Product Monograph

[Pr]AVA-VALSARTAN

(valsartan)

40 mg, 80 mg, 160 mg and 320 mg tablets

Angiotensin II AT_1 Receptor Blocker

Avanstra Inc.
10761-25th street NE, Suite 110,
Calgary, Alberta, Canada
T3N 0A4

Date of Revision: June 12, 2012

Control #: 155868

Table of Contents

PART I: HEALTH PROFESSIONAL INFORMATION....3
SUMMARY PRODUCT INFORMATION....3
INDICATIONS AND CLINICAL USE....3
CONTRAINDICATIONS....4
WARNINGS AND PRECAUTIONS....4
ADVERSE REACTIONS....7
DRUG INTERACTIONS....10
DOSAGE AND ADMINISTRATION....11
OVERDOSAGE....12
ACTION AND CLINICAL PHARMACOLOGY....13
STORAGE AND STABILITY....15
SPECIAL HANDLING INSTRUCTIONS....15
DOSAGE FORMS, COMPOSITION AND PACKAGING....15

PART II: SCIENTIFIC INFORMATION....17
PHARMACEUTICAL INFORMATION....17
CLINICAL TRIALS....18
DETAILED PHARMACOLOGY....23
MICROBIOLOGY....24
TOXICOLOGY....24
REFERENCES....28

PART III: CONSUMER INFORMATION....30

[Pr]AVA-VALSARTAN
(valsartan)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	40 mg, 80 mg, 160 mg and 320 mg tablets	Colloidal silicon dioxide, crospovidone, magnesium stearate, and microcrystalline cellulose, hydroxypropyl methylcellulose, polyethylene glycol, black iron oxide, red iron oxide, yellow iron oxide, and titanium dioxide.

INDICATIONS AND CLINICAL USE

Ava-Valsartan (valsartan) is indicated for:

- **Hypertension**
  - For the treatment of mild to moderate essential hypertension.
  - Ava-Valsartan may be administered alone, or concomitantly with thiazide diuretics.
  - The safety and efficacy of concurrent treatment with Ava-Valsartan and angiotensin converting enzyme inhibitors have not been established.

- **Following Myocardial Infarction**
  - To reduce cardiovascular mortality in clinically stable patients with signs or symptoms of left ventricular dysfunction in conjunction with acute myocardial infarction when the use of an angiotensin-converting enzyme inhibitor (ACEI) is not appropriate.
  - The combination of valsartan and an angiotensin-converting enzyme inhibitor (ACEI) has not been shown to result in clinically relevant improvement in cardiovascular outcome over valsartan use alone. Accordingly, such combined use is not recommended.

- **Chronic Heart Failure**
  - Ava-Valsartan can be used in patients with chronic heart failure who have been shown to be intolerant to an angiotensin converting enzyme inhibitor. There is no evidence that Ava-Valsartan provides added benefits when it is used with ACE inhibitors (See Clinical Trials).

Geriatrics (> 65 years of age)
No overall difference in efficacy or safety observed versus younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Pediatrics (< 18 years of age)
The safety and effectiveness of Ava-Valsartan in children and adolescents (below the age of 18 years) have not been established.

CONTRAINDICATIONS

- Valsartan is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container (see DOSAGE FORMS, COMPOSITION AND PACKAGING).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions
When used in pregnancy **angiotensin receptor (AT_1) blockers (ARB)** can cause injury to or even death of the developing fetus. When pregnancy is detected, valsartan should be discontinued as soon as possible (see WARNINGS AND PRECAUTIONS, Special Populations).

Cardiovascular
Hypotension
Occasionally, symptomatic hypotension has occurred after administration of valsartan, in some cases after the first dose. It is more likely to occur in patients who are volume-depleted by diuretic therapy, dietary salt restriction, dialysis, diarrhea, or vomiting. In these patients, because of the potential fall in blood pressure, therapy should be started under close medical supervision. Similar considerations apply to patients with ischemic heart or cerebrovascular disease, in whom an excessive fall in blood pressure could result in myocardial infarction or cerebrovascular accident.

Caution should be exercised when initiating therapy after acute myocardial infarction. Patients with heart failure or those in the early post-myocardial infarction period that are given valsartan commonly have some reduction in blood pressure, but discontinuation of therapy is usually not necessary if patients are well screened prior to instituting treatment and found to be clinically stable. If symptomatic hypotension does occur, consideration should be given to dosage reduction (see DOSAGE AND ADMINISTRATION - Following Myocardial Infarction). In patients treated following myocardial infarction, the recommended regimen of valsartan has been observed to result in a greater incidence of hypotension as a serious adverse event than the conventional dosage regimen of captopril in this indication (see ADVERSE REACTIONS - Following Myocardial Infarction).

In patients with heart failure, a greater incidence of hypotension has been reported. Monitoring and dose adjustment should be considered.

Valvular Stenosis
There is concern on theoretical grounds that patients with aortic stenosis might be at a particular risk of decreased coronary perfusion, because they do not develop as much afterload reduction.

Hepatic/Biliary/Pancreatic
On average, patients with mild to moderate chronic liver disease have twice the exposure to valsartan of healthy volunteers as measured by AUC and C_{max}. Care should be exercised in administering valsartan to these patients (see ACTION AND CLINICAL PHARMACOLOGY - Pharmacokinetics).

Renal
As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function have been seen in susceptible individuals. In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, such as patients with bilateral renal artery stenosis, unilateral renal artery stenosis to a solitary kidney, or severe congestive heart failure, treatment with agents that inhibit this system has been associated with oliguria, progressive azotemia, and rarely, acute renal failure and/or death. In susceptible patients, concomitant diuretic use may further increase risk.

Following myocardial infarction, major renal dysfunction was observed to occur more frequently with valsartan than with captopril monotherapy (see ADVERSE REACTIONS - Following Myocardial Infarction). The role of modestly lower blood pressure that may occur with valsartan compared to captopril monotherapy is not known.

The incidence of clinically relevant hyperkalemia has also been observed to be increased with valsartan (see ADVERSE REACTIONS - Laboratory Findings). Patients exposed to potassium-sparing diuretics and/or potassium supplements were more likely to develop hyperkalemia. Accordingly, their use should be carefully monitored or avoided (see DRUG INTERACTIONS - Agents Increasing Serum Potassium).

Some patients with heart failure have developed increases in blood urea nitrogen, serum creatinine, and potassium.These effects are more likely to occur in patients with pre-existing renal impairment. Dosage reduction and/or discontinuation of valsartan may be required. In the Valsartan Heart Failure Trial, in which 93% of patients were on concomitant ACE inhibitors, treatment was discontinued for elevations in creatinine or potassium in a total of 1.0% on valsartan vs. 0.2% on placebo.

Use of valsartan should include appropriate assessment of renal function.

Special Populations

Pregnant Women: Drugs that act directly on the renin-angiotensin-aldosterone- system (RAAS) can cause fetal and neonatal morbidity and death when administered to pregnant women. When pregnancy is detected, valsartan should be discontinued as soon as possible.

The use of ARB is not recommended during pregnancy. Epidemiological evidence regarding the risk of teratogenicity following exposure to angiotensin converting enzyme inhibitors (another class of therapeutic products interfering with the RAAS) during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Given the current evidence available on the risk with ARB, similar risks may exist for this class of drugs. Patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with angiotensin II antagonists should be stopped immediately, and, if appropriate, alternative therapy should be started.

The use of ARBS during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia).

There have been reports of spontaneous abortion, oligohydramnios and newborn renal dysfunction, when pregnant women have inadvertently taken valsartan.

Infants with histories of *in utero* exposure to an angiotensin II AT_1 receptor blocker should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion may be required as a means of reversing hypotension and/or substituting for impaired renal function; however, limited experience with those procedures has not been associated with significant clinical benefit. Valsartan is not removed from plasma by dialysis.

Animal Data: No teratogenic effects were observed when valsartan was administered orally to pregnant mice and rats at 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 orally with valsartan at 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 associated with maternal toxicity (mortality) was observed at doses of 5 and 10 mg/kg/day.

Nursing Women: It is not known whether valsartan is excreted in human milk but significant levels have been found in the milk of lactating rats. Because many drugs are excreted in human milk and because of their potential for affecting the nursing infant adversely, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatrics: The safety and effectiveness of valsartan in children and adolescents (below the age of 18 years) have not been established.

Geriatrics (> 65 years of age): In controlled clinical trials no overall age-related differences were seen in the adverse effect profile but greater sensitivity in some older individuals cannot be ruled out.

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Hypertension

Valsartan has been evaluated for safety in over 4300 patients treated for hypertension, including more than 600 treated for over 6 months and more than 330 for over 1 year. Of these, 3634 were treated with valsartan monotherapy in controlled clinical trials.

In controlled clinical trials, discontinuation due to AEs occurred in 3.1% and 4.0% of patients treated with valsartan monotherapy and placebo, respectively.

The following potentially serious adverse reactions have been reported rarely with valsartan in controlled clinical trials: syncope, hypotension.

The following table is based on double-blind controlled trials in patients treated with valsartan monotherapy at doses of 80 to 160 mg/day. The table includes all AEs with an incidence of 1% or greater in the valsartan treatment group, irrespective of causal relationship to study drug. No AE appeared to have an incidence related to dose. Therefore, AEs are grouped irrespective of dose.

Table 1 - Hypertension: Occurrence of adverse events during double-blind controlled trials in patients treated with valsartan monotherapy at doses of 80 to 160 mg/day

	Valsartan N = 2827 %	**Placebo N = 1007 %**
Central Nervous System		
Headache	8.5	13.6
Dizziness	2.8	3.9
Respiratory system		
Upper Respiratory Tract Infection	2.9	2.3
Coughing	2.7	1.3
Rhinitis	1.8	2.0
Sinusitis	1.5	1.7
Pharyngitis	1.3	0.7
Bronchitis	1.1	1.3

Digestive system		
Diarrhea	2.5	1.6
Abdominal Pain	1.3	0.9
Nausea	1.5	2.2
Dyspepsia	1.1	1.8
Musculoskeletal system		
Arthralgia	1.3	0.9
Back Pain	2.2	1.5
Body as a whole		
Fatigue	1.9	1.3
Other		
Viral Infection	3.1	2.6

In a study conducted with patients taking valsartan at starting doses of 20 mg to 320 mg, an increased incidence of dizziness was observed with valsartan 320 mg (9%) compared to valsartan 20 to 160 mg (2 to 4%). In another study where patients were up-titrated to the 320 mg dose of valsartan, the incidence of dizziness was comparable to the 160 mg dose (1%).

In double-blind controlled trials, the following adverse events were reported with valsartan at an occurrence rate of less than 1% regardless of drug relationship: orthostatic effects, chest pain, palpitations, myalgia, asthenia, somnolence, vertigo, impotence, epistaxis, fibrosing alveolitis (one case), allergic reactions, urticaria, pruritus and rash.

Following Myocardial Infarction

The following table shows the frequency of selected serious adverse events (≥ 0.4% in any treatment group) for the valsartan, valsartan + captopril, and captopril treatment groups in a large, randomized double-blind trial. Serious adverse events related to the disease under study have not been included in this table.

Table 2 - Following Myocardial Infarction: Selected serious adverse events by treatment (safety population)

	Valsartan	**Valsartan + Captopril**	**Captopril**
	n = 4885 (%)	**n = 4862 (%)**	**n = 4879 (%)**
Hypotension [1]	2.8	3.3	2.0
Syncope	0.7	0.6	0.6
Dizziness	0.4	0.4	0.3
Renal causes [2]	3.1	3.0	2.0
Hyperkalaemia	0.4	0.6	0.4
Atrial fibrillation	1.0	0.7	0.8
Cough	0.3	0.5	0.4
Taste disturbances [3]	0.1	0.4	0.3

[1] This term includes SAEs related to hypotension, orthostatic hypotension
[2] This term includes SAEs related to acute renal failure, chronic renal failure, blood creatinine increased
[3] This term includes ageusia, dysgeusia, hypogeusia

Major renal dysfunction was observed in 3.8%, 3.7%, and 2.6% of patients in the valsartan, valsartan + captopril, and captopril treatment groups, respectively. Major renal dysfunction was

defined as death from a renal cause, a serious adverse event suggestive of renal failure, and temporary or permanent discontinuation of study drug for a renal cause.

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 for the doses of valsartan used in the Valsartan Heart Failure Trial.

Abnormal Hematologic and Clinical Chemistry Findings
Laboratory Findings
These laboratory findings pertain to trials in hypertension, except as otherwise indicated.

Hyperkalemia: In hypertensive patients, greater than 20% increases in serum potassium were observed in 5.0% of valsartan-treated patients compared to 3.0% of placebo-treated patients. Hyperkalemia as an adverse event occurred in 2.3%, 2.4%, and 1.5% of post-myocardial infarction patients treated with valsartan, valsartan + captopril, and captopril, respectively. 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.

Creatinine: Minor elevations in creatinine occurred in 1.1% of patients treated with valsartan and 0.8% of patients given placebo in controlled clinical trials in hypertensive patients. In post-myocardial infarction patients, doubling of serum creatinine was observed in 4.2% of valsartan-treated patients, 4.8% of valsartan + captopril-treated patients, and 3.4% of captopril-treated patients. In heart failure patients, increases in serum creatinine greater than 50% were observed in 3.9% of valsartan-treated patients compared to 0.9% of placebo-treated patients.

Blood Urea Nitrogen (BUN): In heart failure trials, increases in blood urea nitrogen (BUN) greater than 50% were observed in 16.6% of patients treated with valsartan as compared to 6.3% of patients treated with placebo.

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

Uric Acid: In placebo-controlled trials, elevations of uric acid levels (baseline *versus* terminal lab) occurred in 2.6% of patients receiving valsartan monotherapy, 8.2% receiving valsartan and hydrochlorothiazide, 6.0% receiving hydrochlorothiazide alone and 2.3% receiving placebo.

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

In controlled clinical trials, thrombocytopenia was observed in 0.1% of patients.

Post-Market Adverse Drug Reactions

Other adverse reactions reported rarely in post-marketing use include: anaphylaxis (very rarely), angioedema (involving swelling of the face, lips and/or tongue), renal impairment (very rare), photosensitivity, increase in blood pressure and taste disorders.
Cases of muscle pain, muscle weakness, myositis and rhabdomyolysis have been reported in patients receiving angiotensin II receptor blockers.

DRUG INTERACTIONS

Drug-Drug Interactions

Diuretics
Patients on diuretics, and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction in blood pressure after initiation of therapy with valsartan. The possibility of symptomatic hypotension with the use of valsartan can be minimized by discontinuing the diuretic prior to initiation of treatment (see WARNINGS AND PRECAUTIONS – Cardiovascular - Hypotension). No drug interaction of clinical significance has been identified with thiazide diuretics.

Agents Increasing Serum Potassium
Since valsartan decreases the production of aldosterone, potassium-sparing diuretics or potassium supplements should be given only for documented hypokalemia and with frequent monitoring of serum potassium. Potassium-containing salt substitutes should also be used with caution.

Lithium Salts
As with other drugs which eliminate sodium, lithium clearance may be reduced. Therefore, serum lithium levels should be monitored carefully if lithium salts are to be administered.

Warfarin
Co-administration of valsartan and warfarin over 3 days did not affect the bioavailability of valsartan. Co-administration had no effect on activated partial thromboplastin time (APTT) and resulted in a 12% increase in prothrombin time (PT).

Digoxin
A single dose of digoxin administered with a single dose of valsartan did not result in a clinically significant interaction. No steady state data are available.

Non-Steroidal Anti-Inflammatory Agents (NSAIDs)
Non-Steroidal Anti-Inflammatory Agents (NSAIDs) including Selective Cyclooxygenase-2 Inhibitors (COX-2 Inhibitors): When angiotensin II antagonists are administered simultaneously with NSAIDs, attenuation of the antihypertensive effect may occur.

Furthermore, in patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, concomitant use of angiotensin II antagonists and NSAIDs may lead to an increased risk of worsening of renal function including possible acute renal

failure. Therefore, monitoring of renal function is recommended when initiating or modifying the treatment and periodically in patients on valsartan who are taking NSAIDs concomitantly.

Drug-Food Interactions
See ACTION AND CLINICAL PHARMACOLOGY – Pharmacokinetics - Absorption

DOSAGE AND ADMINISTRATION

Dosing Considerations
Hepatic Impairment
No initial dosage adjustment is required in patients with mild to moderate liver disease. Care should be exercised in patients with liver disease (see ACTION AND CLINICAL PHARMACOLOGY - Pharmacokinetics, and WARNINGS AND PRECAUTIONS - Hepatic/Biliary/Pancreatic).

Renal Impairment
No initial dosage adjustment is required for patients with renal impairment including those patients requiring hemodialysis. Appropriate monitoring of these patients is however recommended (see ACTION AND CLINICAL PHARMACOLOGY - Pharmacokinetics, and WARNINGS AND PRECAUTIONS - Renal).

Elderly
No dosage adjustment is usually necessary (see WARNINGS AND PRECAUTIONS - Special Populations - Geriatrics).

Concomitant Diuretic Therapy
In patients receiving diuretics, Ava-Valsartan therapy should be initiated with caution, since these patients may be volume-depleted and thus more likely to experience hypotension following initiation of additional anti-hypertensive therapy. Whenever possible, all diuretics should be discontinued two to three days prior to the administration of Ava-Valsartan to reduce the likelihood of hypotension (see WARNINGS AND PRECAUTIONS - Hypotension, and DRUG INTERACTIONS - Diuretics). If this is not possible because of the patient's condition, Ava-Valsartan should be administered with caution and the blood pressure monitored closely. Thereafter, the dosage should be adjusted according to the individual response of the patient.

Recommended Dose and Dosage Adjustment
Hypertension
Initiation of therapy requires consideration of recent antihypertensive drug treatment, the extent of blood pressure elevation, salt restriction, and other pertinent clinical factors (see WARNINGS AND PRECAUTIONS- Hypotension). The dosage of antihypertensive agents used with Ava-Valsartan may need to be adjusted.

The recommended initial dose of Ava-Valsartan is 80 mg once daily. The antihypertensive effect is present within 2 weeks and maximal reduction is usually attained within 4 weeks following

initiation of therapy. In patients whose blood pressure is not adequately controlled, the daily dose may be increased to a maximum of 320 mg or a thiazide diuretic added.

It is not recommended to prescribe the maximum dose of 320 mg without prior up-titration.

Ava-Valsartan should be administered consistently with or without food (See ACTION AND CLINICAL PHARMACOLOGY - Pharmacokinetics).

Following Myocardial Infarction
Ava-Valsartan may be initiated as early as 12 hours after a myocardial infarction in clinically stable patients. In order to diminish the risk of hypotension, the recommended starting dose is 20 mg twice daily. Thereafter, patients may be uptitrated within 7 days to 40 mg twice daily, with subsequent titrations to a target maintenance dose of 160 mg twice daily, as tolerated. If symptomatic hypotension or renal dysfunction occurs, consideration should be given to dosage reduction. Ava-Valsartan should be given with other standard post-myocardial infarction treatment, including thrombolytics, aspirin and statins, as indicated.

Concomitant use of beta-blockers is to be encouraged with Ava-Valsartan in this clinical setting, if indicated, since further substantial relative risk reduction may be expected with such use over that of valsartan alone (see PHARMACOLOGY - Following Myocardial Infarction).

Heart Failure
The recommended starting dose of Ava-Valsartan is 40 mg twice daily. Titration every two weeks to 80 mg and 160 mg twice daily should be done to the highest dose tolerated by the patient. Consideration should be given to reduce the dose of concomitant diuretics. The maximum recommended dose is 160 mg twice daily.

Missed Dose
Patients should try to take their dose at the same time each day, preferably in the morning. However, if they have forgotten to take the dose during the day, they should carry on with the next dose at the usual time. They should not double doses.

OVERDOSAGE

Limited data are available in regard to overdosage with valsartan in humans. The most likely manifestations of overdosage would be hypotension and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. Depressed level of consciousness, circulatory collapse and shock have been reported. If symptomatic hypotension should occur, supportive treatment should be instituted.

Valsartan is not removed from the plasma by dialysis.

For the management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Valsartan is an orally active angiotensin II AT_1 receptor blocker.

Valsartan acts selectively on AT_1, the receptor subtype that mediates the known cardiovascular actions of angiotensin II, the primary vaso-active hormone of the renin-angiotensin-system. The AT_2 receptor subtype, found in tissues such as brain, endometrium, myometrium and fetal kidney and adrenals, plays no known role in cardiovascular homeostasis to date. Valsartan does not exhibit any partial AT_1 receptor agonist activity and has essentially no activity at the AT_2 receptor. Valsartan does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation. The primary metabolite, valeryl 4-hydroxy valsartan, is essentially inactive.

Angiotensin II has a wide variety of physiological effects; many are either directly or indirectly involved in blood pressure regulation. A potent vasoconstrictor, angiotensin II exerts a direct pressor response. In addition, it promotes sodium retention and aldosterone secretion.

Blockade of angiotensin II AT_1 receptors results in two- to three-fold increase in plasma renin and angiotensin II plasma concentrations in hypertensive patients. Long-term effects of increased AT_2 receptor stimulation by angiotensin II are unknown.

Valsartan does not inhibit angiotensin converting enzyme (ACE), also known as kininase II, the enzyme that converts angiotensin I to angiotensin II and degrades bradykinin.

Administration of valsartan to patients with type II diabetes and microalbuminuria has resulted in significant reduction of urinary albumin excretion.

Pharmacodynamics

Valsartan inhibits the pressor effect of an angiotensin II infusion. An oral dose of 80 mg inhibits the pressor effect by about 80% at peak with approximately 30% inhibition persisting for 24 hours.

After a single oral dose, the antihypertensive activity of valsartan has an onset within approximately 2 hours and peaks within 4-6 hours in most patients.

The anti-hypertensive effect of valsartan persists for 24 hours after dosing. Trough/peak ratio ranges from 0.54 to 0.76. Valsartan reduces blood pressure in hypertensive patients without affecting pulse rate.

During repeated dosing, the maximum blood pressure reduction with any dose is generally attained within 4 weeks, and is sustained during long-term therapy. Combinations with hydrochlorothiazide produce additional reduction in blood pressure.

There is no apparent rebound effect after abrupt withdrawal of valsartan therapy.

Although data available to date indicate a similar pharmacodynamic effect of valsartan in black and white hypertensive patients, this should be viewed with caution since antihypertensive drugs that affect the renin-angiotensin system, such as ACE inhibitors and angiotensin II AT_1 receptor blockers, have generally been found to be less effective in low-renin hypertensives (frequently blacks).

Pharmacokinetics

Since its pharmacokinetics are linear in the 80 to 320 mg dose range, valsartan does not accumulate appreciably in plasma following repeated administration.

The valsartan tablet and capsule dosage forms were found to be bioequivalent in a two-treatment, three period, repeated measure, randomized cross-over study conducted in 40 healthy volunteers and comparing the 320 mg tablet formulation to 2 X 160 mg capsule. The median T_{max} values were similar and the mean C_{max} values were nearly identical (2.75h *versus* 3.00 h and 6.162 mg/dL *versus* 6.164 mg/dL, respectively for the tablet and capsule). The $AUC_{0\rightarrow\infty}$ was of 42.68 h·mg/L for the tablet and 39.829 h·mg/L for the capsule**.**

Absorption: The mean absolute bioavailability of valsartan is about 23%, but with high variability. Peak plasma concentration is reached 2 to 4 hours after dosing. Giving valsartan with food reduces the area under the valsartan plasma concentration curve (AUC) by 48%. After about 8 hours however, plasma valsartan concentrations are similar in the fed and fasted state.

Distribution: Valsartan is 94-97% bound to serum protein, mainly serum albumin. Steady-state volume of distribution is about 17 L, indicating that valsartan does not distribute into tissues extensively.

Metabolism: Following intravenous administration, valsartan shows bi-exponential decay kinetics ($t_{1/2}\alpha$ <1 hour and $t_{1/2}\beta$ between 5-9 hours). Plasma clearance is relatively slow (about 2 L/hr) when compared with hepatic blood flow (about 30 L/hr). Valsartan biotransformation does not seem to involve the cytochrome P-450 system. The enzyme(s) responsible for valsartan metabolism have not been identified.

Excretion: Following administration of an oral solution of ^{14}C labelled valsartan, 83% of absorbed valsartan is excreted in the feces and 13% in the urine, mainly as unchanged compound.

Special Populations and Conditions

Pediatrics: The safety and effectiveness of valsartan in children and adolescents (below the age of 18 years) have not been established.

Geriatrics: Exposure to valsartan is about 50% higher as measured by AUC and C_{max} and the half life is longer in elderly subjects than in young subjects. However, this difference has not been shown to have any clinical significance.

Gender: Plasma concentrations are similar in males and females.

Hepatic Insufficiency: On average, patients with mild to moderate chronic liver disease have twice the exposure to valsartan of healthy volunteers as measured by AUC and C_{max} (see WARNINGS AND PRECAUTIONS, and DOSAGE AND ADMINISTRATION).

Renal Insufficiency: Renal clearance accounts for only 30% of total plasma clearance. There is no apparent correlation between renal function and exposure to valsartan, as measured by AUC and C_{max}, in patients with different degrees of renal impairment. In patients with renal failure undergoing hemodialysis, limited information showed that exposure to valsartan is comparable to that in patients with creatinine clearance > 10 mL/min.

STORAGE AND STABILITY

Protect from moisture and heat (store at 15-30°C).

SPECIAL HANDLING INSTRUCTIONS

Not applicable

DOSAGE FORMS, COMPOSITION AND PACKAGING

Availability
Ava-Valsartan 40 mg tablets are supplied in bottles of 100 and 500 tablets and in cartons containing 2 blister strips of 15 tablets. Since the 40 mg tablets are scored on one side, these may be used to initiate therapy following myocardial infarction (see DOSAGE AND ADMINISTRATION, Following Myocardial Infarction).

Ava-Valsartan 80 mg tablets are supplied in bottles of 100 and 500 tablets and in cartons containing 2 blister strips of 15 tablets.

Ava-Valsartan 160 mg tablets are supplied in bottles of 100 and 500 tablets and in cartons containing 2 blister strips of 15 tablets.

Ava-Valsartan 320 mg tablets are supplied in bottles of 100 and in cartons containing 2 blister strips of 15 tablets.

Composition
Ava-Valsartan 40 mg Tablets
Ava-Valsartan tablets, 40 mg are yellow, ovaloid, scored on one side, slightly convex, with bevelled edges, debossed on one side with DO and with NVR on the other side. Each tablet

contains 40 mg of valsartan and the following non-medicinal ingredients: colloidal silicon dioxide, crospovidone, magnesium stearate, and microcrystalline cellulose. The coating contains: hydroxypropyl methylcellulose, polyethylene glycol, black iron oxide, red iron oxide, yellow iron oxide, and titanium dioxide.

Ava-Valsartan 80 mg Tablets
Ava-Valsartan tablets, 80 mg are pale red, round shaped tablets with bevelled edges, debossed with DV on one side and NVR on the other. Each tablet contains 80 mg of valsartan and the following non-medicinal ingredients: colloidal silicon dioxide, crospovidone, magnesium stearate, and microcrystalline cellulose. The coating contains: hydroxypropyl methylcellulose, polyethylene glycol, black iron oxide, red iron oxide, and titanium dioxide.

Ava-Valsartan 160 mg Tablets
Ava-Valsartan tablets, 160 mg are grey orange, ovaloid shaped tablets with bevelled edges, debossed with DX on one side and NVR on the other. Each tablet contains 160 mg of valsartan and the following non-medicinal ingredients: colloidal silicon dioxide, crospovidone, magnesium stearate, and microcrystalline cellulose. The coating contains: hydroxypropyl methylcellulose, polyethylene glycol, black iron oxide, red iron oxide, yellow iron oxide, and titanium dioxide.

Ava-Valsartan 320 mg Tablets
Ava-Valsartan tablets, 320 mg are dark grey-violet, ovaloid with bevelled edges, slightly convex, debossed with DXL on one side and NVR on the other. Each tablet contains 320 mg of valsartan and the following non-medicinal ingredients: colloidal silicon dioxide, crospovidone, magnesium stearate, and microcrystalline cellulose. The coating contains: hydroxypropyl methylcellulose, polyethylene glycol, black iron oxide, red iron oxide, yellow iron oxide, and titanium dioxide.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

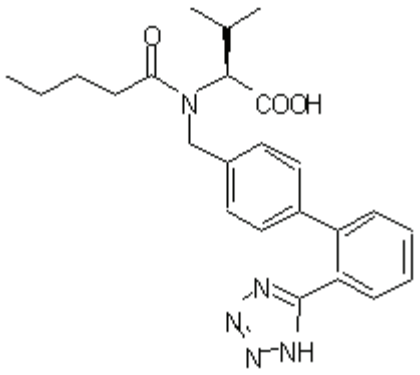
Drug Substance

Proper name: Valsartan

Chemical name: (*S*)-*N*-valeryl-*N*-{[2'-(1H-tetrazol-5-yl) biphenyl-4-yl] methyl}-valine

Molecular formula and molecular mass: $C_{24}H_{29}N_5O_3$ / 435.5

Structural formula:



Physicochemical properties:

Description: Fine white to practically white, practically odourless powder.

Solubility:

Solvent	**Temp. (^{O}C)**	**Resulting pH**	**Solubility (g/L)**
Water	25	3.8	0.18
water	37	3.8	0.21
0.1 N HCl	22	1.12	0.084
0.01 N HCl	37	1.0	0.10
0.067 M phosphate buffer, pH = 5.2	22	4.41	0.64
0.067 M phosphate buffer, pH = 8.0	22	5.29	16.8
chloroform	27	-	56 - 61
ethanol 96%	26	-	> 300
methanol p.a.	26	-	> 500

Melting Range: 105 - 110^{O}C with decomposition.

pK_a Values:

pK_a-Values	**Solvent**	**Temp. (^{O}C)**	**Assignment**
4.73	water	22	tetrazole group

pK_a-Values	Solvent	Temp. (^{O}C)	Assignment
3.90	water	22	carboxylic group

CLINICAL TRIALS

Study demographics and trial design
Not Applicable

Study results
Hypertension
In a 6-week controlled study of the incidence of cough in hypertensive patients with a history of cough during ACE inhibitor therapy, the incidence of cough reported in patients receiving valsartan was significantly less than in patients rechallenged with an ACE inhibitor. In addition, an overall analysis of double-blind clinical trials in 4,565 patients revealed that the incidence of spontaneously reported cough was 2.7% in patients treated with valsartan 80 and 160 mg (n=2827), compared to 1.3% in patients treated with placebo (n=1007), whereas the incidence of cough with ACE inhibitors (n=731) was 12.6%.

The antihypertensive effects of valsartan were demonstrated principally in 9 placebo-controlled, 4- to 12-week trials (one in patients over 65) 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 of response by gender, age, and race.

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 two years. The antihypertensive effect is independent of age, gender or race.

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

The 9 studies of valsartan monotherapy included over 2800 patients randomized to various doses of valsartan and about 1100 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

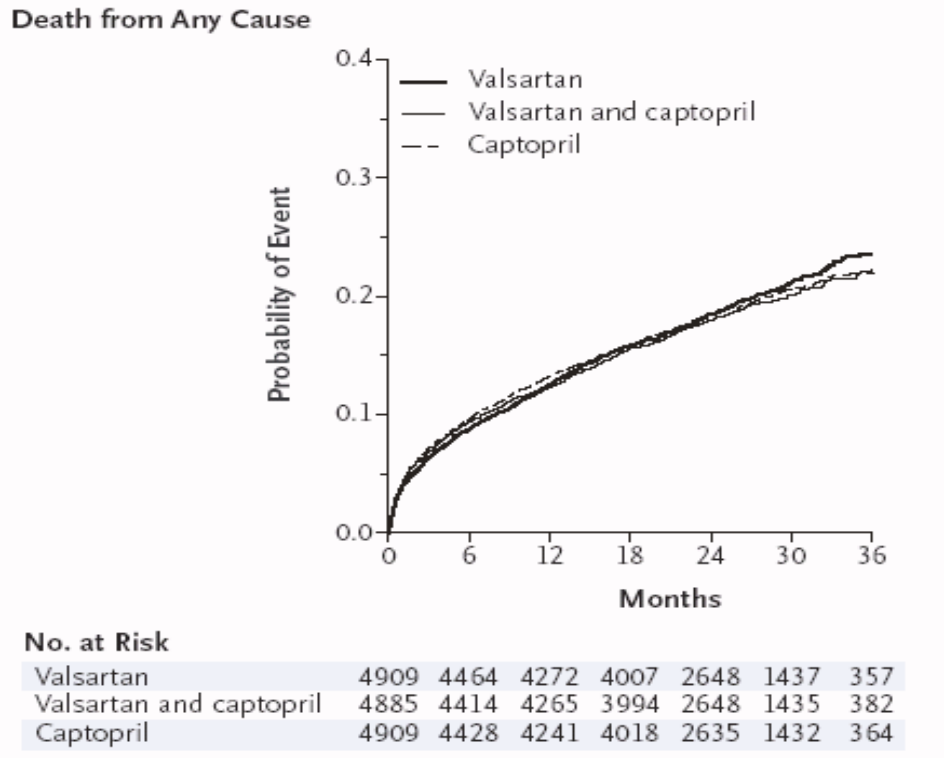
placebo of approximately 6-9/3-5 mmHg at 80-160 mg and 8-9/4-7 mmHg at 320 mg. In another study, patients randomized to valsartan 320 mg once daily had an incremental blood pressure reduction of 2.6/1.2 mmHg lower than did patients randomized to valsartan 160 mg once daily.

Patients with an inadequate response to valsartan 80 mg once daily were titrated to either valsartan 160 mg once daily or valsartan 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 was essentially no change in heart rate in valsartan-treated patients in controlled trials.

Following Myocardial Infarction
The VALsartan In Acute myocardial iNfarcTion trial (VALIANT) was a randomized, controlled, multinational, double-blind study in 14,703 patients with acute myocardial infarction and signs or symptoms of congestive heart failure and/or evidence of left ventricular systolic dysfunction (manifested as an ejection fraction ≤ 40% by radionuclide ventriculography or ≤ 35% by echocardiography or ventricular contrast angiography). Patients were randomized within 12 hours to 10 days after the onset of myocardial infarction symptoms to one of three treatment groups: valsartan (titrated from 20 mg twice daily to highest tolerated dose up to a maximum of 160 mg twice daily), the ACE inhibitor captopril (titrated from 6.25 mg three times daily to highest tolerated dose up to a maximum of 50 mg three times daily), or the combination of valsartan plus captopril. In the combination group, the dose of valsartan was titrated from 20 mg twice daily to highest tolerated dose up to a maximum of 80 mg twice daily; the dose of captopril was the same as for monotherapy. The mean treatment duration was two years. The mean daily dose of valsartan in the monotherapy group was 217 mg, while that of captopril in the monotherapy group was 104 mg, and that of valsartan 103 mg and captopril 93 mg when used in combination. Baseline therapy included acetylsalicylic acid (91%), beta-blockers (70%), ACE inhibitors (40%), thrombolytics (35%), and statins (34%). The population studied was 69% male, 94% Caucasian, and 53% were 65 years of age or older. The primary endpoint was time to all-cause mortality.

All-cause mortality was similar in the valsartan (19.9%), captopril (19.5%), and valsartan + captopril (19.3%) groups. Note that combining valsartan with captopril did not add further benefit over captopril alone. The hazard ratio for all-cause mortality for valsartan versus captopril was 1.00 (97.5% CI, 0.90 to 1.11; p=0.98), and for valsartan + captopril versus captopril was 0.98 (97.5% CI, 0.89 to 1.09; p=0.73), when adjusted for age and prior MI.



Further, there was no difference in all-cause mortality or cardiovascular mortality between study treatment groups when beta-blockers were administered concomitantly with valsartan, captopril, or the combination of valsartan with captopril. Irrespective of study drug treatment, mortality was about 70% higher in patients not treated with a beta-blocker, suggesting that the known beta-blocker benefit in this population was maintained in this trial.

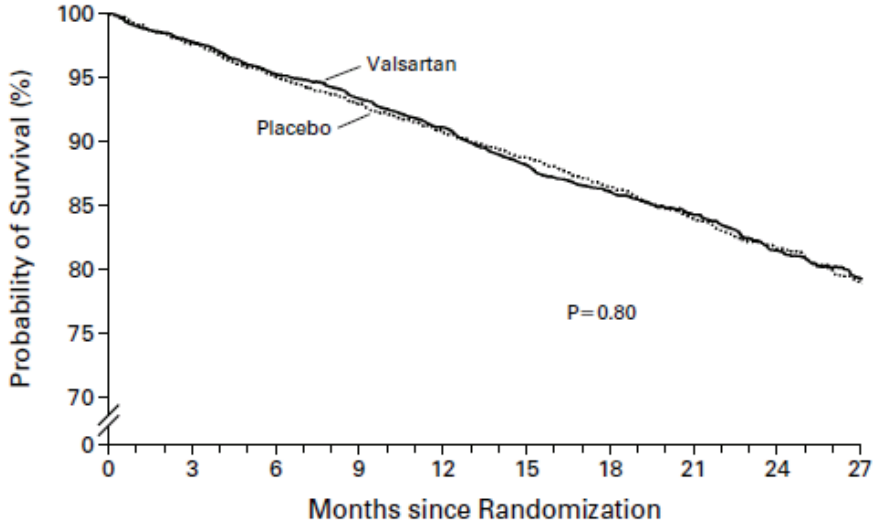
Heart Failure

A study called Val-HeFT (valsartan in heart failure trial) was carried out in 5,010 patients, predominantly NYHA Class II (62%) and III (36%), male (80%), white (90%) with heart failure primarily due to coronary heart disease (57%) or idiopathic origin (31%) and left ventricular ejection fraction less than 40%. Forty seven percent of the patients were 65 years or older. Patients were randomized double-blindly to valsartan 160 mg (target dose) or placebo twice daily. The double-blind therapy was given in addition to what treating physicians considered adequate treatment: diuretic (86%), digoxin (67%), beta-blocker (35%: carvedilol 15%, metoprolol 12%) and ACE inhibitor 93%. Blood pressure was on average 3/2 mmHg lower in the valsartan group at the end of the trial (average 2 years). The trial was designed with two co-primary endpoints: (1) mortality from any cause and (2) the combined endpoint of all cause mortality and morbidity which was defined as cardiac arrest with resuscitation, hospitalization for worsening heart failure, or intravenous administration of inotropic or vasodilator drugs for 4 hours or longer without hospitalization.

It can be seen in Figure 2 and Table 3 there was no significant difference in mortality (the first primary endpoint) between the two groups of patients. The second co-primary endpoint was

statistically significant in favour of valsartan (Table 3). The predominant benefit on the combined endpoint was largely due to a lower incidence of hospitalization for worsening heart failure with valsartan compared to placebo (p=0.001).

Figure 2 Kaplan-Meier Analysis of the Probability of Survival[#]



[#]Cohn et al, NEJM 2001; 345:1667-75

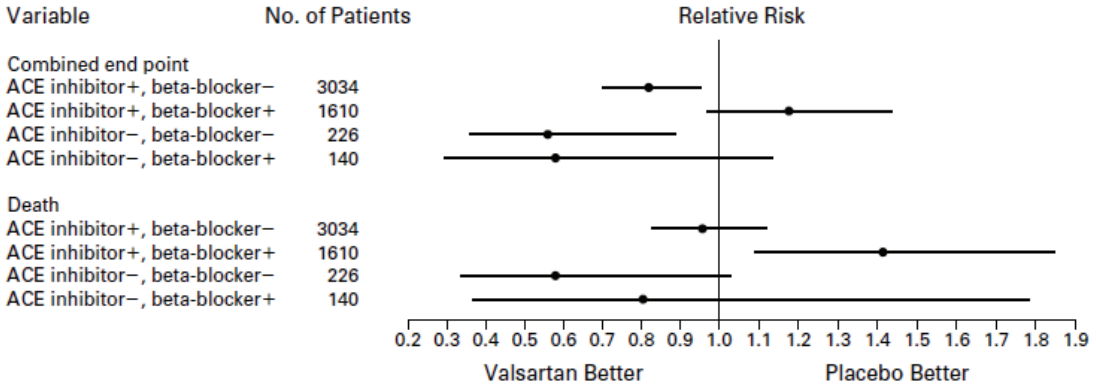
Table 3 Incidence and relative risk of the primary endpoints[#]

Event	Valsartan Group (N = 2511)	Placebo Group (N = 2499)	Relative Risk (CI)[+]	P Value[†]
no. with event (%)				
Death from any cause (during entire trial)	495 (19.7)	484 (19.4)	1.02 (0.88 - 1.18)	0.80
Combined end point			0.87 (0.77 - 0.97)	
Death from any cause (at first event)	723 (28.8)	801 (32.1)		0.009
Hospitalization for heart failure	356 (14.2)	315 (12.6)		
Cardiac arrest with resuscitation				
Intravenous therapy	346 (13.8)	455 (18.2)		
	16 (0.6)	26 (1.0)		
	5 (0.2)	5 (0.2)		

[+] The 98% confidence interval (CI) was calculated for the mortality end point (death from any cause), and the 97.5% confidence interval was calculated for the combined mortality-morbidity end point.
[†] P values were calculated by the log-rank test from time to first event.
[#]Cohn et al, NEJM 2001; 345:1667-75

The results obtained from patients on different background therapies are given in Figure 3. The benefits of valsartan were most apparent in patients not receiving either an ACE inhibitor or a beta blocker. However, risk ratios favoring placebo were observed for those patients treated with the triple combination of a beta blocker, an ACE inhibitor and an ARB (angiotensin II receptor blocker), valsartan. These data, however, were obtained from post hoc analyses and could have occurred by chance. Further studies such as VALIANT, where mortality was not increased in these patients, have reduced the concerns regarding the triple combination.

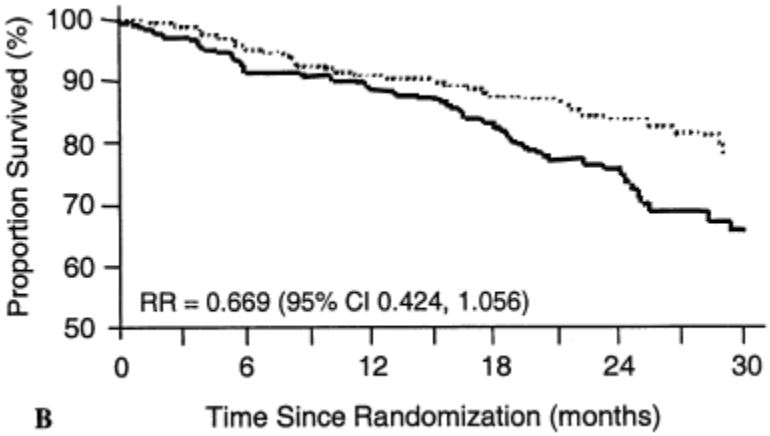
Figure 3 Relative Risks and 95% Confidence Intervals for the Combined End Point (Death from Any Cause, Cardiac Arrest with Resuscitation, Hospitalization for Worsening Heart Failure, or Therapy with Intravenous Inotropes or Vasodilators)[#]



According to the Background Therapy at Base Line, as Calculated by Means of a Cox Regression Model.
ACE denotes angiotensin-converting enzyme, + the use of the drug, and - nonuse.
[#]Cohn et al, NEJM 2001; 345:1667-75

The results of another subgroup in patients not treated with an ACE inhibitor are provided in the following Figure 4 and Table 4. These results suggest that valsartan may be beneficial in patients who are not treated with an ACE inhibitor but remain to be confirmed by results from trials specifically designed to support this suggestion.

Figure 4 Kaplan-Meier curves for mortality in the valsartan (dotted line) and placebo (solid line) groups without angiotensin-converting enzyme (ACE) inhibitor background therapy (p = 0.017 by log-rank test)[†].



[†]Maggioni AP et al J Am Coll Cardiol 2002; 40:1414-1421

Table 4 Clinical Events in Patients Not Treated with Angiotensin-Converting Enzyme Inhibitors: A) Mortality and Morbidity End Points and B) Total Investigator- Assessed Hospital Admissions[†]

A	Valsartan Group (n = 185)	Placebo Group (n = 181)	RR[+]	95% CI[+]	p Value[†]

Primary end points					
All-cause mortality	32 (17.3%)	49 (27.1%)	0.67	0.42-1.06	0.017‡
Mortality/morbidity	46 (24.9%)	77 (42.5%)	0.56	0.39-0.81	< 0.001‡
Secondary mortality/morbidity end points (first occurrence)					
Cardiovascular deaths	29 (15.7%)	40 (22.1%)	0.76	0.46-1.24	0.074
Nonfatal morbid event	24 (13.0%)	49 (27.1%)	0.46	0.28-0.76	< 0.001‡
Sudden death with resuscitation	1 (0.5%)	2 (1.1%)	0.46	0.04-5.25	0.529
Therapy for HF	0	1 (0.6%)	---	---	---
Hospital admission for HF	24 (13.0%)	48(26.5%)	0.47	0.29-0.78	< 0.001‡
B	**Valsartan**	**Placebo**	**Diff.§**	**% Diff.**	**p Value¶**
Hospitalization cause					
All-cause	199	262	-63	-24.0	0.260
HF	51	117	-66	-56.4	0.010‡
Non-HF	148	145	3	2.1	0.567

+ Risk ratio (RR) and 95% confidence interval (CI) obtained using Cox regression, adjusting for New York Heart Association (NYHA) class, left ventricular ejection fraction baseline beta-blocker usage, etiology, and age group.
†Based on log-rank tests.
‡ Statistically significant at $p < 0.05$.
§ Difference (valsartan - placebo); % Diff = 100 x Diff/placebo.
¶ Based on the Cochran-Mantel-Haenzel test for the number of hospital admissions stratified by beta-blocker usage and NYHA class, using modified ridit scores.
HF = heart failure.
┼ Maggioni AP et al J Am Coll Cardiol 2002; 40:1414-1421

Table 5 Permanent Study Treatment Discontinuations┼

	Valsartan (n = 185)	**Placebo (n= 181)**	**Total (n = 366)**	**p Value+**
Adverse events	18 (9.7%)	23 (12.7%)	41 (11.2%)	0.367
Life-threatening laboratory abnormalities	1 (0.5%)	1 (0.06%)	2 (0.05%)	0.988
Hypotension H	1 (0.5%)	1 (0.06%)	2 (0.05%)	0.988
Other	12 (6.5%)	20 (11.1%)	32 (8.7%)	0.122
Total	32 (17.3%)	45 (24.9%)	77 (21.0%)	0.076

+ By chi-square test. H Persistent standing systolic blood pressure < 80 mm Hg or symptoms of hypotension.
┼ Maggioni AP et al J Am Coll Cardiol 2002; 40:1414-1421

The most common adverse events regardless of causality were for valsartan and placebo, respectively, dizziness (24% and 19%), and hypotension (15% and 6%). The mean increase in serum creatinine was significantly higher in the valsartan-treated patients (0.18 ± 0.02 vs. 0.10 ± 0.02 mg/dL, p=0.009).

Comparative Bioavailability Studies
Not applicable

DETAILED PHARMACOLOGY

Pharmacodynamics
The *in vitro* data support that valsartan is a specific antagonist of the AT1 sub-type receptor, that valsartan does not react at other receptor sites and has an affinity for the receptor that is similar in the rat, marmoset and human; whereas the affinity of valsartan for the AT1 sub-type receptor

in the dog is significantly smaller. This is further reinforced by data from in vivo studies and the literature. From animal and human studies, there is also no evidence that AT1 receptor blockade by valsartan together with the resulting Ang II increase causes any arrhythmogenic effects.

Vascular reactivity in the rat to exogenous Ang II is attenuated by sodium restriction and increased during sodium loading. These effects are opposite to those exhibited by the adrenal glomerulosa where sensitivity to Ang II increases during sodium restriction. This phenomenon is the consequence of changes in circulating Ang II levels linked to the altered sodium balance. As expected, in rats, after treatment with valsartan, there is a high level of circulating Ang II, so a down regulation of the receptor could therefore be expected which would reduce the efficacy of valsartan, but vascular receptor density and therefore vascular reactivity in the liver does not decrease after chronic treatment. So valsartan, should not produce internalisation of the Ang II receptor and hence, tolerance. With the increase in circulating Ang II, there is the possibility of some effects through stimulation of the AT2 receptor. The role of the AT2 receptor is currently unknown. No untoward effects were noted in preclinical or clinical studies that might suggest an AT2 receptor mediated action.

The correlation between plasma levels and pharmacological response is not very clear. A similar effect is also seen in the clinic where there is also not a very clear relationship between plasma levels and blood pressure reduction. The variability of the plasma levels is most likely due to the variability in absorption which is pH dependent and thus there will be a limited window of absorption in the alimentary tract. However the critical factor in the relationship between plasma drug levels and effect is that once the AT1 receptors are blocked, increasing plasma concentrations produce very little further action. Therefore this individual variability is not of major importance.

Pharmacokinetics
Results from the absorption, distribution, metabolism and excretion studies show a fairly similar pattern for the rat, marmoset and human though the volume of distribution is greater in the two former species. In the rat the distribution is rapid and valsartan is found mainly in the blood, plasma, liver, lung and renal cortex. In all 3 species the extent of protein binding is comprised between 94% and 97% and the metabolism is fairly low (> 10%) with excretion mainly via the bile. The vast majority of the dose is cleared within 24 hours and there does not appear to be any accumulation on repeated dosing. It does not cross the blood/brain barrier or transfer into the foetus.

MICROBIOLOGY

Not applicable

TOXICOLOGY

In toxicity studies conducted in several animal species, there was no evidence of systemic or target organ toxicity, apart from fetotoxicity. Offsprings from rats treated at 600 mg/kg during the last trimester and lactation showed a slightly reduced survival rate and a slight delay in developmental milestones. The main preclinical safety findings involving the kidney and related effects are attributed to the pharmacological action of the compound. There was no evidence of mutagenicity, clastogenicity or carcinogenicity.

Acute Toxicity

Species	Route	Duration	Dose mg/kg	Major findings
Rat	Gavage	Acute	100	No adverse findings.
Rat	Gavage	Acute	1000, 2000	2000 mg/kg: Diarrhea, white substance (similar to test substance) in feces. Approximate LD_{50} >2000 mg/kg.
Marmoset	Gavage	Acute	600, 1000	No effect 600 mg/kg. 1000 mg/kg: Vomiting, white substance (similar to test substance) in vomitus. Approximate LD_{50} >1000 mg/kg.

Long-Term Toxicity

Species	Route	Duration	Dose mg/kg	Major findings
Rat	Gavage	14 day	60, 200, 600	Increase in urea at 200 and 600 mg/kg. NOEL = 60 mg/kg.
Marmoset	Gavage	14 day	60, 200, 600	Vomiting and mild to moderate increase in urea at 600 mg/kg. NOEL - 200 mg/kg.
Rat	Intra-venous	14 day	10, 30, 100	No adverse findings. NOAEL = 100 mg/kg.
Marmoset	Intra-venous	14 day	6, 20, 60	No adverse findings. NOAEL = 60 mg/kg.
Rat	Gavage	91 day	60, 200, 600	200 & 600 mg/kg: Increase in urea 600 mg/kg: Renal tubular hyperplasia, glomerular arteriolar hypertrophy. Anemia with regenerative response. NOEL = 60 mg/kg.
Marmoset	Gavage	91 day	30, 60, 200, 600 → 400	Plasma urea & creatinine↑from 200 mg/kg. Nephropathy at 200 & 600 mg/kg. Alk. Phos. ↑ at 400 mg/kg. Anemia from 200 mg/kg. Hypertrophy of glomerular arteriole at 400 mg/kg. Adrenal cortex hypertrophy from 200 mg/kg in F. Cachexia including 3 deaths at 600 mg/kg. One death at 200 mg/kg. One death at 400 mg/kg during the recovery period. NOEL = 60 mg/kg.

Rat	Gavage	12 months	20, 60, 200	Increase in urea at 60 mg/kg, and anemia and renal arteriolar hypertrophy at 200 mg/kg. NOAEL = 20 mg/kg.
Marmoset	Gavage	12 months	12, 40, 120	Increase in urea and creatinine at 40 mg/kg and 120 mg/kg. NOAEL = 12 mg/kg.

NOEL No observable effect level.
NOAEL No observable adverse effect level.

Reproduction and Teratology

Segment I

Species	Route	Duration of dosing	Dose mg/kg	Major findings
Rat	Gavage	M - 90 days F - day 14 to 19 or 14 to +20	10, 50, 200	↓ in field motor actvity at 200 mg/kg in F; no effect on fertility, reproductive performance in F_o & F_1 and on F_1 development. No effect on kidney development.

Segment II

Mouse	Gavage	Day 6 to 15	60, 200, 600	No embryotoxicity, fetotoxicity or teratogenicity at 600 mg/kg.
Rat	Gavage	Day 6 to 15	60, 200, 600	Reduced maternal body weight gain at 200 & 600 mg/kg and fetal weights at 600 mg/kg. No embryotoxicity, fetotoxicity or teratogenicity at 600 mg/kg.
Rabbit (range finding)	Drench	Day 6 to 18	2.5, 15, 30, 45, 50, 150	Litter losses and deaths at 15 mg/kg and above. One litter loss (1/5) at 2.5 mg/kg.
Rabbit	Gavage	Day 6 to 18 Day 7 to 19	2, 5, 10	Increased incidence of low fetal weights at 5 mg/kg. Litter loss and abortion at 5 & 10 mg/kg. No teratogenicity at 10 mg/kg.

Segment III

Rat	Gavage	Day 15 to 20 or + 20	60, 200, 600	Slightly reduced post-natal F_1 survival and development in the presence of reduced maternal body weight gain at 600 mg/kg. No effect on kidney development.

+ - Number of days post-parturition

Mutagenicity

There is no evidence of compound-related mutagenicity and clastogenicity in a battery of mutagenicity studies covering various end points.

In vitro

Test	System	µg/mL or *plate	Comments
Mutagenicity	Bacteria**	*5.0 - 5000.0	Negative
Mutagenicity	Bacteria***	*5000.0	Negative
Gene mutation	Chinese hamster cells (V79)	81.88 - 5550.00	Negative
Chromosome aberration	Chinese hamster cells (ovary)	81.88 - 1310.00	Negative

In-vivo

Test	System	mg/kg	Comments
Micro-nucleus	Rat	781.3 - 3 125.0	Negative

** S typhimurium - TA98, TA100, TA 1537 E coli - WP2uvrA
*** S typhimurium - TA98, TA100, TA1535, TA 1537 E coli - WP2uvrA

Carcinogenicity

Mouse	Diet	2 years	10, 40, 160	Hyperplasia of gastric mucosa in males. ↓ body weight gain at 10 mg/kg. No carcinogenic effect
Rat	Diet	2 years	10, 50, 200	↓ body weight gain, anemia, nephropathy at ≥ 50 mg/kg. ↑ urea and creatinine, ↓total proteins and albumin at 200 mg/kg. No carcinogenic effect.

REFERENCES

1. Benz J, Oshrain C, *et al*. Valsartan, a new Angiotensin II receptor antagonist: A double-blind study comparing the incidence of cough with Lisinopril and Hydrochlorothiazide. J Clin Pharmacol 1997; 37: 101-107.

2. Black HR, Graff A, *et al*. Valsartan, a new angiotensin II antagonist for the treatment of essential hypertension: Efficacy, tolerability and safety compared to an angiotensin-converting enzyme inhibitor, lisinopril. J of Human Hypertension 1997; 11: 483-489.

3. Bremner AD, Mehring GH and Meilenbrock S. Long-term systemic tolerability of valsartan compared with lisinopril in elderly hypertensive patients. Advances in Therapy 1997; 14 (5): 245-253, 1997.

4. Holwerda NJ, Fogari R, *et al*. Valsartan, a new angiotensin II antagonist for the treatment of essential hypertension: Efficacy and safety compared with placebo and enalapril. J of Hypertension. 1996; 14: 1147-1151.

5. Mallion J-M, Boutelant S, *et al*. Valsartan, a new angiotensin II antagonist; blood pressure reduction in essential hypertension compared with an angiotensin converting enzyme inhibitor, enalapril. J Blood Pressure Monitoring. 1997; 2 (3-4): 1-5.

6. Neutel J, Weber M, *et al*. Valsartan, a new angiotensin II antagonist: Antihypertensive effects over 24 hours. Clin Therapeutics. 1997; 19 (3): 447-458.

7. Oparil S, Dyke S, *et al*. The efficacy and safety of valsartan compared with placebo in the treatment of patients with essential hypertension. Clin Therapeutics. 1996; 18 (5): 797-810.

8. Viberti G, Wheeldon NM et al., for the Microalbuminuria Reduction With VALsartan (MARVAL) Study Investigators. Microalbuminuria reduction with valsrtan in patients with type 2 diabetes mellitus: a blood pressure-independent effect. Circulation. 106: 672-678, 2002.

9. Muirhead N, Feagan BF, Mahon J, et al. The effects of valsartan and captopril on reducing microalbuminuria in patients with type 2 diabetes mellitus: a placebo-controlled trial. Curr. Ther. Res. 60: 650-660, 1999.

10. Pfeffer MA, McMurray JJV, Velazquez EJ, et al. The VALsartan In Acute myocardial iNfarcTion trial (VALIANT). N Engl J Med. 349(20): 1893-1906, 2003.

11. Cohn JN, Tognoni G; for the Valsartan Heart Failure Trial Investigators. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. N Engl J Med. 345(23):1667-75, 2001

12. Maggioni AP, Anand I, Gottlieb SO, et al. on behalf of the Val-HeFT Investigators. Effects

of Valsartan on morbidity and mortality in patients with heart failure not receiving angiotensin-converting enzyme inhibitors. JACC 40:1414-21, 2002.

13. Novartis Pharmaceuticals Canada Inc., DIOVAN (valsartan tablets), Control no. 147665, Date of Revision: August 16, 2011.

PART III: CONSUMER INFORMATION

[Pr]Ava-Valsartan
valsartan tablets

This leaflet is part III of a three-part "Product Monograph" published when Ava-Valsartan was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Ava-Valsartan. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
Ava-Valsartan is used to lower blood pressure or to treat people after a heart attack (myocardial infarction) when the use of an angiotensin-converting enzyme (ACE) inhibitor, considered part of standard therapy for this condition, is not appropriate.

Ava-Valsartan is also used in patients with chronic heart failure, when they are unable to tolerate the standard treatment with medications called ACE inhibitors. There is no evidence that Ava-Valsartan provides added benefit when it is used with ACE inhibitors.

High blood pressure increases the workload of the heart and arteries. If this condition continues for a long time, damage to the blood vessels of the brain, heart, and kidneys can occur, and may eventually result in a stroke, heart failure or kidney failure. High blood pressure also increases the risk of heart attacks. Reducing your blood pressure decreases your risk of developing these illnesses.

What it does:
Ava-Valsartan belongs to a class of medicines known as angiotensin II receptor blocker, which help to control high blood pressure or other heart-related problems. Angiotensin II is a natural hormone produced in the body to keep blood pressure at normal levels. One function of angiotensin II is to increase blood pressure, usually when it becomes too low. Ava-Valsartan works by blocking the effect of angiotensin II. As a result, blood pressure is lowered.

When it should not be used:
You should not take Ava-Valsartan if:
- you have ever had an unusual or allergic reaction to valsartan or to any other component of this product,
- you are pregnant or plan to become pregnant.

Ava-Valsartan is not recommended for children and adolescents (below the age of 18 years).

What the medicinal ingredient is:
Valsartan

What the important nonmedicinal ingredients are:
Ava-Valsartan also contains the following non-medicinal ingredients:

40 mg tablets: Colloidal silicon dioxide, crospovidone, magnesium stearate, and microcrystalline cellulose, hydroxypropyl methylcellulose, polyethylene glycol, black iron oxide, red iron oxide, yellow iron oxide, and titanium dioxide.

80 mg tablets: Colloidal silicon dioxide, crospovidone, magnesium stearate, and microcrystalline cellulose, hydroxypropyl methylcellulose, polyethylene glycol, black iron oxide, red iron oxide, and titanium dioxide.

160 mg tablets: Colloidal silicon dioxide, crospovidone, magnesium stearate, and microcrystalline cellulose, hydroxypropyl methylcellulose, polyethylene glycol, black iron oxide, red iron oxide, yellow iron oxide, and titanium dioxide.

320 mg tablets: Colloidal silicon dioxide, crospovidone, magnesium stearate, and microcrystalline cellulose, hydroxypropyl methylcellulose, polyethylene glycol, black iron oxide, red iron oxide, yellow iron oxide, and titanium dioxide.

If you are on a special diet, or if you are allergic to any substance, ask your doctor or pharmacist whether any of these ingredients may cause a problem.

What dosage forms it comes in:
Ava-Valsartan is available in four tablet strengths containing valsartan 40 mg, 80 mg, 160 mg and 320 mg.

Ava-Valsartan 40 mg is a divisible film-coated tablet. The 20 mg dose may be obtained by dividing a 40 mg tablet in half at the break line.
- Ava-Valsartan 40 mg tablet is yellow, ovaloid, scored on one side, slightly convex, with bevelled edges, debossed on one side with DO and with NVR on the other side and contains 40 mg of valsartan.
- Ava-Valsartan 80 mg tablet is pale red, round shaped tablets with bevelled edges, debossed with DV on one side and NVR on the other and contains 80 mg of valsartan.
- Ava-Valsartan 160 mg tablet is grey orange, ovaloid shaped tablets with bevelled edges, debossed with DX on one side and NVR on the other and contains 160 mg of valsartan.
- Ava-Valsartan 320 mg tablet is dark grey-violet, ovaloid with bevelled edges, debossed with DXL on one side and NVR on the other and contains 320 mg of valsartan.

WARNINGS AND PRECAUTIONS

Serious warnings and precautions
Ava-Valsartan should not be used during pregnancy. If you discover that you are pregnant while taking Ava-Valsartan, stop the medication and please contact your physician.

BEFORE you use Ava-Valsartan talk to your doctor or pharmacist if:
- **you have liver disease**

- **you have kidney disease or are undergoing dialysis**
- **you are being treated with diuretics**
- **you are suffering from excess vomiting or diarrhea**
- **you have any allergies to this drug or its ingredients or components of the container**

You are pregnant, breast-feeding or thinking of becoming pregnant?
Taking **Ava-Valsartan** during pregnancy can cause injury and even death to your baby. This medicine should not be used during pregnancy. If you are planning to become pregnant while taking **Ava-Valsartan**, contact immediately your doctor.

It is possible that **Ava-Valsartan** passes into breast milk. You should discuss with you doctor about taking **Ava-Valsartan** while breastfeeding

Similar medicines were associated with serious harm to fetuses when they were taken after the first three months of pregnancy. (It is not known if they are harmful during the first three months). It is therefore important to tell your doctor immediately if you think you may have become pregnant, or planning to become pregnant. Your doctor will discuss with you the potential risk of taking Ava-Valsartan during pregnancy.

Although it is not known whether Ava-Valsartan can pass into human breast milk, this does happen in animals. Therefore do not breast-feed during treatment. Tell your doctor if you are breast-feeding, so that other treatment options can be tried.

Like many other medicines used to treat high blood pressure, Ava-Valsartan may rarely cause dizziness and affect your concentration. So before you drive a vehicle, use machinery, or do other things that need concentration, make sure you know how you react to the effects of Ava-Valsartan.

INTERACTIONS WITH THIS MEDICATION

As with other medicines, interactions with other drugs are possible. Therefore, do not take any other medicines unless you have discussed the matter with your physician or your pharmacist.

Drugs that may interact with Ava-Valsartan include:

- medicines used to lower blood pressure, including diuretics (water pills),
- potassium-sparing medicines, potassium supplements, or salt substitutes containing potassium,
- lithium therapy,
- certain type of pain killers called non-steroidal anti-inflammatory medicines (NSAIDs) or Selective Cyclooxygenase-2 Inhibitors (Cox-2 Inhibitors). Your doctor may also check your kidney function.

Before taking Ava-Valsartan make sure your doctor knows about all the medications you are taking, including those not prescribed by your doctor. It may be necessary to change the dose, take other precautions, or perhaps stop one of the medicines. This applies to both prescription and non-prescription medicines.

PROPER USE OF THIS MEDICATION

If your doctor has prescribed Ava-Valsartan for you following a heart attack, it is important to continue to take it even if you feel well, so that Ava-Valsartan can help to reduce the chance of another heart attack occurring.

Patients who have high blood pressure often do not notice any signs or symptoms of this condition. So even though you are feeling well, your health may be getting worse. This makes it all the more important for you to continue your treatment program and to keep your appointments with your doctor.

Remember that this medicine does not cure your high blood pressure; it only may help to control it. Therefore, if you want to lower your blood pressure and keep it down, you must continue to take Ava-Valsartan as directed.

Usual dose:
It is very important that you take this medicine exactly as your doctor tells you in order to get the best results and reduce the chance of side effects.

High blood pressure (hypertension)
The usual dosage for the treatment of high blood pressure is one 80 mg tablet once a day. In some cases, your doctor may increase the dose to 160 mg and then eventually to 320 mg or prescribe it together with another medicine (e.g., a diuretic).

Following a heart attack (myocardial infarction)
Treatment is generally started as soon as 12 hours following the heart attack, usually at a low dose of 20 mg twice daily in order to minimise side effects including hypotension (low blood pressure). Your doctor may increase this dose gradually over several weeks to a maximum of 160 mg twice daily.

Failing heart (heart failure)
Treatment is generally started at a dose of 40 mg twice daily in order to minimize side effects including low blood pressure. Your doctor may increase this dose gradually over several weeks to a maximum of 160 mg twice daily.

Swallow Ava-Valsartan tablets with a glass of water. You can take Ava-Valsartan with or without food, but it should be taken the same way each day and at the same time.

Overdose:
If you have accidentally taken too many tablets of Ava-Valsartan, seek medical assistance immediately.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Missed Dose:
Try to take your dose at the same time each day, preferably in the morning. However, if you have forgotten to take your dose during

the day, carry on with the next one at the usual time. Do not take a double dose to make up for the forgotten tablet.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, Ava-Valsartan may cause unwanted reactions, so-called side effects. Most patients do not experience side effects from Ava-Valsartan. **Examples of occasional side effects include:**

- **Dizziness**
- **Light headedness**
- **Muscle pain or muscle weakness**
- **Unusual tiredness and/or weakness**
- **Headache**
- **Diarrhea**

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common	*Allergic reactions* Skin rash, skin eruption or other effect on the skin or eyes			✓
Uncommon	*Low blood pressure (hypotension)* Fainting when the blood pressure is too low			✓
	Allergic reactions Swelling of the lips, face or neck, accompanied by difficulty in breathing or speaking			✓
	Kidney and Liver disorder Symptoms such as nausea, vomiting dark/brown urine			✓
	Muscle tenderness or weakness, generalized weakness (sign of rhabdomyoly-sis)		✓	
	Abdominal pain		✓	

This is not a complete list of side effects. For any unexpected effects while taking Ava-Valsartan, contact your doctor or pharmacist.

HOW TO STORE IT

Do not take Ava-Valsartan past the expiry date shown on the pack.

Store your Ava-Valsartan tablets in a dry place at room temperature (15 to 30°C).

Always remember
This medicine has been prescribed to you for your current medical problem only. Do not give it to other people.

Keep this medicine out of the reach of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701E
    Ottawa, Ontario
    K1A 0K9

  Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

Please consult your doctor or pharmacist with any questions or concerns you may have regarding your individual condition.

This document plus the full Product Monograph, prepared for health professionals can be obtained by contacting the sponsor, Avanstra Inc., at 1-855-708-3678.

or by e-mail, at :
medinfo@avanstra.com

This leaflet was prepared by **Avanstra Inc.**

Last revised: June 12, 2012