HIGHLIGHTS OF PRESCRIBING INFORMATION

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

VALSARTAN Tablets, USP for oral use

Initial U.S. Approval: 1996

WARNING: FETAL TOXICITY

See full prescribing information for complete boxed warning.

- **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 USP are an angiotensin II receptor blocker (ARB) indicated for:

- Treatment of **hypertension**, to lower blood pressure. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions (1.1)
- Treatment of **heart failure** (NYHA class II-IV); Valsartan tablets USP significantly reduced hospitalization for heart failure (1.2)

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

Indication	Starting Dose	Dose Range	Target Maintenance Dose*
Adult Hypertension (2.1)	80 or 160 mg once daily	80-320 mg once daily	---
Pediatric Hypertension (6-16 years) (2.2)	1.3 mg/kg once daily (up to 40 mg total)	1.3-2.7 mg/kg once daily (up to 40-160 mg total)	---
Heart Failure (2.3)	40 mg twice daily	40-160 mg twice daily	160 mg twice daily

* as tolerated by patient

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

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

----------CONTRAINDICATIONS----------

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

----------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)

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)
- NSAID use may lead to increased risk of renal impairment and loss of antihypertensive effect (7)
- Dual inhibition of the renin-angiotensin system: Increased risk of renal impairment, hypotension, and hyperkalemia (7)
- Lithium: Increases in serum lithium concentrations and lithium toxicity (7)

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

Nursing Mothers: Nursing or drug should be discontinued (8.3); **Pediatrics:** Efficacy and safety data support use in 6-16 year old patients; use is not recommended in patients <6 years old (6.1, 8.4)

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

Revised: 12/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

WARNING: FETAL TOXICITY
- **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)**

1 INDICATIONS AND USAGE

1.1 Hypertension

Valsartan tablets USP 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 the class to which valsartan principally belongs. There are no controlled trials in hypertensive patients demonstrating risk reduction with valsartan tablets USP.

Control of high blood pressure should be part of comprehensive cardiovascular risk management, including, as appropriate, lipid control, diabetes management, antithrombotic therapy, smoking cessation, exercise, and limited sodium intake. Many patients will require more than 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). These considerations may guide selection of therapy.

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

1.2 Heart Failure

Valsartan tablets USP are indicated for the treatment of heart failure (NYHA class II-IV). In a controlled clinical trial, valsartan tablets USP significantly reduced hospitalizations for heart failure. There is no evidence that valsartan tablets USP provides added benefits when it is used with an adequate dose of an ACE inhibitor *[see Clinical Studies (14.2)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Adult Hypertension

The recommended starting dose of valsartan 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 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.

No initial dosage adjustment is required for elderly patients, for patients with mild or moderate renal impairment, or for patients with mild or moderate liver insufficiency. Care should be exercised with dosing of valsartan in patients with hepatic or severe renal impairment.

Valsartan may be administered with other antihypertensive agents.

Valsartan may be administered with or without food.

2.2 Pediatric Hypertension 6 to 16 Years of Age

For children who can swallow tablets, the usual recommended starting dose is 1.3 mg/kg once daily (up to 40 mg total). The dosage should be adjusted according to blood pressure response. Doses higher than 2.7 mg/kg (up to 160 mg) once daily have not been studied in pediatric patients 6 to 16 years old.

For children who cannot swallow tablets, or children for whom the calculated dosage (mg/kg) does not correspond to the available tablet strengths of valsartan, the use of a suspension is recommended. Follow the suspension preparation instructions below (see **Preparation of Suspension**) to administer valsartan as a suspension. When the suspension is replaced by a tablet, the dose of valsartan may have to be increased. The exposure to valsartan with the suspension is 1.6 times greater than with the tablet.

No data are available in pediatric patients either undergoing dialysis or with a glomerular filtration rate <30 mL/min/1.73 m^2 *[see Pediatric Use (8.4)]*.

Valsartan is not recommended for patients <6 years old *[see Adverse Reactions (6.1), Clinical Studies (14.1)]*.

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 homogenous 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 (2-8°C/35-46°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.

2.3 Heart Failure

The recommended starting dose of valsartan is 40 mg twice daily. Uptitration to 80 mg and 160 mg twice daily should be done to the highest dose, as tolerated by the patient. Consideration should be given to reducing the dose of concomitant diuretics. The maximum daily dose administered in clinical trials is 320 mg in divided doses.

3 DOSAGE FORMS AND STRENGTHS

Valsartan Tablets USP are available as:

40 mg tablets are yellow, capsule shaped, biconvex, film-coated with a functional scoreline on one side, debossed with 'C' on one side of scoreline and 'I' on other side of scoreline and plain on the other side.

80 mg tablets are peach, round, biconvex, film-coated, debossed with 'C3' on one side and 'C' on other side.

160 mg tablets are yellow, oval shaped, biconvex, film-coated, debossed with 'C4' on one side and 'C' on the other side.

320 mg tablets are yellow, oval shaped, biconvex, film-coated, debossed with 'C5' on one side and 'C' on the 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)]*.

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 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.

Caution should be observed when initiating therapy in patients with heart failure. Patients with heart failure 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.

If excessive 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. 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 Studies 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%).

Headache, dizziness, upper respiratory infection, cough, diarrhea, rhinitis, sinusitis, nausea, pharyngitis, edema, and arthralgia occurred at a more than 1% rate but at about the same incidence in placebo and valsartan patients.

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

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%).

Valsartan has been used concomitantly with hydrochlorothiazide without evidence of clinically important adverse interactions.

Other adverse reactions that occurred in controlled clinical trials of patients treated with valsartan (>0.2% of valsartan patients) are listed below. It cannot be determined whether these events were causally related to valsartan.

Body as a Whole: Allergic reaction and asthenia

Cardiovascular: Palpitations

Dermatologic: Pruritus and rash

Digestive: Constipation, dry mouth, dyspepsia, and flatulence

Musculoskeletal: Back pain, muscle cramps, and myalgia

Neurologic and Psychiatric: Anxiety, insomnia, paresthesia, and somnolence

Respiratory: Dyspnea

Special Senses: Vertigo

Urogenital: Impotence

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

Pediatric Hypertension

Valsartan has been evaluated for safety in over 400 pediatric patients aged 6 to 17 years and more than 160 pediatric patients aged 6 months to 5 years. No relevant differences were identified between the adverse experience profile for pediatric patients aged 6 to 16 years and that previously reported for adult patients. Headache and hyperkalemia were the most common adverse events suspected to be study drug-related in older children (6 to 17 years old) and younger children (6 months to 5 years old), respectively. Hyperkalemia was mainly observed in children with underlying renal disease.

Neurocognitive and developmental assessment of pediatric patients aged 6 to 16 years revealed no overall clinically relevant adverse impact after treatment with valsartan for up to 1 year.

Valsartan is not recommended for pediatric patients under 6 years of age. In a study (n=90) of pediatric patients (1 to 5 years), two deaths and three cases of on-treatment transaminase elevations were seen in the one-year open-label extension phase. These 5 events occurred in a study population in which patients frequently had significant co-morbidities. A causal relationship to valsartan has not been established. In a second study in which 75 children aged 1 to 6 years were randomized, no deaths and one case of marked liver transaminase elevations occurred during a 1 year open-label extension.

Heart Failure

The adverse experience profile of valsartan in heart failure patients was consistent with the pharmacology of the drug and the health status of the patients. In the Valsartan Heart Failure Trial, 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 NOS, nausea, renal impairment NOS, syncope, blurred vision, upper abdominal pain and vertigo. (NOS = not otherwise specified).

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

6.2 Postmarketing Experience

The following additional adverse reactions have been reported in Postmarketing experience:

Hypersensitivity: There are rare reports of angioedema. 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

Renal: Impaired renal function, renal failure

Clinical Laboratory Tests: Hyperkalemia

Dermatologic: Alopecia, bullous dermatitis

Blood and Lymphatic: There are very rare reports of thrombocytopenia

Vascular: Vasculitis

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

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.

7 DRUG INTERACTIONS

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.

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.

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.

Dual Blockade of the Renin-Angiotensin System (RAS): Dual blockade of the RAS with angiotensin receptor blockers, ACE inhibitors, or aliskiren is associated with increased risks of hypotension, hyperkalemia, and changes in renal function (including acute renal failure) compared to monotherapy. Most patients receiving the combination of two RAS inhibitors do not obtain any additional benefit compared to monotherapy. In general, avoid combined use of RAS inhibitors. Closely monitor blood pressure, renal function and electrolytes in patients on valsartan and other agents that affect the RAS.

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

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

PATIENT INFORMATION

Valsartan Tablets USP

Read the Patient Information that comes with valsartan tablets USP before you take 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 medical condition or treatment. If you have any questions about valsartan tablets USP, ask your doctor or pharmacist.

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

Valsartan tablets USP 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 tablets USP, tell your doctor right away.

What are valsartan tablets USP?

Valsartan tablets USP are prescription medicine called an angiotensin receptor blocker (ARB). It is used in adults to:

- lower high blood pressure (hypertension) in adults and children, 6 to 16 years of age.
- treat heart failure in adults. In these patients, valsartan tablets USP may lower the need for hospitalization that happens from heart failure.

Valsartan tablets USP are not for children under 6 years of age or children with certain kidney problems.

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 tablets USP can help your blood vessels relax so your blood pressure is lower. Medicines that lower your blood pressure lower your chance 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.

Heart Failure occurs when the heart is weak and cannot pump enough blood to your lungs and the rest of your body. Just walking or moving can make you short of breath, so you may have to rest a lot.

What should I tell my doctor before taking valsartan tablets USP?

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

- have any allergies. See the end of this leaflet for a complete list of ingredients in valsartan tablets USP.
- have a heart condition
- have liver problems
- have kidney problems
- **are pregnant or planning to become pregnant.** See **"What is the most important information I should know about valsartan tablets USP?"**
- are breastfeeding. It is not known if valsartan passes into your breast milk. You and your doctor should decide if you will take valsartan tablets USP or breastfeed, but not both. Talk with your doctor about the best way to feed your baby if you take valsartan tablets USP.
- have ever had a reaction called angioedema, to another blood pressure medicine. Angioedema causes swelling of the face, lips, tongue and/or throat, and may cause difficulty breathing.

Tell your doctor about all the medicines you take including prescription and nonprescription medicines, vitamins and herbal supplements. Especially tell your doctor if you take:

- other medicines for high blood pressure or a heart problem
- water pills (also called "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
- Nonsteroidal anti-inflammatory drugs (like ibuprofen or naproxen)
- 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.
- Lithium, a medicine used in some types of depression

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 tablets USP?

- Take valsartan tablets USP exactly as prescribed by your doctor.
- For treatment of high blood pressure, take valsartan tablets USP one time each day, at the same time each day.
- If your child cannot swallow tablets, or if tablets are not available in the prescribed strength, your pharmacist will mix valsartan tablets USP as a liquid suspension for your child. If your child switches between taking the tablet and the suspension, your doctor will adjust the dose as needed. Shake the bottle of suspension well for at least 10 seconds before pouring the dose of medicine to give to your child.
- For adult patients with heart failure, take valsartan tablet two times each day, at the same time each day. Your doctor may start you on a low dose of valsartan tablets USP and may increase the dose during your treatment.
- Valsartan tablets USP 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. Take the next dose at your regular time.
- If you take too much valsartan tablets USP, call your doctor or Poison Control Center, or go to the nearest hospital emergency room.

What are the possible side effects of valsartan tablets USP?

Valsartan tablets USP may cause the following serious side effects:

Injury or death to an unborn baby. See **"What is the most important information I should know about valsartan tablets USP?"**

Low Blood Pressure (Hypotension). Low blood pressure is most likely to happen if you also take water pills, are on a low-salt diet, get dialysis treatments, have heart problems, or get sick with vomiting or diarrhea. Lie down, if you feel faint or dizzy. Call your doctor right away.

Kidney problems. Kidney problems may get worse if you already have kidney disease. Some patients will have changes on blood tests for kidney function and may need a lower dose of valsartan tablets USP. Call your doctor if you get swelling in your feet, ankles, or hands, or unexplained weight gain. If you have heart failure, your doctor

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Last modified: 19. December 2014, 12:31 PM

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Reason for Artwork: Revised as per Deficiency letter received from Agency (dated: 17 Dec. 2014).	JUBILANT GENERICS	**Dimension: 455 x 540 mm**
Item Code: 7524000570		**Superseded Item Code: 7524000548**
Substrate: 40 GSM Bible paper		
Site Packaging Development Sign and Date		**Production Sign and Date** / **QA Sign and Date**

should check your kidney function before prescribing valsartan tablets USP.

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

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

Side effects were generally mild and brief. They generally have not caused patients to stop taking valsartan tablets USP.

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

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

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

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

How do I store valsartan tablets USP?

- Store at room temperature between 68° to 77°F (20°C to 25°C).
- Keep valsartan tablets USP in a closed container in a dry place.
- Store bottles of valsartan suspension at room temperature less than 86°F (30°C) for up to 30 days, or refrigerate between 35°F-46°F (2°C-8°C) for up to 75 days.
- Keep valsartan tablets USP and all medicines out of the reach of children.

General information about valsartan tablets USP

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use valsartan tablets USP for a condition for which it was not prescribed. Do not give valsartan tablets USP 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 tablets USP. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about valsartan tablets USP that is written for health professionals.

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

What are the ingredients in valsartan tablets USP?

Active ingredient: valsartan USP

Inactive ingredients: anhydrous lactose, crospovidone, dental-type silica, hypromellose, iron oxide yellow, magnesium stearate, microcrystalline cellulose, polyethylene glycol, and titanium dioxide; and iron oxide red in 80 mg.

Rx Only

Manufactured by:
Jubilant Generics Limited
Roorkee-247661, India

Marketed by:
Jubilant Cadista Pharmaceuticals Inc.
Salisbury, MD-21801, USA

Revised: December 2014

7.1 Clinical Laboratory Test Findings

In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with administration of valsartan.

Creatinine: Minor elevations in creatinine occurred in 0.8% of patients taking valsartan and 0.6% given placebo in controlled clinical trials of hypertensive patients. 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.

Hemoglobin and Hematocrit: Greater than 20% decreases in hemoglobin and hematocrit were observed in 0.4% and 0.8%, respectively, of valsartan patients, compared with 0.1% and 0.1% in placebo-treated patients. One valsartan patient discontinued treatment for microcytic anemia.

Liver Function Tests: Occasional elevations (greater than 150%) of liver chemistries occurred in valsartan-treated patients. Three patients (< 0.1%) treated with valsartan discontinued treatment for elevated liver chemistries.

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

Serum Potassium: In hypertensive patients, greater than 20% increases in serum potassium were observed in 4.4% of valsartan-treated patients compared to 2.9% of placebo-treated patients. In heart failure patients, greater than 20% increases in serum potassium were observed in 10.0% of valsartan-treated patients compared to 5.1% of placebo-treated patients.

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.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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 as soon as possible. These adverse outcomes are usually associated with use of these drugs in the second and third trimesters 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, 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 for hypotension, oliguria, and hyperkalemia *[see Use in Specific Populations (8.4)]*.

8.3 Nursing Mothers

It is not known whether valsartan is excreted in human milk. Valsartan was excreted in the milk of lactating rats; however, animal breast milk drug levels may not accurately reflect human breast milk levels. Because many drugs are excreted into human milk and because of the potential for adverse reactions in nursing infants from valsartan, 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

The antihypertensive effects of valsartan have been evaluated in two randomized, double-blind clinical studies in pediatric patients from 1-5 and 6-16 years of age *[see Clinical Studies (14.1)]*. The pharmacokinetics of valsartan have been evaluated in pediatric patients 1 to 16 years of age *[see Pharmacokinetics, Special Populations, Pediatric (12.3)]*. Valsartan was generally well tolerated in children 6-16 years and the adverse experience profile was similar to that described for adults.

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.

Valsartan is not recommended for pediatric patients under 6 years of age due to safety findings for which a relationship to treatment could not be excluded *[see Adverse Reactions, Pediatric Hypertension (6.1)]*.

No data are available in pediatric patients either undergoing dialysis or with a glomerular filtration rate <30 mL/min/1.73 m^2.

There is limited clinical experience with valsartan in pediatric patients with mild to moderate hepatic impairment *[see Warnings and Precautions (5.3)]*.

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 expected exaggerated pharmacological effects that are observed if rats are treated during the first 13 days of life. Since this period coincides with up to 44 weeks after conception in humans, it is not considered to point toward an increased safety concern in 6 to 16 year old children.

Neonates with a history of in utero exposure to valsartan:

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, 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.

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. There were no notable differences in efficacy or safety between older and younger patients in this trial.

8.6 Renal Impairment

Safety and effectiveness of valsartan in patients with severe renal impairment (CrCl ≤ 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

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, supportive treatment should be instituted.

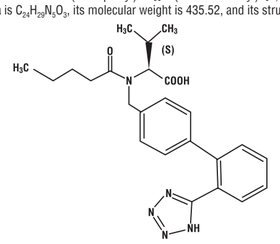
Valsartan is not removed from the plasma by hemodialysis.

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 maximum recommended human 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 *N*-(1-oxopentyl)-*N*-[[2′-(1*H*-tetrazol-5-yl) [1,1′-biphenyl]-4-yl]methyl]-L-valine. Its empirical formula is $C_{24}H_{29}N_5O_3$, its molecular weight is 435.52, and its structural formula is



Valsartan USP is a white to off white hygroscopic powder. It is soluble in ethanol and methanol and slightly soluble in water.

Valsartan is available as tablets for oral administration, containing 40 mg, 80 mg, 160 mg and 320 mg of valsartan USP. The inactive ingredients of the tablets are anhydrous lactose, crospovidone, dental-type silica, hypromellose, iron oxide yellow, magnesium stearate, microcrystalline cellulose, polyethylene glycol, and titanium dioxide; and iron oxide red in 80 mg.

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 AT_1 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 AT_2 receptor found in many tissues, but AT_2 is not known to be associated with cardiovascular homeostasis. Valsartan has much greater affinity (about 20,000-fold) for the AT_1 receptor than for the AT_2 receptor. The increased plasma levels of angiotensin II following AT_1 receptor blockade with valsartan may stimulate the unblocked AT_2 receptor. The primary metabolite of valsartan is essentially inactive with an affinity for the AT_1 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.

12.2 Pharmacodynamics

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.

In multiple-dose studies in hypertensive patients with stable renal insufficiency and patients with renovascular hypertension, valsartan had no clinically significant effects on glomerular filtration rate, filtration fraction, creatinine clearance, or renal plasma flow.

In multiple-dose studies in hypertensive patients, valsartan had no notable effects on total cholesterol, fasting triglycerides, fasting serum glucose, or uric acid.

12.3 Pharmacokinetics

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 valsartan is about 25% (range 10% to 35%). The bioavailability of the suspension *[see Dosage and Administration; Pediatric Hypertension (2.2)]* is 1.6 times greater than with the tablet. With the tablet, 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.

Metabolism and Elimination: 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. 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.

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).

Distribution: 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.

Special Populations:

Pediatric: In a study of pediatric hypertensive patients (n=26, 1 to 16 years of age) given single doses of a suspension of valsartan (mean: 0.9 to 2 mg/kg), the clearance (L/h/kg) of valsartan for children was similar to that of adults receiving the same formulation.

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. No dosage adjustment is necessary *[see Dosage and Administration (2.1)]*.

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

Heart Failure: The average time to peak concentration and elimination half-life of valsartan in heart failure patients are similar to those observed in healthy volunteers. AUC and C_{max} values of valsartan increase linearly and are almost proportional with increasing dose over the clinical dosing range (40 to 160 mg twice a day). The average accumulation factor is about 1.7. The apparent clearance of valsartan following oral administration is approximately 4.5 L/h. Age does not affect the apparent clearance in heart failure patients.

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. Consequently, dose adjustment is not required in patients with mild-to-moderate renal dysfunction. No studies have been performed in patients with severe impairment of renal function (creatinine clearance <10 mL/min). Valsartan is not removed from the plasma by hemodialysis. In the case of severe renal disease, exercise care with dosing of valsartan *[see Dosage and Administration (2.1)]*.

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). In general, no dosage adjustment is needed in patients with mild-to-moderate liver disease. Care should be exercised in patients with liver disease *[see Dosage and Administration (2.1)]*.

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 maximum recommended human dose on a mg/m^2 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 6 times the maximum recommended human dose on a mg/m^2 basis. (Calculations assume an oral dose of 320 mg/day and a 60-kg patient.)

13.2 Animal Toxicology and/or Pharmacology

Reproductive Toxicology Studies

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 maximum recommended human dose on a mg/m^2 basis. Calculations assume an oral dose of 320 mg/day and a 60-kg patient.

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 comparable 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

The antihypertensive effects of valsartan were evaluated in two randomized, double-blind clinical studies.

In a clinical study involving 261 hypertensive pediatric patients 6 to 16 years of age, patients who weighed < 35 kg received 10, 40 or 80 mg of valsartan daily (low, medium and high doses), and patients who weighed ≥ 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, -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.

In a clinical study involving 90 hypertensive pediatric patients 1 to 5 years of age with a similar study design, there was some evidence of effectiveness, but safety findings for which a relationship to treatment could not be excluded mitigate against recommending use in this age group *[see Adverse Reactions (6.1)]*.

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 <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% 65 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	484 (19.4%)	495 (19.7%)	1.02 (0.90-1.15)	0.8
HF morbidity	801 (32.1%)	723 (28.8%)	0.87 (0.79-0.97)	0.009
* CI = Confidence Interval				

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=2,318)	**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)	
p-value	0.0002		0.0965	

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.

Secondary end points in the subgroup not receiving ACE inhibitors were as follows.

	Placebo (N=181)	**Valsartan (N=185)**	**Hazard Ratio (95% CI)**
Components of HF morbidity			
All-cause mortality	49 (27.1%)	32 (17.3%)	0.59 (0.37, 0.91)
Sudden death with resuscitation	2 (1.1%)	1 (0.5%)	0.47 (0.04, 5.20)
CHF therapy	1 (0.6%)	0 (0.0%)	–
CHF hospitalization	48 (26.5%)	24 (13.0%)	0.43 (0.27, 0.71)
Cardiovascular mortality	40 (22.1%)	29 (15.7%)	0.65 (0.40, 1.05)
Non-fatal morbidity	49 (27.1%)	24 (13.0%)	0.42 (0.26, 0.69)

In patients not receiving an ACE inhibitor, valsartan-treated patients had an increase in ejection fraction and reduction in left ventricular internal diastolic diameter (LVIDD).

Effects were generally consistent across subgroups defined by age and gender for the population of patients not receiving an ACE inhibitor. The number of black patients was small and does not permit a meaningful assessment in this subset of patients.

16 HOW SUPPLIED/STORAGE AND HANDLING

Valsartan Tablets USP are available as follows:

40 mg tablets are yellow, capsule shaped, biconvex, film-coated with a functional scoreline on one side, debossed with 'C' on one side of scoreline and 'I' on other side of scoreline and plain on the other side.

Bottle of 30's	59746-360-30
Bottle of 90's	59746-360-90
Bottle of 500's	59746-360-05
Carton of 10x10's	59746-360-03

80 mg tablets are peach, round, biconvex, film-coated, debossed with 'C3'on one side and 'C' on other side.

Bottle of 30's	59746-361-30
Bottle of 90's	59746-361-90
Bottle of 500's	59746-361-05
Carton of 10x10's	59746-361-03

160 mg tablets are yellow, oval shaped, biconvex, film-coated, debossed with 'C4' on one side and 'C' on the other side.

Bottle of 30's	59746-362-30
Bottle of 90's	59746-362-90
Bottle of 500's	59746-362-05
Carton of 10x10's	59746-362-03

320 mg tablets are yellow, oval shaped, biconvex, film-coated, debossed with 'C5' on one side and 'C' on the other side.

Bottle of 30's	59746-363-30
Bottle of 90's	59746-363-90
Bottle of 400's	59746-363-67
Carton of 3x10's	59746-363-32

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15-30°C (59-86°F) [See USP Controlled Room Temperature].

Protect from moisture.

Dispense in tight container (USP).

17 PATIENT COUNSELING INFORMATION

Information for Patients

Pregnancy: Female patients of childbearing age should be told about the consequences of exposure to valsartan 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.

Rx Only

Manufactured by:
Jubilant Generics Limited
Roorkee-247661, India

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Salisbury, MD-21801, USA

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Reason for Artwork: Revised as per Deficiency letter received from Agency (dated: 17 Dec. 2014).	JUBILANT GENERICS	**Dimension: 455 x 540 mm**
Item Code: 7524000570		**Superseded Item Code: 7524000548**
Substrate: 40 GSM Bible paper		
Site Packaging Development Sign and Date		**Production Sign and Date** / **QA Sign and Date**