according to blood pressure response and tolerability, up to a maximum dose of 4 mg/kg once daily (maximum daily dose 160 mg).

No data are available in pediatric patients either undergoing dialysis or with a glomerular filtration rate < 30 mL/min/1.73 m² [see *Use in Specific Populations* (8.4)].

Use of valsartan tablets is not recommended in children less than 1 year of age [see *Adverse Reactions* (6.1), *Pediatric Use in Specific Populations* (8.4), *Nonclinical Toxicology* (13.2)].

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2.4 Heart Failure

The recommended starting dose of valsartan is 40 mg twice daily. Upitrate to 80 mg and 160 mg twice daily or to the highest dose tolerated by the patient. Consider reducing the dose of concomitant diuretics. The maximum daily dose administered in clinical trials is 320 mg in divided doses.

2.5 Post-Myocardial Infarction

Valsartan tablets may be initiated as early as 12 hours after a myocardial infarction. The recommended starting dose of valsartan tablets is 20 mg twice daily. Patients may be upitrate within 7 days to 40 mg twice daily, with subsequent titrations to a target maintenance dose of 160 mg twice daily, as tolerated by the patient. If symptomatic hypotension or renal dysfunction occurs, consider dosage reduction. Valsartan tablets may be given with other standard post-myocardial infarction treatment, including thrombolytics, aspirin, beta-blockers, and statins.

2.6 Missed Dose

If a dose of valsartan tablet is missed, it should be administered as soon as possible, unless it is almost time for the next dose. The dose should not be doubled to make up for a missed dose.

3 DOSAGE FORMS AND STRENGTHS

Valsartan tablets, USP are available as:

- 40 mg tablets are yellow colored, capsule shaped, biconvex, film coated tablets, with a scoreline on one side, debossed with 'C' on one side of scoreline and '1' on the other side of scoreline and plain on the other side.
- 80 mg tablets are peach colored, round, biconvex, film coated tablets, debossed with 'C3' on one side and 'C' on other side.
- 160 mg tablets are yellow colored, oval shaped, biconvex, film coated tablets, debossed with 'C4' on one side and 'C' on other side.
- 320 mg tablets are yellow colored, oval shaped, biconvex, film coated tablets, debossed with 'C5' on one side and 'C' on other side.

4 CONTRAINDICATIONS

Do not use in patients with known hypersensitivity to any component.

Do not coadminister aliskiren with valsartan in patients with diabetes [see *Drug Interactions* (7.3)].

5 WARNINGS AND PRECAUTIONS**5.1 Fetal Toxicity**

Valsartan can cause fetal harm when administered to a pregnant woman. Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. When pregnancy is detected, discontinue valsartan as soon as possible [see *Use in Specific Populations* (8.1)].

5.2 Hypotension

Excessive hypotension was rarely seen (0.1%) in patients with uncomplicated hypertension treated with valsartan alone. 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, or the treatment should start under close medical supervision.

Patients with heart failure or post-myocardial infarction patients given valsartan commonly have some reduction in blood pressure, but discontinuation of therapy because of continuing symptomatic hypotension usually is not necessary when dosing instructions are followed. In controlled trials in heart failure patients, the incidence of hypotension in valsartan-treated patients was 5.5% compared to 1.8% in placebo-treated patients. In the VALsartan In Acute myocardial InfarcTion trial (VALIANT), hypotension in post-myocardial infarction patients led to permanent discontinuation of therapy in 1.4% of valsartan-treated patients and 0.8% of captopri-treated patients.

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

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

5.4 Hyperkalemia

Some patients with heart failure have developed increases in potassium. These effects are usually minor and transient, and they are more likely to occur in patients with pre-existing renal impairment. Dosage reduction and/or discontinuation of valsartan may be required [see *Adverse Reactions* (6.1)].

6 ADVERSE REACTIONS**6.1 Clinical Trials Experience**

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

Adult Hypertension

Valsartan has been evaluated for safety in more than 4,000 patients, including over 400 treated for over 6 months, and more than 160 for over 1 year. Adverse reactions have generally been mild and transient in nature and have only infrequently required discontinuation of therapy. The overall incidence of adverse reactions with valsartan was similar to placebo.

The overall frequency of adverse reactions was neither dose-related nor related to gender, age, race, or regimen. Discontinuation of therapy due to side effects was required in 2.3% of valsartan patients and 2.0% of placebo patients. The most common reasons for discontinuation of therapy with valsartan were headache and dizziness.

The adverse reactions that occurred in placebo-controlled clinical trials in at least 1% of patients treated with valsartan and at a higher incidence in valsartan (n=2,316) than placebo (n=888) patients included viral infection (3% vs. 2%), fatigue (2% vs. 1%), and abdominal pain (2% vs. 1%).

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

Dose-related orthostatic effects were seen in less than 1% of patients. An increase in the incidence of dizziness was observed in patients treated with valsartan 320 mg (8%) compared to 10 to 160 mg (2% to 4%).

Pediatric Hypertension

Valsartan has been evaluated for safety in over 400 patients aged 6 to 17 years. No relevant differences were identified between the adverse experience profile for pediatric patients and that previously reported for adult patients. Hyperkalemia was more frequently observed in pediatric patients with underlying chronic kidney disease (CKD).

Heart Failure

In the Valsartan Heart Failure Trial (Val-HeFT), comparing valsartan in total daily doses up to 320 mg (n=2,506) to placebo (n=2,494), 10% of valsartan patients discontinued for adverse reactions vs. 7% of placebo patients.

The table shows adverse reactions in double-blind short-term heart failure trials, including the first 4 months of the Valsartan Heart Failure Trial, with an incidence of at least 2% that were more frequent in valsartan-treated patients than in placebo-treated patients. All patients received standard drug therapy for heart failure, frequently as multiple medications, which could include diuretics, digitalis, beta-blockers. About 93% of patients received concomitant ACE inhibitors.

	Valsartan (n=3,282)	Placebo (n=2,740)
Dizziness	17%	9%
Hypotension	7%	2%
Diarrhea	5%	4%
Arthralgia	3%	2%
Fatigue	3%	2%
Back Pain	3%	2%
Dizziness, postural	2%	1%
Hyperkalemia	2%	1%
Hypotension, postural	2%	1%

Discontinuations occurred in 0.5% of valsartan-treated patients and 0.1% of placebo patients for each of the following: elevations in creatinine and elevations in potassium.

Other adverse reactions with an incidence greater than 1% and greater than placebo included headache, nausea, renal impairment, syncope, blurred vision, upper abdominal pain and vertigo.

From the long-term data in the Valsartan Heart Failure Trial, there did not appear to be any significant adverse reactions not previously identified.

Post-Myocardial Infarction

The table shows the percentage of patients discontinued in the valsartan and captopril-treated groups in the VALsartan In Acute myocardial Infarction trial (VALIANT) with a rate of at least 0.5% in either of the treatment groups.

Discontinuations due to renal dysfunction occurred in 1.1% of valsartan-treated patients and 0.8% of captopril-treated patients.

	Valsartan (n=3,885)	Captopril (n=4,879)
Discontinuation for adverse reaction	5.8%	7.7%
Adverse reactions		
Hypotension NOS	1.4%	0.8%
Cough	0.6%	2.5%
Blood creatinine increased	0.6%	0.4%
Rash NOS	0.2%	0.6%

Clinical Laboratory Test Findings

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

Neutropenia: Neutropenia was observed in 1.9% of patients treated with valsartan and 0.8% of patients treated with placebo.

Blood Urea Nitrogen (BUN): In heart failure trials, greater than 50% increases in BUN were observed in 16.6% of valsartan-treated patients compared to 6.3% of placebo-treated patients [see *Warnings and Precautions* (5.3)].

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6.2 Postmarketing Experience

The following additional adverse reactions have been reported in postmarketing use of valsartan. 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: Angioedema has been reported. Some of these patients previously experienced angioedema with other drugs, including ACE inhibitors. Valsartan should not be re-administered to patients who have had angioedema.

Digestive: Elevated liver enzymes and very rare reports of hepatitis

Musculoskeletal: Rhabdomyolysis

Renal: Impaired renal function, renal failure

Dermatologic: Alopecia, bullous dermatitis

Blood and Lymphatic: Thrombocytopenia

Vascular: Vasculitis

7 DRUG INTERACTIONS**7.1 Agents Increasing Serum Potassium**

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

7.2 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.

7.3 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 [see *Clinical Studies* (14.3)]. In general, avoid combined use of RAS inhibitors. Closely monitor blood pressure, renal function and electrolytes in patients on valsartan and other agents that affect the RAS.

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

7.4 Lithium

Increases in serum lithium concentrations and lithium toxicity have been reported during concomitant administration of lithium with angiotensin II receptor antagonists. Monitor serum lithium levels during concomitant use.

8 USE IN SPECIFIC POPULATIONS**8.1 Pregnancy****Risk Summary**

Valsartan can cause fetal harm when administered to

The most common side effects of valsartan tablets when used to treat people with high blood pressure include:

- headache
- dizziness
- flu symptoms
- tiredness
- stomach (abdominal) pain

The most common side effects of valsartan tablets when used to treat people with heart failure include:

- dizziness
- low blood pressure
- diarrhea
- joint and back pain
- tiredness
- high blood potassium

The most common side effects of valsartan tablets when used to treat people after a heart attack that cause them to stop taking valsartan tablets include:

- low blood pressure
- cough
- high blood creatinine (decreased kidney function)

You should not stop taking valsartan tablets without talking to your healthcare provider. These are not all of the possible side effects of valsartan tablets. For more information, ask your healthcare provider or pharmacist.

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

How should I store valsartan tablets?

- Store valsartan tablets at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep valsartan tablets container tightly closed and in a dry place to protect from moisture.
- Valsartan suspension is provided in a glass bottle with a child-resistant screw-cap closure.
- Store bottles of valsartan suspension at room temperature less than 86°F (30°C) for up to 30 days, or refrigerate between 35°F to 46°F (2°C to 8°C) for up to 75 days.

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

General information about the safe and effective use of valsartan tablets.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information Leaflet. Do not use valsartan tablets for a condition for which it was not prescribed. Do not give valsartan tablets to other people, even if they have the same symptoms you have. It may harm them.

You can ask your healthcare provider or pharmacist for information about valsartan tablets that is written for health professionals.

What are the ingredients in valsartan tablets?

Active ingredient: valsartan USP

Inactive ingredients: anhydrous lactose, crospovidone, dental-type silica, ferric oxide red (80 mg only), ferric oxide yellow, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, and titanium dioxide.

For more information about valsartan tablets, ask your pharmacist or doctor, or call **1-800-313-4623**.

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Rx Only
Made in India
Marketed by:
Jubilant Cadista Pharmaceuticals Inc.
Yardley, PA 19067, USA

Additional pediatric use information is approved for Novartis Pharmaceuticals Corporation's Diován (valsartan) tablets. However, due to Novartis Pharmaceuticals Corporation's marketing exclusivity rights, this drug product is not labeled with that information.

This Patient Information has been approved by the U.S. Food and Drug Administration.

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Data
<i>Animal Data</i>
No teratogen effects were observed when valsartan was administered to pregnant mice and rats at oral doses of up to 600 mg/kg/day (9 and 18 times the maximum recommended human dose (MRHD)) on a mg/m ² basis) and to pregnant rabbits at oral doses of up to 10 mg/kg/day.
In rats, oral valsartan administered at maternally toxic doses (600 mg/kg/day) during organogenesis or late gestation and lactation, resulted in decreased fetal and pup weight, pup survival and delayed developmental milestones. In rabbits administered maternally toxic doses of 5 and 10 mg/kg/day, fetotoxicity was observed.
8.2 Lactation
Risk Summary
There is no information regarding the presence of valsartan in human milk, the effects on the breastfed infant, or the effects on milk production. Valsartan is present in rat milk. Because of the potential for serious adverse reactions in breastfed infants from exposure to valsartan, advise a nursing woman that breastfeeding is not recommended during treatment with valsartan.
Data
Valsartan was detected in the milk of lactating rats 15 minutes after oral administration of a 3 mg/kg dose.
8.4 Pediatric Use
The antihypertensive effects of valsartan have been evaluated in a clinical study in pediatric patients from 6-16 years of age <i>[see Clinical Studies (14.1)]</i> . The pharmacokinetics of valsartan have been evaluated in pediatric patients 1 to 16 years of age <i>[see Clinical Pharmacology (12.3)]</i> . The adverse experience profile of valsartan was similar to that described for adults <i>[see Adverse Reactions (8.1)]</i> .
In children and adolescents with hypertension where underlying renal abnormalities may be more common, renal function and serum potassium should be closely monitored as clinically indicated.
Use of valsartan tablet is not recommended in children less than 1 year of age <i>[see Nonclinical Toxicology (13.2)]</i> . It is not known whether post-natal use of valsartan, before maturation of renal function is complete, has a long-term deleterious effect on the kidney.
No data are available in pediatric patients either undergoing dialysis or with a glomerular filtration rate less than 30 mL/min/1.73 m ² .
<i>Additional pediatric use information is approved for Novartis Pharmaceuticals Corporation's Diován (valsartan) tablets. However, due to Novartis Pharmaceuticals Corporation's marketing exclusivity rights, this drug product is not labeled with that information.</i>
8.5 Geriatric Use
In the controlled clinical trials of valsartan, 1 214 (36.2%) hypertensive patients treated with valsartan were ≥ 65 years and 265 (7.9%) were ≥ 75 years. No overall difference in the efficacy or safety of valsartan was observed in this patient population, but greater sensitivity of some older individuals cannot be ruled out. Exposure [measured by area under the curve (AUC)] to valsartan is higher by 70% in the elderly than in the young, however no dosage adjustment is necessary <i>[see Clinical Pharmacology (12.3)]</i> .
Of the 2,511 patients with heart failure randomized to valsartan in the Valsartan Heart Failure Trial, 45% (1,141) were 65 years of age or older. In the Valsartan in Acute myocardial InFarction trial (VALIANT), 53% (2,596) of the 4,909 patients treated with valsartan and 51% (2,515) of the 4,885 patients treated with valsartan + captopril were 65 years of age or older. There were no notable differences in efficacy or safety between older and younger patients in either trial.
8.6 Renal Impairment
Safety and effectiveness of valsartan in patients with severe renal impairment (glomerular filtration rate less than 30 mL/min/1.73 m ²) have not been established. No dose adjustment is required in patients with mild (glomerular filtration rate 60 to 90 mL/min/1.73 m ²) or moderate (glomerular filtration rate 30 to 60 mL/min/1.73 m ²) renal impairment.
8.7 Hepatic Impairment
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.
10 OVERDOSAGE
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, institute supportive treatment.
Valsartan is not removed from the plasma by hemodialysis.
Valsartan was without grossly observable adverse effects at single oral doses up to 2000 mg/kg in rats and up to 1000 mg/kg in marmosets, except for salivation and diarrhea in the rat and vomiting in the marmoset at the highest dose (60 and 31 times, respectively, the MRHD dose on a mg/m ² basis) (Calculations assume an oral dose of 320 mg/day and a 60-kg patient).
11 DESCRIPTION
Valsartan USP is a nonpeptide, orally active, and specific angiotensin II receptor blocker acting on the AT ₁ receptor subtype. Valsartan is chemically described as <i>N</i> -(1-oxo-pentyl)-N-[2'-(1 <i>H</i> -Tetrazol-5-yl) [1,1'-biphenyl]-4-yl]methyl]-L-valine. Its empirical formula is C ₂₀ H ₂₆ N ₄ O ₂ , its molecular weight is 435.52, and its structural formula is:

13.2 Animal Toxicology and/or Pharmacology
Daily oral dosing of neonatal/juvenile rats with valsartan at doses as low as 1 mg/kg/day (about 10% of the maximum recommended pediatric dose on a mg/m ² basis) from postnatal day 7 to postnatal day 70 produced persistent, irreversible kidney damage. These kidney effects in neonatal rats represent exaggerated pharmacological effects that are observed if rats are treated during the first 13 days of life. This period coincides with 36 weeks of gestation in humans, which included bacterial mutagenicity tests with <i>Salmonella</i> (Ames) and <i>E. coli</i> a gene mutation test with Chinese hamster V79 cells; a cytogenetic test with Chinese hamster ovary cells; and a micronucleus test.
Valsartan had no adverse effects on the reproductive performance of male or female rats at oral doses up to 200 mg/kg. This dose is 8 times the MRHD on a mg/m ² basis (Calculations assume an oral dose of 320 mg/day and a 60-kg patient).

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14 CLINICAL STUDIES
14.1 Hypertension
Adult Hypertension
The antihypertensive effects of valsartan were demonstrated principally in 7 placebo-controlled, 4-to-12-week trials (1 in patients over 65 years) of dosages from 10 to 320 mg/day in patients with baseline diastolic blood pressures of 95-115 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 blood pressure-lowering effect of valsartan and thiazide-type diuretics are approximately additive. The 7 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, 160 and 320 mg produced dose-related decreases in systolic and diastolic blood pressure, with the difference from placebo of approximately 6-9/3-5 mmHg at 80 to 160 mg and 9/6 mmHg at 320 mg. In a controlled trial the addition of HCTZ to valsartan 80 mg resulted in additional lowering of systolic and diastolic blood pressure by approximately 6/3 and 12/5 mmHg for 12.5 and 25 mg of HCTZ, respectively, compared to valsartan 80 mg alone.

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 similar response in both groups. 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 are no trials of valsartan demonstrating reductions in cardiovascular risk in patients with hypertension, but at least one pharmacologically similar drug has demonstrated such benefits.

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

Pediatric Hypertension
Children Between 6 to 16 Years of Age
In a clinical study involving 261 hypertensive pediatric patients 6 to 16 years of age, patients who weighed less than 35 kg received 10, 40 or 80 mg of valsartan daily (low, medium and high doses), and patients who weighed greater than or equal to 35 kg received 20, 80, and 160 mg of valsartan daily (low, medium and high doses). Renal and urinary disorders, and essential hypertension with or without obesity were the most common underlying causes of hypertension in children enrolled in this study. At the end of 2 weeks, valsartan reduced both systolic and diastolic blood pressure in a dose-dependent manner. Overall, the three dose levels of valsartan (low, medium and high) significantly reduced systolic blood pressure by 8, 10, and 12 mmHg from the baseline, respectively. Patients were re-randomized to either continue receiving the same dose of valsartan or were switched to placebo. In patients who continued to receive the medium and high doses of valsartan, systolic blood pressure at trough was 4 and 7 mmHg lower than patients who received the placebo treatment. In patients receiving the low dose of valsartan, systolic blood pressure at trough was similar to that of patients who received the placebo treatment. Overall, the dose-dependent antihypertensive effect of valsartan was consistent across all the demographic subgroups.

Additional pediatric use information is approved for Novartis Pharmaceuticals Corporation's Diován (valsartan) tablets. However, due to Novartis Pharmaceuticals Corporation's marketing exclusivity rights, this drug product is not labeled with that information.

14.2 Heart Failure
The Valsartan Heart Failure Trial (Val-HeFT) was a multinational, double-blind study in which 5 010 patients with NYHA class II (62%) to IV (2%) heart failure and LVEF less than 40%, on baseline therapy chosen by their physicians, were randomized to placebo or valsartan (titrated from 40 mg twice daily to the highest tolerated dose or 160 mg twice daily) and followed for a mean of about 2 years. Although Val-HeFT's primary goal was to examine the effect of valsartan when added to an ACE inhibitor, about 7% were not receiving an ACE inhibitor. Other background therapy included diuretics (86%), digoxin (67%), and beta-blockers (36%). The population studied was 80% male, 46% 55 years or older and 89% Caucasian. At the end of the trial, patients in the valsartan group had a blood pressure that was 4 mmHg systolic and 2 mmHg diastolic lower than the placebo group. There were two primary end points, both assessed as time to first event: all-cause mortality and heart failure morbidity, the latter defined as all-cause mortality, sudden death with resuscitation, hospitalization for heart failure, and the need for intravenous inotropic or vasodilatory drugs for at least 4 hours. These results are summarized in the following table.

	Placebo (N=2,499)	Valsartan (N=2,511)	Hazard Ratio (95% CI)*	Nominal p-value
All-cause mortality	483 (19.3%)	493 (19.7%)	1.02 (0.96-1.15)	0.9
HF morbidity	801 (32.1%)	723 (28.8%)	0.87 (0.79-0.97)	0.009
<i>p</i> -value			0.0065	

Although the overall morbidity result favored valsartan, this result was largely driven by the 7% of patients not receiving an ACE inhibitor, as shown in the following table.

	Without ACE Inhibitor		With ACE Inhibitor	
	Placebo (N=181)	Valsartan (N=185)	Placebo (N=2,316)	Valsartan (N=2,326)
Events (%)	77 (42.5%)	46 (24.9%)	724 (31.2%)	677 (29.1%)
Hazard ratio (95% CI)	0.51 (0.35, 0.73)		0.92 (0.82, 1.02)	
<i>p</i> -value			0.0665	

The modest favorable trend in the group receiving an ACE inhibitor was largely driven by the patients receiving less than the recommended dose of ACE inhibitor. Thus, there is little evidence of further clinical benefit when valsartan is added to an adequate dose of ACE inhibitor.

Metabolism:
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.

Excretion
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).

The apparent clearance of valsartan following oral administration is approximately 4.5 L/h in heart failure patients. Age does not affect the apparent clearance in heart failure patients.

Specific 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 *[see Use in Specific Populations (8.5)]*.

Pediatric: In a study of pediatric hypertensive patients (n=26, 1 to 16 years of age) given single doses of a suspension of valsartan (measured by AUC) to valsartan in patients with different degrees of renal impairment (down to creatinine clearance of 10 mL/min). Valsartan is not removed from the plasma by hemodialysis *[see Use in Specific Populations (8.6)]*.

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

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 (down to creatinine clearance of 10 mL/min). Valsartan is not removed from the plasma by hemodialysis *[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 Interaction Studies
Not 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.

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.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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 micronucleus test.

Valsartan had no adverse effects on the reproductive performance of male or female rats at oral doses up to 200 mg/kg. This dose is 8 times the MRHD on a mg/m² basis (Calculations assume an oral dose of 320 mg/day and a 60-kg patient).

13.2 Animal Toxicology and/or Pharmacology
Daily oral dosing of neonatal/juvenile rats with valsartan at doses as low as 1 mg/kg/day (about 10% of the maximum recommended pediatric dose on a mg/m² basis) from postnatal day 7 to postnatal day 70 produced persistent, irreversible kidney damage. These kidney effects in neonatal rats represent exaggerated pharmacological effects that are observed if rats are treated during the first 13 days of life. This period coincides with 36 weeks of gestation in humans, which 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 micronucleus test.

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