PRODUCT MONOGRAPH

PrTEVA-VALSARTAN

Valsartan

40 mg, 80 mg, 160 mg and 320 mg Tablets

Angiotensin II AT_1 Receptor Blocker

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
Oral	Tablet / 40 mg, 80 mg, 160 mg and 320 mg	Colloidal silicon dioxide, croscarmellose sodium, iron oxide yellow, iron oxide red, iron oxide black, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, povidone, talc and titanium dioxide.

INDICATIONS AND CLINICAL USE

Teva-Valsartan is indicated for:

• **Hypertension**
- For the treatment of mild to moderate essential hypertension.
- Teva-Valsartan may be administered alone, or concomitantly with thiazide diuretics.
- The safety and efficacy of concurrent treatment with Teva-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**
- Teva-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 Teva-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 Teva-Valsartan in children and adolescents (below the age of 18 years) have not been established.

CONTRAINDICATIONS

- Teva-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).
- Teva-Valsartan is contraindicated in pregnant and nursing women (see WARNINGS AND PRECAUTIONS, Special Populations, Nursing Women).
- Concomitant use of angiotensin receptor antagonists (ARBs) - including Teva-Valsartan - or of angiotensin-converting enzyme inhibitors (ACEIs) with aliskiren-containing drugs in patients with diabetes mellitus (type 1 or type 2) or moderate to severe renal impairment (GFR <60 mL/min/1.73 m^2) is contraindicated (see WARNINGS AND PRECAUTION, Cardiovascular, Dual Blockade of the Renin-Angiotensin System (RAS) and Renal and DRUG INTERACTIONS, Drug-Drug Interactions, Dual Blockade of the Renin-Angiotensin System (RAS) with ARBs, ACEIs, or aliskiren-containing drugs).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions
When used in pregnancy, **angiotensin receptor (AT1) blockers (ARB)** can cause injury to or even death of the developing fetus. When pregnancy is detected, Teva-Valsartan should be discontinued as soon as possible **(**see **WARNINGS AND PRECAUTIONS, Special Populations).**

Angioedema
Angioedema, including swelling of the larynx and glottis, causing airway obstruction and/or swelling of the face, lips, pharynx, and/or tongue has been reported in patients treated with valsartan: some of these patients previously experienced angioedema with other drugs including ACE inhibitors. Teva-Valsartan should be immediately discontinued in patients who develop angioedema, and Teva-Valsartan should not be re-administered.

If laryngeal stridor or angioedema of the face, extremities, lips, tongue, or glottis occurs, Teva-Valsartan should be discontinued immediately, the patient treated appropriately in accordance with accepted medical care, and carefully observed until the swelling disappears. In instances where swelling is confined to the face and lips, the condition generally resolves without treatment, although antihistamines may be useful in relieving symptoms. Where there is involvement of tongue, glottis, or larynx, likely to cause airway obstruction, appropriate therapy (including, but not limited to 0.3 to 0.5 mL of subcutaneous epinephrine solution 1:1000) should be administered promptly (see ADVERSE REACTIONS – Post-Marketing Adverse Drug Reactions).

Patients with a known hypersensitivity (anaphylaxis) or angioedema to ARBs should not be treated with Teva-Valsartan (see ADVERSE REACTIONS – Post-Market Adverse Drug Reactions).

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 Teva-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.

Dual Blockade of the Renin-Angiotensin System (RAS)

There is evidence that co-administration of angiotensin receptor antagonists (ARBs), including Teva-Valsartan, or of angiotensin-converting enzyme inhibitors (ACEIs) with aliskiren increases the risk of hypotension, syncope, stroke, hyperkalemia and deterioration of renal function, including renal failure, in patients with diabetes mellitus (type 1 or type 2) and/or moderate to severe renal impairment (GFR<60 mL/min/1.73 m^2). Therefore, the use of Teva-Valsartan in combination with aliskiren-containing drugs is contraindicated in these patients. Co-administration of ARBs, including Teva-Valsartan, with other agents blocking the RAS such as ACEIs or aliskiren-containing drugs is not recommended in any patient, as adverse outcomes cannot be excluded.

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 Teva-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, Drug-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 Teva-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.

The use of ARBs – including Teva-Valsartan – or of ACEIs with aliskiren-containing drugs is contraindicated in patients with moderate to severe renal impairment (GFR <60 mL/min/1.73 m^2) (see CONTRAINDICATIONS and DRUG INTERACTIONS, Drug-Drug Interactions, Dual Blockade of the Renin-Angiotensin-System (RAS) with ARBs, ACEIs, or aliskiren-containing drugs).

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, Teva-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 antihypertensive 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 Teva-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
Hyperkalemia	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 in post-marketing use include: anaphylaxis (very rarely), angioedema (involving swelling of the face, lips and/or tongue), dermatitis bullous (unknown frequency), renal impairment (very rare), photosensitivity, increase in blood pressure and taste disorders.

The following serious adverse events, irrespective of causality and with unknown frequency, have been reported from clinical studies or post-marketing experiences: Toxic epidermal necrolysis (TEN), Stevens-Johnsons syndrome (SJS), erythema multiforme (EM), toxic skin eruption, skin necrosis, exfoliative rash, pemphigus and pemphigoid.

Cases of muscle pain, muscle weakness, myositis and rhabdomyolysis have been reported in patients receiving angiotensin II receptor blockers.

The following other adverse drug reactions with unknown frequency have been reported from clinical studies or post-marketing experiences: Hypersensitivity including serum sickness, vasculitis, insomnia and libido decrease.

Hepato-biliary disorder: Hepatic enzyme increased including blood bilirubin increased.

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
Concomitant use of potassium-sparing diuretics (e.g., spironolactone, triamterene, amiloride), or other drugs that can increase potassium levels (e.g., heparin, non-steroidal antiinflammatory drugs [NSAID], trimethoprim-sulfamethoxazole), potassium supplements, or salt substitutes containing potassium, may lead to increases in serum potassium.

Since Teva-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
Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors or angiotensin II receptor antagonists, including valsartan. Therefore, careful monitoring of serum lithium levels is recommended during concomitant use. If a diuretic is also used, the risk of lithium toxicity may presumably be increased further with valsartan.

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.

OATP1B1 and/or MPR2 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. Co-administration of inhibitors of the uptake transporter (rifampin, cyclosporine) or efflux transporter (ritonavir) may increase the systemic exposure to valsartan.

Dual blockade of the Renin-Angiotensin System (RAS) with ARBs, ACEIs, or aliskiren-containing drugs
See WARNINGS AND PRECAUTIONS, Cardiovascular, Dual Blockade of the Renin-Angiotensin System (RAS).

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, Teva-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 antihypertensive therapy. Whenever possible, all diuretics should be discontinued two to three days prior to the administration of Teva-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, Teva-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 Teva-Valsartan may need to be adjusted.

The recommended initial dose of Teva-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.

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

Following Myocardial Infarction

Teva-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 up-titrated 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. Teva-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 Teva-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 Teva-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 Teva-Valsartan (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 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 antihypertensive 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 (2.75 h *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: Following oral administration of valsartan alone, peak plasma concentrations of valsartan are reached in 2 – 4 hours. The mean absolute bioavailability of valsartan is about 23%, but with high variability. 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. These food effect data were obtained with the capsule formulation of valsartan. The effect of food on the tablet formulation of valsartan remains unknown thus far**.**

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

Metabolism: Valsartan is not biotransformed to a high extent as only about 20% of dose is recovered as metabolites. A hydroxyl metabolite has been identified in plasma at low concentrations (less than 10% of the valsartan AUC). This metabolite is pharmacologically

inactive. 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 intravenous administration, valsartan shows bi-exponential decay kinetics ($t_{1/2}\alpha$ <1 hour and $t_{1/2}\beta$ between 5-9 hours). Following administration of an oral solution of ^{14}C labelled valsartan, 83% of absorbed valsartan is primarily excreted in the feces and 13% in the urine, mainly as unchanged compound. Following intravenous administration, plasma clearance of valsartan is about 2 L/h. The half-life of valsartan is 6 hours.

Special Populations and Conditions

Pediatrics: The safety and effectiveness of Teva-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

Store Teva-Valsartan tablets in a dry place between 15ºC and 30ºC, protect from heat, light and humidity.

SPECIAL HANDLING INSTRUCTIONS

Not applicable

DOSAGE FORMS, COMPOSITION AND PACKAGING

Teva-Valsartan (valsartan) 40 mg tablets are supplied in bottles of 100 and blisters of 30 (3 x 10 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).

Teva-Valsartan (valsartan) 80 mg tablets are supplied in bottles of 100, 500 and blisters of 30 (3 x 10 tablets).

Teva-Valsartan (valsasrtan) 160 mg tablets are supplied in bottles of 100, 500 and blisters of 30 (3 x 10 tablets).

Teva-Valsartan (valsartan) 320 mg tablets are supplied in bottles of 100 and blisters of 30 (3 x 10 tablets).

Composition

Teva-Valsartan (valsartan) 40 mg Tablets
Teva-Valsartan tablets, 40 mg are yellow, ovaloid-shaped, slightly convex coated tablets with beveled edges, engraved with "rph" on one side and "V34" on the other side with a deep score. Each tablet contains 40 mg of valsartan and the following non-medicinal ingredients: colloidal silicon dioxide, croscarmellose sodium, iron oxide yellow, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, povidone, talc and titanium dioxide.

Teva-Valsartan (valsartan) 80 mg Tablets
Teva-Valsartan tablets, 80 mg are pale red, round shaped, coated tablets with beveled edges, engraved with "rph" on one side and "V33" on the other side. Each tablet contains 80 mg of valsartan and the following non-medicinal ingredients: colloidal silicon dioxide, croscarmellose sodium, iron oxide red, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, povidone, talc and titanium dioxide.

Teva-Valsartan (valsartan) 160 mg Tablets
Teva-Valsartan tablets, 160 mg are grey orange, ovaloid-shaped, coated tablets with beveled edges, engraved with "rph" on one side and "V32" on the other side. Each tablet contains 160 mg of valsartan and the following non-medicinal ingredients: colloidal silicon dioxide, croscarmellose sodium, iron oxide yellow, iron oxide red, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, povidone, talc and titanium dioxide.

Teva-Valsartan (valsartan) 320 mg Tablets
Teva-Valsartan tablets, 320 mg are dark grey-violet, ovaloid-shaped, slightly convex coated tablets with beveled edges, engraved with "rph" on one side and "V31" on the other side. Each tablet contains 320 mg of valsartan and the following non-medicinal ingredients: colloidal silicon dioxide, croscarmellose sodium, iron oxide black, iron oxide red, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, povidone, talc and titanium dioxide.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

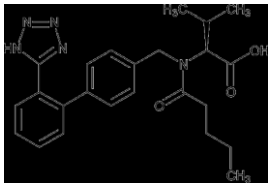
Drug Substance

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 g/mol

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°C with decomposition.

pKa values:

pKa Values	Solvent	Temp. (°C)	Assignment
4.73	Water	22	Tetrazole group
3.90	Water	22	Carboxylic group

CLINICAL TRIALS

Comparative Bioavailability Studies

A randomized, two period, two treatment crossover comparative bioavailability study of Teva-Valsartan 160 mg tablets (ratiopharm inc., Canada) and DIOVAN® 160 mg tablets (Novartis Pharmaceuticals, Canada Inc.) administered as a single 1 x 160 mg dose, was conducted in 42 healthy adult male and female subjects under fasting conditions. A summary of the bioavailability data is presented below.

Valsartan (1 x 160 mg) Geometric Mean[2] Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means[1]	90% Confidence Interval[1]
AUC_{0-t} (ng·h/mL)	16195.95 17730.97 (39.65)	14852.06 16522.19 (46.79)	109.05%	95.86% to 124.06%
AUC_{0-inf} (ng·h/mL)	17573.99 18678.25 (36.42)	15286.63 16760.47 (43.69)	114.96%	102.87% to 128.48%
C_{max} (ng/mL)	2731.07 3150.78 (46.23)	2442.74 2900.92 (55.02)	111.80%	91.66% to 136.37%
T_{max}§ (h)	3.52 (98.38)	3.04 (39.73)		
$T_{½\ el}$§ (h)	8.08 (24.33)	8.35 (31.21)		

* Teva-Valsartan 160 mg tablets (Ratiopharm Inc., Canada)
† Diovan® 160 mg tablets (Novartis Pharmaceuticals, Canada Inc.) Purchased in Canada
§ Expressed as the arithmetic mean (CV%) only
[1] Based on least-squares mean estimates
[2] Geometric least-squares mean are presented for unbalanced study

The study demonstrates that Teva-Valsartan Tablets are bioequivalent to DIOVAN® Tablets.

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 2,800 patients randomized to various doses of valsartan and about 1,100 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.

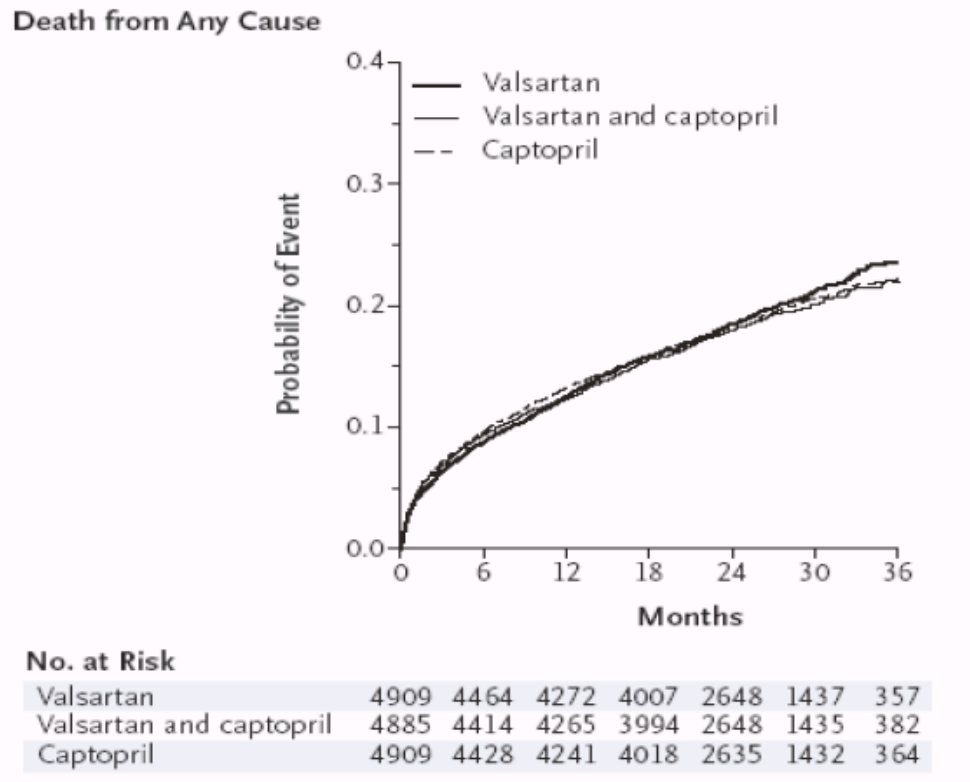
Patients with an inadequate response to valsartan 80 mg once daily were titrated to either valsartan 160 mg once daily or valsartan 80 mg twice daily, which resulted in a comparable response in both groups. In controlled trials, the antihypertensive effect of once-daily valsartan 80 mg was similar to 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.

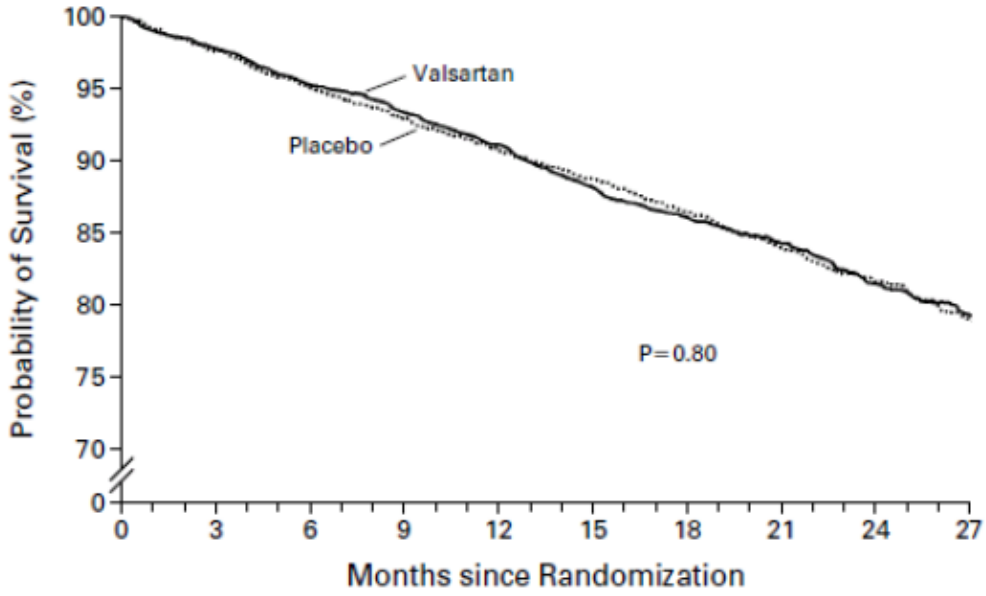
Heart Failure

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[#]

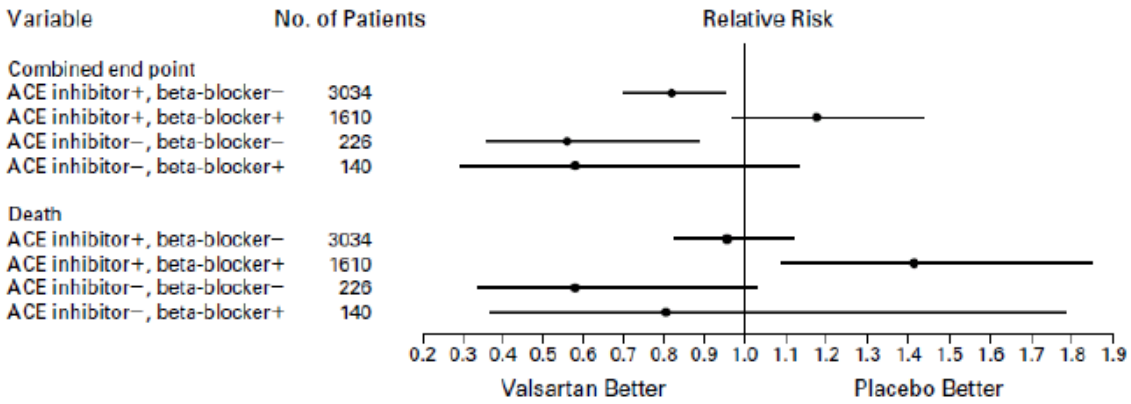
Event	Valsartan Group (N = 2511)	Placebo Group (N = 2499)	Relative Risk (CI)[+]	P Value[†]
	no. with event (%)			
Death from any cause (during entire trial)	495 (19.7)	484 (19.4)	1.02 (0.88-1.18)	0.80
Combined end point	723 (28.8)	801 (32.1)	0.87 (0.77-0.97)	0.009
Death from any cause (at first event)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

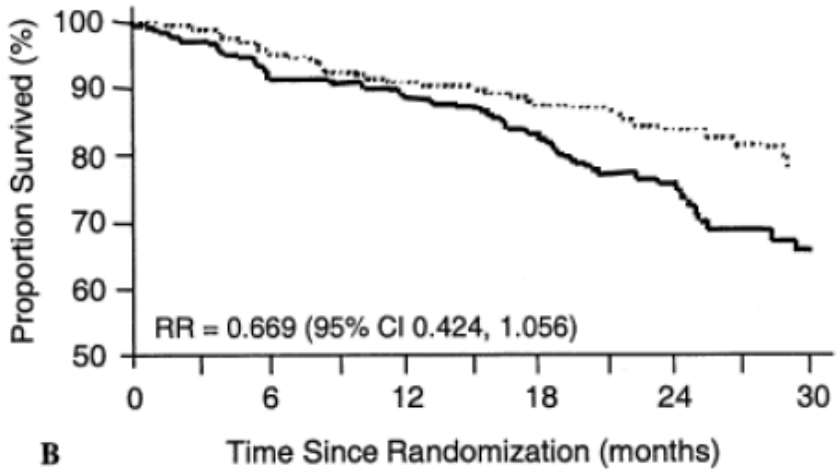
Figure 3 Relative Risks and 95% Confidence Intervals for the Combined End Point (Death from Any Cause, Cardiac Arrest with Resuscitation, Hospitalization for Worsening Heart Failure, or Therapy with Intravenous Inotropes or Vasodilators)[#]



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 ‡	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. ‡ 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).

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 preclinical safety studies, high doses of valsartan (200 to 600 mg/kg body weight) caused in rats a reduction of red blood cell parameters (erythrocytes, hemoglobin, hematocrit) and evidence of changes in renal hemodynamics (slightly raised plasma urea, and renal tubular hyperplasia and basophilia in males).

These doses in rats (200 and 600 mg/kg/day) are approximately 6 and 18 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). In marmosets at similar doses, the changes were similar though more severe, particularly in the kidney where the changes developed to a nephropathy which included raised urea and creatinine. Hypertrophy of the renal juxtaglomerular cells was also seen in both species. All changes were considered to be caused by the pharmacological action of valsartan which produces prolonged hypotension, particularly in marmosets. In embryofetal development studies (Segment II) in mice rats and rabbits, fetotoxicity was observed in association with maternal toxicity in rats and valsartan doses of ≥ 200 mg/kg/days and in rabbits at doses of ≥ 10 mg/kg/day. In a peri- and postnatal development toxicity (segment III) study, the offspring 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 (see WARNINGS AND PRECAUTIONS, Special Populations, Pregnant Women). 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, abnormal reproductive performance in rats or carcinogenicity in mice and rats.

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_0 & 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.

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13. Product Monograph DIOVAN®, Control number 181889, Novartis Pharmaceuticals Canada Inc., dated May 12, 2015.

PART III: CONSUMER INFORMATION

[Pr]Teva-Valsartan
Valsartan

Read this carefully before you start taking Teva-Valsartan and each time you get a refill. This leaflet is a summary and will not tell you everything about Teva-Valsartan. Talk to your doctor, nurse, or pharmacist about your medical condition and treatment and ask if there is any new information about Teva-Valsartan.

ABOUT THIS MEDICATION

What the medication is used for:

High blood pressure (hypertension):
Teva-Valsartan lowers high blood pressure.

Following a heart attack (myocardial infarction):
Teva-Valsartan is used to treat people after a heart attack when an angiotensin-converting enzyme (ACE) inhibitor, considered part of standard therapy for this condition, is not appropriate.

Chronic heart failure:
Teva-Valsartan is 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 Teva-Valsartan provides added benefit when it is used with ACE inhibitors.

What it does:
Teva-Valsartan is an angiotensin receptor blocker (ARB). You can recognize an ARB because its medicinal ingredient ends in **"-SARTAN".**

This medicine does not cure your disease. It helps to control it. Therefore, it is important to continue taking Teva-Valsartan regularly even if you feel fine.

When it should not be used:
Do not take Teva-Valsartan if you:

- Are allergic to valsartan or to any non-medicinal ingredient in the formulation.
- Have experienced an allergic reaction (angioedema) with swelling of the hands, feet, or ankles, face, lips, tongue, throat, or sudden difficulty breathing or swallowing, to any ARB. Be sure to tell your doctor, nurse, or pharmacist that this has happened to you.
- Are taking a medicine that contains aliskiren (such as Rasilez) and you have diabetes or kidney disease.
- Are pregnant or intend to become pregnant. Taking Teva-Valsartan during pregnancy can cause injury and even death to your baby.
- Are breastfeeding. It is possible that Teva-Valsartan passes into breast milk.

What the medicinal ingredient is:
Valsartan

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

40 mg tablets: colloidal silicon dioxide, croscarmellose sodium, iron oxide yellow, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, povidone, purified water, talc, and titanium dioxide.

80 mg tablets : colloidal silicon dioxide, croscarmellose sodium, iron oxide red, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, povidone, purified water, talc, and titanium dioxide.

160 mg tablets: colloidal silicon dioxide, croscarmellose sodium, iron oxide yellow, iron oxide red, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, povidone, purified water, talc, and titanium dioxide.

320 mg tablets: colloidal silicon dioxide, croscarmellose sodium, iron oxide black, iron oxide red, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, povidone, purified water, talc, and titanium dioxide.

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

Teva-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.

- Teva-Valsartan tablets, 40 mg are yellow, ovaloid-shaped, slightly convex coated tablets with beveled edges, engraved with "rph" on one side and "V34" on the other side with a deep score and contain 40 mg of valsartan.
- Teva-Valsartan tablets, 80 mg are pale red, round shaped, coated tablets with beveled edges, engraved with "rph" on one side and "V33" on the other side and contains 80 mg of valsartan.

- Teva-Valsartan tablets, 160 mg are grey orange, ovaloid-shaped, coated tablets with beveled edges, engraved with "rph" on one side and "V32" on the other side and contain 160 mg of valsartan.
- Teva-Valsartan tablets, 320 mg are dark grey-violet, ovaloid-shaped, slightly convex coated tablets with beveled edges, engraved with "rph" on one side and "V31" on the other side and contain 320 mg of valsartan.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions – Pregnancy
Teva-Valsartan should not be used during pregnancy. If you discover that you are pregnant while taking Teva-Valsartan, stop the medication and contact your doctor, nurse or pharmacist as soon as possible.

BEFORE you use Teva-Valsartan talk to your doctor, nurse or pharmacist if you:

- Have experienced an allergic reaction to any drug, including drugs used to lower blood pressure, such as angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB).
- Have narrowing of an artery or a heart valve.
- Have had a heart attack or stroke.
- Have heart failure.
- Have diabetes, liver or kidney disease.
- Are on dialysis.
- Are dehydrated or suffer from excessive vomiting, diarrhea, or sweating.
- Are taking a salt substitute that contains potassium, potassium supplements, or a potassium-sparing diuretic (a specific kind of "water pill" that makes your body keep potassium).
- Are on a low-salt diet.
- Are taking a medicine that contains aliskiren, such as Rasilez, used to lower high blood pressure. The combination with Teva-Valsartan is not recommended.
- Are taking an angiotensin converting enzyme (ACE) inhibitor.
- Are less than 18 years old.

Driving and using machines: Before you perform tasks which may require special attention, wait until you know how you respond to Teva-Valsartan. Dizziness, lightheadedness, or fainting can especially occur after the first dose and when the dose is increased.

INTERACTIONS WITH THIS MEDICATION

As with most medicines, interactions with other drugs are possible. Tell your doctor, nurse, or pharmacist about all the medicines you take, including drugs prescribed by other doctors, vitamins, minerals, natural supplements, or alternative medicines.

The following may interact with Teva-Valsartan:

- Agents increasing serum potassium, such as a salt substitute that contains potassium, potassium supplements, a potassium-sparing diuretic (a specific kind of "water pill") or other drugs that may increase potassium levels.
- Lithium, a medicine used to treat some types of psychiatric illness such as bipolar disease.
- Nonsteroidal anti-inflammatory drugs (NSAIDs), used to reduce pain and swelling. Examples include ibuprofen, naproxen, and celecoxib.
- Other blood pressure lowering drugs, including diuretics ("water pills"), ACE inhibitors or aliskiren.
- Rifampin an antibiotic
- Cyclosporine a drug used to protect against transplant rejection.
- Ritonavir an antiretroviral drug used to treat HIV/AIDS infection.

PROPER USE OF THIS MEDICATION

Take Teva-Valsartan exactly as prescribed. Swallow Teva-Valsartan tablets with a glass of water. It is recommended to take your dose at about the same time everyday preferably in the morning. You can take Teva-Valsartan with or without food, but it should be taken the same way each day. Do not exceed the recommended dose.

Usual Adult Dose:
High blood pressure (hypertension):
Recommended initial dose: 80 mg once a day. Dose should be increased gradually.
Maximum dose: 320 mg a day

Following a heart attack (myocardial infarction):
Recommended starting dose: 20 mg twice a day.
Dose can be increased gradually.
Target maintenance dose: 160 mg twice a day

Chronic heart failure:
Recommended starting dose: 40 mg twice a day.
Dose should be increased gradually.
Maximum dose: 160 mg twice a day

Overdose:

If you think you have taken too much Teva-Valsartan, contact your doctor, nurse, pharmacist, hospital emergency department or regional Poison control Centre immediately, even if there are no symptoms.

Missed Dose:
If you have forgotten to take your dose during the day, carry on with the next one at the usual time. Do not double dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Side effects may include:

- Dizziness, light headedness,
- drowsiness,
- rash,
- diarrhea, vomiting, nausea,
- headache,
- back or leg pain, muscle cramps,
- Muscle pain , muscle weakness,
- Unusual tiredness, weakness,
- Cough,
- Impotence,
- Nose bleed,
- Blistering skin (sign of dermatitis bullous)

If any of these affects you severely, tell your doctor, nurse or pharmacist.

Teva-Valsartan can cause abnormal blood test results. Your doctor will decide when to perform blood tests and will interpret the results.

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 seek immediate medical help
		Only if severe	In all cases	
Common	**Allergic reactions:** Skin rash, skin eruption or other effect on the skin or eyes			✓
	Increased levels of potassium in the blood: Irregular heartbeats, muscle weakness and generally feeling unwell		✓	
Uncommon	**Low blood pressure (hypotension):** Dizziness, fainting, light-headedness may occur when you go from lying or sitting to standing up	✓		
	Angioedema / Allergic reactions: Rash, hives, swelling of the lips, face or neck, tongue or throat accompanied by difficulty in breathing, swallowing or speaking			✓
	Kidney disorder: Change in frequency of urination, nausea, vomiting, swelling of extremities, fatigue		✓	
	Liver disorder: Yellowing of the skin or eyes, dark urine, abdominal pain, nausea, vomiting, loss of		✓	

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 seek immediate medical help
		Only if severe	In all cases	
	appetite			
	Rhabdomyol-ysis: Muscle pain that you cannot explain, muscle tenderness or weakness, dark brown urine		✓	
	Abdominal pain		✓	
	Cardiac failure: Breathlessness, difficulty breathing when lying down, swelling of the feet or legs		✓	
	Vasculitis: Inflammation of blood vessels purplished-red spots, fever, itching	✓		
	Decreased platelets: Bruising, unusual bleeding, fatigue and weakness		✓	
	Anemia: Fatigue, loss of energy, weakness, shortness of breath		✓	
	Decreased white blood cells: Infections, fatigue, fever, aches, pains, and flu-like symptoms, sore throat or mouth ulcers		✓	
	Insomnia	✓		
	Flu like symptoms, joint pain, pharyngitis, inflammation of sinuses, runny or stuffy nose, swollen hands, ankles or feet, upper respiratory tract infection, viral infection	✓		
	Palpitations: Irregular heartbeats		✓	
Unknown	Change in libido	✓		
	Blistering skin reactions with symptoms such as rash, red skin, blistering of the lips, eyes or mouth, skin peeling and fever			✓

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

HOW TO STORE IT

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

Store your Teva-Valsartan tablets in a dry place at room temperature (15°C to 30°C), protect from heat, light and humidity.

Keep this medicine out of the reach and sight of children.

Reporting Side Effects
You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:

- Online at MedEffect (http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php);
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:

- Fax to 1-866-678-6789 (toll-free), or
- Mail to: Canada Vigilance Program
  Health Canada
  Postal Locator 0701E
  Ottawa, ON
  K1A 0K9

Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect (http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php).

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph prepared for health professionals can be found by contacting Teva Canada Limited at:

1-800-268-4127 ext. 1255005 (English);
1-877-777-9117 (French); or
druginfo@tevacanada.com

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