PRODUCT MONOGRAPH

[Pr]AVA-VALSARTAN HCT

(valsartan and hydrochlorothiazide tablets)

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

Angiotensin II AT_1 Receptor Blocker and Diuretic

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Date of Revision: June 12, 2012

Submission Control No: 155873

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Non-medicinal Ingredients
Oral	Tablets: 80mg/12.5mg 160mg/12.5mg 160mg/25mg 320mg/12.5mg 320mg/25mg	Ava-Valsartan HCT 80/12.5 mg tablets: Colloidal silicon dioxide, crospovidone, magnesium stearate, microcrystalline cellulose, hydroxypropyl methylcellulose, polyethylene glycol, red iron oxide, talc, titanium dioxide and yellow iron oxide. The other strengths also contain: Ava-Valsartan HCT 160/25 mg: Black iron oxide Ava-Valsartan HCT 320/12.5 mg: Black iron oxide

INDICATIONS AND CLINICAL USE

Ava-Valsartan HCT (valsartan and hydrochlorothiazide) is indicated for the treatment of mild to moderate essential hypertension in patients for whom combination therapy is appropriate.

Ava-Valsartan HCT is not indicated for initial therapy (see DOSAGE AND ADMINISTRATION).

Patients should be titrated on individual drugs. If the fixed combination represents the dose and dosing frequency determined by this titration, the use of Ava-Valsartan HCT may be more convenient in the management of patients. If during maintenance therapy dosage adjustment is necessary it is advisable to use the individual drugs.

Geriatrics (> 65 years of age):
No overall age-related differences were seen in the adverse effect profile but greater sensitivity in some older individuals cannot be ruled out and appropriate caution is recommended.

Pediatrics (< 18 years of age):
The safety and efficacy of Ava-Valsartan HCT in children and adolescents (below the age of 18 years) have not been established and use in this age group is not recommended.

CONTRAINDICATIONS

- Valsartan and hydrochlorothiazide 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).
- Because of the hydrochlorothiazide component, it is also contraindicated in patients with anuria, severe progressive renal disease and if increasing azotemia and oliguria occur during treatment.
- Patients who are hypersensitive to other sulfonamide-derived drugs.
- Valsartan and hydrochlorothiazide is also contraindicated in pregnant women.
- Thiazide diuretics are contraindicated in patients with hyponatremia, hypercalcemia, symptomatic hyperuricemia, and conditions involving enhanced potassium loss.

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 and hydrochlorothiazide should be discontinued as soon as possible (see CONTRAINDICATIONS and 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.

Valvular Stenosis

There is concern on theoretical grounds that patients with aortic stenosis might be at a particular risk of decreased coronary perfusion when treated with vasodilators, because they do not develop as much after load reduction.

Endocrine and Metabolism

Serum electrolyte changes

Concomitant use with potassium supplements, potassium-sparing diuretics, salt substitutes containing potassium, or other drugs that may increase potassium levels (heparin, etc.) should be used with caution. Thiazide diuretics can precipitate new onset hypokalemia or exacerbate pre-existing hypokalemia. Thiazide diuretics are contraindicated in patients with conditions involving enhanced potassium loss (refractory hypokalemia), for example salt-losing

nephropathies and prerenal (cardiogenic) impairment of kidney function. All patients receiving thiazide diuretics should be monitored for imbalances in electrolytes, particularly potassium.

Thiazide diuretics can precipitate new onset hyponatremia and hypochloremic alkalosis or exacerbate pre-existing hyponatremia. Hyponatremia, accompanied by neurological symptoms (nausea, progressive disorientation, apathy) has been observed in isolated cases. Regular monitoring of serum sodium concentrations is recommended. Patients receiving thiazides should be carefully observed for clinical signs of fluid and electrolyte imbalance (hyponatremia, hypochloremic alkalosis and hypokalemia). Periodic determinations of serum electrolytes to detect possible electrolyte disturbance should be performed at appropriate intervals. Warning signs or symptoms of fluid and electrolyte imbalance include dryness of the mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Other metabolic disturbances
Like other diuretics, hydrochlorothiazide may raise the serum uric acid level due to reduced clearance of uric acid and may cause or exacerbate hyperuricemia and precipitate gout in susceptible patients. Thiazides are contraindicated in patients with symptomatic hyperuricemia.

Thiazides decrease urinary calcium excretion and may cause mild elevation of serum calcium in the absence of known disorders of calcium metabolism. Since hydrochlorothiazide can increase serum calcium concentrations, it should not be used (see Contraindications) in patients with hypercalcemia.

Pathological changes in the parathyroid gland of patients with hypercalcemia and hypophosphatemia have been observed in a few patients on prolonged thiazide therapy. If hypercalcemia occurs, further diagnostic clarification is necessary and thiazides should be discontinued.

Hypokalemia may develop, especially with brisk diuresis, when severe cirrhosis is present, or after prolonged therapy.

Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia can sensitize or exaggerate the response of the heart to the toxic effects of digitalis (e.g. increased ventricular irritability).

Any chloride deficit during thiazide therapy is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction rather than administration of salt, except in rare instances, when the hyponatremia is life threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Thiazides may decrease serum PBI levels without signs of thyroid disturbance.

Increases in cholesterol, triglyceride and glucose levels may be associated with thiazide diuretic therapy, including hydrochlorothiazide.

Hepatic/Biliary/Pancreatic

Hydrochlorothiazide should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance or of serum ammonia may precipitate hepatic coma.

In general, no dosage adjustment is needed in patients with mild to moderate liver disease. Due to the hydrochlorothiazide component, valsartan and hydrochlorothiazide should not be used (not recommended) in patients with severe hepatic impairment (see DOSAGE AND ADMINISTRATION, Hepatic impairment). However, care should be exercised in patients with liver disease, especially in those patients with biliary obstructive disorders, as the major portion of valsartan is eliminated in the bile. No information is available in patients with severe liver disease (see ACTION AND CLINICAL PHARMACOLOGY-Pharmacokinetics).

Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Ophthalmologic

Acute Angle-Closure Glaucoma

Hydrochlorothiazide, a sulfonamide, has been associated with an idiosyncratic reaction resulting in acute transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to week of a drug initiation. Untreated acute-angle glaucoma can lead to permanent vision loss.

The primary treatment is to discontinue hydrochlorothiazide as rapidly as possible. Prompt medical or surgical treatment may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle closure glaucoma may include a history of sulfonamide or penicillin allergy.

Renal

Renal Impairment

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.

Use of valsartan should include appropriate assessment of renal function.

Thiazides should be used with caution.

No dosage adjustment is required for patients with mild to moderate renal impairment (GFR ≥30 mL/min). Because of the hydrochlorothiazide component, valsartan and hydrochlorothiazide should not be used in patients with severe renal impairment (GFR<30 mL/min). Thiazide diuretics may precipitate azotemia in patients with chronic kidney disease. They are ineffective as monotherapy in severe renal impairment (GFR<30 mL/min) (see DOSAGE AND ADMINISTRATION, renal impairment, and ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics).

Azotemia
Azotemia may be precipitated or increased by hydrochlorothiazide. Cumulative effects of the drug may develop in patients with impaired renal function. If increasing azotemia and oliguria occur during treatment of severe progressive renal disease the diuretic should be discontinued.

Sensitivity/Resistance
Sensitivity reactions to hydrochlorothiazide may occur in patients with or without a history of allergy or bronchial asthma.

The possibility of exacerbation or activation of systemic lupus erythematosus has been reported in patients treated with hydrochlorothiazide.

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 and hydrochlorothiazide 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 ARBs 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.

Thiazides cross the placental barrier and appear in cord blood. The routine use of diuretics, including hydrochlorothiazide in otherwise healthy pregnant women is not recommended and exposes mother and fetus to unnecessary hazard including fetal or neonatal jaundice, thrombocytopenia and possibly other adverse experiences which have occurred in the adult. Diuretics do not prevent development of toxemia of pregnancy and there is no satisfactory evidence that they are useful in the treatment of toxemia.

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. Thiazides appear in human milk. 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 (< 18 years of age): The safety and efficacy of valsartan and hydrochlorothiazide in children and adolescents (below the age of 18 years) have not been established and use in this age group is not recommended.

Geriatrics (> 65 years of age): No overall age-related differences were seen in the adverse effect profile but greater sensitivity in some older individuals cannot be ruled out and appropriate caution is recommended.

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.

Valsartan and hydrochlorothiazide has been evaluated for safety in more than 7616 patients treated for essential hypertension. Of these, 4372 were treated with valsartan and hydrochlorothiazide in controlled clinical trials with a mean exposure of 8 weeks.

In controlled clinical trials, discontinuation due to Adverse Experiences (AEs) occurred in 2.3 % and 3.1 % of patients treated with valsartan and hydrochlorothiazide and placebo, respectively. The most common AEs resulting in discontinuation of therapy with valsartan and hydrochlorothiazide were dizziness and headache.

The most common serious AEs with valsartan and hydrochlorothiazide were myocardial infarction and chest pain.

The following table is based on double-blind, active or placebo-controlled trials in patients treated with valsartan and hydrochlorothiazide at doses of 80mg/12.5mg, 80mg/25mg, 160mg/12.5mg, 160mg/25mg, 320mg/12.5mg and 320mg/25mg, valsartan at doses of 80mg, 160mg, and 320 mg, and HCT at doses of 12.5mg and 25mg (see CLINICAL TRIALS). The table includes all AEs with an incidence of 1% or greater in either the valsartan and hydrochlorothiazide, valsartan monotherapy, hydrochlorothiazide monotherapy, or placebo group, irrespective of causal relationship to study drug.

Table 1 Occurrence of adverse events during double-blind controlled trials in patients treated with valsartan and hydrochlorothiazide at doses of 80mg/12.5mg, 80mg/25mg, 160mg/12.5mg, 160mg/25mg, 320mg/12.5mg and 320mg/25mg.

	Valsartan / HCTZ N= 4372	Valsartan N= 2447	Hydrochlorothiazide N= 535	Placebo N= 262
	n (%)	n (%)	n (%)	n (%)
Ear and Labyrinth disorders				
Vertigo	35 (0.8)	10 (0.4)	6 (1.1)	1 (0.4)
Gastrointestinal disorders				
Diarrhoea	48 (1.1)	41 (1.7)	10 (1.9)	3 (1.1)
Nausea	37 (0.8)	21 (0.9)	10 (1.9)	4 (1.5)
Dyspepsia	25 (0.6)	18 (0.7)	6 (1.1)	1 (0.4)
Vomiting	13 (0.3)	11 (0.4)	1 (0.2)	4 (1.5)
Toothache	9 (0.2)	4 (0.2)	1 (0.2)	3 (1.1)
Constipation	6 (0.1)	3 (0.1)	12 (2.2)	2 (0.8)
General Disorders				
Fatigue	72 (1.6)	26 (1.1)	22 (4.1)	4 (1.5)
Oedema Peripheral	25 (0.6)	27 (1.1)	10 (1.9)	3 (1.1)
Infections				
Nasopharyngitis	103 (2.4)	67 (2.7)	15 (2.8)	5 (1.9)
Upper respiratory tract infection	53 (1.2)	49 (2.0)	23 (4.3)	9 (3.4)
Influenza	37 (0.8)	22 (0.9)	8 (1.5)	3 (1.1)
Bronchitis	33 (0.8)	15 (0.6)	6 (1.1)	3 (1.1)
Sinusitis	29 (0.7)	23 (0.9)	7 (1.3)	6 (2.3)
Urinary tract infection	26 (0.6)	12 (0.5)	7 (1.3)	1 (0.4)
Metabolic and nutrition disorders				
Hypokalaemia	7 (0.2)	2 (0.1)	13 (2.4)	2 (0.8)
Musculoskeletal and connective tissue disorders				
Back pain	52 (1.2)	37 (1.5)	11 (2.1)	7 (2.7)

Arthralgia	44 (1.0)	25 (1.0)	8 (1.5)	3 (1.1)
Myalgia	25 (0.6)	15 (0.6)	6 (1.1)	1 (0.4)
Pain in extremity	21 (0.5)	10 (0.4)	11 (2.1)	0 (0.0)
Muscle cramp	18 (0.4)	3 (0.1)	10 (1.9)	3 (1.1)
Nervous system disorders				
Headache	161 (3.7)	126 (5.1)	54 (10.1)	38 (14.5)
Dizziness	153 (3.5)	49 (2.0)	27 (5.0)	10 (3.8)
Somnolence	11 (0.3)	8 (0.3)	1 (0.2)	3 (1.1)
Hypoaesthesia	10 (0.2)	5 (0.2)	2 (0.4)	4 (1.5)
Sinus headache	4 (0.1)	7 (0.3)	3 (0.6)	3 (1.1)
Migraine	2 (0.0)	7 (0.3)	0 (0.0)	4 (1.5)
Psychiatric disorders				
Insomnia	16 (0.4)	12 (0.5)	3 (0.6)	3 (1.1)
Renal and urinary disorders				
Pollakiuria	30 (0.7)	11 (0.4)	8 (1.5)	2 (0.8)
Respiratory, thoracic and mediastinal disorders				
Cough	52 (1.2)	37 (1.5)	11 (2.1)	2 (0.8)
Pharyngolaryngeal pain	30 (0.7)	12 (0.5)	6 (1.1)	1 (0.4)
Sinus congestion	19 (0.4)	7 (0.3)	12 (2.2)	3 (1.1)
Nasal congestion	16 (0.4)	14 (0.6)	7 (1.3)	0 (0.0)
Skin and subcutaneous tissue disorders				
Rash	11 (0.3)	10 (0.4)	6 (1.1)	1 (0.4)

Evaluation of the AEs in the total active-, or placebo-controlled safety population, showed that the most common events, regardless of relationship to treatment in patients treated with valsartan 320 mg/HCTZ were, dizziness, nasopharyngitis, headache and fatigue. The incidence of hypotension was 0.7% in patients treated with valsartan 320mg/HCTZ.

The following adverse reactions have been reported in patients treated with thiazide diuretics alone, including hydrochlorothiazide:

Very common: mainly at higher doses, hypokalemia, blood lipids increased (total cholesterol and triglycerides).

Common: Hyponatremia, hypomagnesemia, hyperuricemia, urticaria and other forms of rash, decreased appetite, mild nausea and vomiting, orthostatic hypotension, which may be aggravated by alcohol, anaesthetics or sedatives, and impotence.

Rare: Hypercalcemia, hyperglycemia, glycosuria and worsening of diabetic metabolic state, photosensitivity reaction, abdominal discomfort, constipation, diarrhoea, cholestasis or jaundice, arrhythmias, headache, dizziness, sleep disorders, depression, paresthesia, visual impairment, thrombocytopenia, sometimes with purpura.

Very rare: Hypochloremic alkalosis, vasculitis necrotising, toxic epidermal necrolysis, cutaneous lupus erythematosus-like reactions, reactivation of cutaneous lupus erythematosus, pancreatitis, leukopenia, agranulocytosis, bone marrow failure, haemolytic anaemia, hypersensitivity reactions, respiratory distress including pneumonitis and pulmonary oedema.

Less Common Clinical Trial Adverse Drug Reactions (<1%)

Body as a whole: arthritis, asthenia, hypersensitivity, influenza, contusion, insomnia, peripheral oedema, pyrexia, sprains and strains
Cardiovascular: angina pectoris, hypotension, myocardial infarction, palpitations, tachycardia, ventricular systoles
Digestive: motion sickness, stomach discomfort
Ear and Labyrinth: ear pain
Gastrointestinal: abdominal pain, dry mouth, dyspepsia, flatulence, gastritis, toothache, vomiting
Muscoskeletal and connective tissue: arthralgia, myalgia, muscle strain
Metabolic and Nutritional: diabetes mellitus, gout, hypokalaemia, hyperuricaemia
Nervous system/Psychiatric: anxiety, somnolence
Renal and urinary system: micturition frequency, urinary tract infection, pollakiuria
Respiratory, thoracic, mediastinal: bronchitis, chest discomfort/pain, dyspnea pharyngolaryngeal pain, sinus congestion, sinusitis
Reproductive: erectile dysfunction
Skin and subcutaneous tissue: rash
Special senses: blurred vision, conjunctivitis, vertigo, tinnitus, visual disturbance
Other: viral infection

Abnormal Hematologic and Clinical Chemistry Findings

Laboratory Findings:

Potassium: In the double-blind, active or placebo-controlled trials potassium decrease of >20% was observed most frequently with HCTZ 25mg (9.7%), followed by HCTZ 12.5mg (6.3%), valsartan/HCTZ 320/25 mg (4.5%), valsartan 320/12.5 mg (3.8%), and valsartan 320mg (2.0%) compared to placebo (3.1%). Also some patients showed serum potassium increase >20 % but no dose relationship could be demonstrated.

Liver Function Tests: Occasional elevations of liver enzymes occurred in valsartan and hydrochlorothiazide treated patients.

Creatinine/Blood urea nitrogen (BUN)/Uric acid: Minor elevations in creatinine and BUN occurred in 1.9% and 14.7%, respectively, of patients treated with valsartan and hydrochlorothiazide and 0.4% and 6.3%, respectively, of patients given placebo in controlled clinical trials. Uric acid increase of > 50% was observed most frequently with valsartan/HCTZ 320/25mg (5.5%), followed by valsartan/HCTZ 320/12.5mg (2.8%), HCTZ 25mg (2.0%), valsartan 320mg (1.7%), and HCTZ 12.5mg (0.8%) compared to placebo (1.6%).

Hemoglobin and Hematocrit: Greater than 20% decreases in hemoglobin and hematocrit were observed in less than 0.1% of patients treated with valsartan and hydrochlorothiazide compared with 0.0% of patients given placebo.

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

Post-Market Adverse Drug Reactions

Other adverse reactions reported rarely in post-marketing use of valsartan alone include: anaphylaxis (very rarely), angioedema (involving swelling of the face, lips and/or tongue), photosensitivity, increase in blood pressure and taste disorders. Very rare cases of impaired renal function have also been reported.

The following adverse drug reactions have also been identified based on post-marketing experiences. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequencies. Therefore, the frequency assigned is "not known": Acute renal failure, renal disorder, aplastic anemia, erythema multiforme, pyrexia, muscle spasm, asthenia, acute angle-closure glaucoma.

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

Cases of syncope were reported with valsartan and hydrochlorothiazide. It is unknown whether these effect were causally related to the therapy.

DRUG INTERACTIONS

Drug-Drug Interactions

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 when valsartan therapy is instituted. Potassium-containing salt substitutes should also be used with caution. Concomitant thiazide diuretic use may attenuate any effect that valsartan may have on serum potassium.

Alcohol, barbiturates or narcotics

Concomitant administration of thiazide diuretics with alcohol, barbiturates, or narcotics may potentiate orthostatic hypotension.

Allopurinol

Coadministration of thiazide diuretics (including hydrochlorothiazide) may increase the incidence of hypersensitivity reactions to allopurinol.

Amantadine

Coadministration of thiazide diuretics (including hydrochlorothiazide) may increase the risk of adverse effects caused by amantadine.

Anticholinergic Agents

The bioavailability of *thiazide-type* diuretics may be increased by *anticholinergic agents* (e.g. atropine, biperiden), apparently due to a decrease in gastrointestinal motility and the stomach emptying rate. This leads to significantly increased absorption and bioavailability of thiazides when coadministred with anticholinergic agents. Conversely, prokinetic drugs such as cisapride

act as a serotonin 5-HT4 receptor agonist, resulting in increased gastric motility, which in turn may decrease the bioavailability of thiazide diuretics.

Antineoplastic agents (e.g. cyclophosphamide, methotrexate):
Concomitant use of thiazide diuretics may reduce renal excretion of cytotoxic agents and enhance their myelosuppressive effects. Caution and monitoring is advised. Dosage should be adjusted if necessary.

Calcium salts
Concomitant use of thiazide type diuretics may lead to hypercalcemia by increasing tubular calcium reabsorption. Nonprescription medications, especially vitamin supplements and antacids, should not be overlooked as sources for calcium salts when this interaction is suspected. Discontinuation of one or both medication may be necessary.

Corticosteroids, ACTH
Intensified electrolyte depletion, particularly hypokalemia, may occur when steroids are given concomitantly with diuretics.

Cyclosporine
Concomitant treatment with cyclosporine may increase the risk of hyperuricemia and gout-type complications.

Diazoxide
Thiazide diuretics may enhance the hyperglycemic effect of diazoxide.

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. Thiazide-induced electrolyte disturbances may predispose to digitalis-induced arrhythmias.

Insulin
Insulin requirements in diabetic patients treated with diuretics may be increased, decreased or unchanged. Diabetes mellitus which has been latent may become manifest during thiazide administration.

Ion exchange resins
Absorption, and hence bioavailability, C_{max}, AUC, of thiazide diuretics, including hydrochlorothiazide, is decreased by cholestyramine or colestipol, resulting in sub-therapeutic effect of the drugs. However, staggering the dosage of hydrochlorothiazide and resin such that hydrochlorothiazide is administered at least 4 h before or 4-6 h after the administration of resins would potentially minimize the interaction.

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

be administered with valsartan. Lithium generally should not be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity.

Medicinal products affecting serum potassium level
The hypokalemic effect of diuretics may be synergetically aggravated by concomitant administration of kaliuretic diuretics, corticosteroids, ACTH, amphotericin, carbenoxolone, penicillin G, salicylic acid derivatives or antiarrhythmics, β2-agonists, pseudoephedrine, ephedrine, chloroquine, and antibiotics. Monitoring of serum electrolyte balance is recommended. Simultaneous administration of potassium supplements may be necessary.

Medicinal products decreasing serum sodium level
The hyponatremic effect of diuretics may be intensified by concomitant administration of drugs such as antidepressants, antipsychotics, antiepileptics, etc. Caution is advised during the administration of these drugs (see Warnings and Precautions, Serum electrolyte changes). Such patients should therefore be advised about the possibility of hyponatremic reactions, and should be monitored accordingly.

Methlydopa
There have been reports in the literature of hemolytic anemia occurring with concomitant use of *hydrochlorothiazide and methyldopa*.

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 have compromised renal function, concomitant use of angiotensin II antagonists and NSAIDs may lead to an increased risk of worsening of renal function. Therefore, monitoring of renal function is recommended when initiating or modifying the treatment in patients on valsartan who are taking NSAIDs concomitantly.

Other antihypertensive drugs
Thiazides potentiate the antihypertensive action of other antihypertensive drugs (e.g. guanethidine, methyldopa, beta-blockers, vasodilators, calcium channel blockers, ACE inhibitors, Angiotensin Receptor Blockers (ARBs) and Direct Renin Inhibitors (DRIs).

Pressor amines (e.g. norepinephrine):
Hydrochlorothiazide may reduce the response to pressor amines such as norepinephirne but the clinical significance of this effect is not sufficient to preclude their use.

Skeletal muscle relaxants
Thiazide drugs, including hydrochlorothiazide, may increase the responsiveness of skeletal muscle relaxants such as curare derivatives (d-tubocurarine).

Vitamin D
Administration of *thiazide diuretics*, including hydrochlorothiazide, with vitamin D or with calcium salts may potentiate the rise in serum calcium.

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

Drug-Food Interactions
Valsartan and hydrochlorothiazide may be administered with our without food, however it should be taken consistently with respect to food intake (see DOSAGE AND ADMINISTRATION).

DOSAGE AND ADMINISTRATION

Dosing Considerations
Dosage must be individualized. The fixed combination is not for initial therapy. The dose of Ava-Valsartan HCT (valsartan and hydrochlorothiazide) should be determined by the titration of the individual components.

Hepatic Impairment
No initial dosage adjustment in valsartan is required in patients with mild to moderate hepatic impairment. Due to the hydrochlorothiazide component, Ava-Valsartan HCT is not recommended in patients with severe hepatic impairment (see WARNINGS AND PRECAUTIONS). Because thiazide diuretics may precipitate hepatic coma, care should be exercised when administering a fixed combination product containing hydrochlorothiazide (see WARNINGS AND PRECAUTIONS). Due to the valsartan component, Ava-Valsartan HCT should be used with particular caution in patients with biliary obstructive disorders (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS).

Renal Impairment
No dosage adjustment is required for patients with mild to moderate renal impairment (Glomerular Filtration Rate (GFR) ≥30 mL/min). Due to the hydrochlorothiazide component, Ava-Valsartan HCT is contraindicated in patients with severe renal impairment (creatinine clearance < 30 mL/min) and with anuria (see CONTRAINDICATIONS) and should be used with caution in patients with severe renal impairment (GFR <30 mL/min) (see WARNINGS AND PRECAUTIONS for use and ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics).

Elderly
No dosage adjustment is usually necessary however see WARNINGS AND PRECAUTIONS.

Recommended Dose and Dosage Adjustment
Once the patient has been stabilized on the individual components as described below, Ava-Valsartan HCT tablet, 80mg/12.5mg, 160mg/12.5mg, 160 mg/25, 320mg/12.5mg, or 320mg/25mg once daily may be substituted if the doses on which the patient was stabilized are

the same as those in the fixed combination (see INDICATIONS AND CLINICAL USE and WARNINGS AND PRECAUTIONS).

The maximum recommended dose is 320 mg valsartan and 25 mg hydrochlorothiazide and the titration will be based on physician's judgment according to severity of hypertension and other associated risk factors.

Ava-Valsartan HCT may be administered with our without food, however it should be taken consistently with respect to food intake.

Valsartan monotherapy
The recommended starting dose of 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.

Diuretic-Treated Patients
In patients receiving diuretics, 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 HCT to reduce the likelihood of hypotension (see WARNINGS AND PRECAUTIONS and DRUG INTERACTIONS). If this is not possible because of the patient's condition, Ava-Valsartan HCT 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.

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

No specific information is available on the treatment of overdosage with valsartan and hydrochlorothiazide. Treatment is symptomatic and supportive.

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

Valsartan
Limited data are available in regard to overdosage with valsartan in humans. The most likely manifestations of overdosage would be hypotension, which could lead to depressed level of consciousness, circulatory collapse and/or shock, and/or tachycardia. If symptomatic hypotension should occur, supportive treatment should be instituted.

Valsartan is not removed from the plasma by dialysis.

Hydrochlorothiazide
The most common signs and symptoms observed are those caused by electrolyte depletion (hypokalemia, hypochloremia, hyponatremia) and dehydration resulting from excessive diuresis. If digitalis has also been administered, hypokalemia may accentuate cardiac arrhythmias.

The degree to which hydrochlorothiazide is removed by hemodialysis has not been established.

ACTION AND CLINICAL PHARMACOLOGY

Valsartan and hydrochlorothiazide combines the actions of valsartan, an orally active angiotensin II AT_1 receptor blocker, and that of a diuretic, hydrochlorothiazide.

Mechanism of Action

Valsartan
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.

Hydrochlorothiazide
Hydrochlorothiazide is a thiazide diuretic. Thiazides affect the renal tubular mechanism of electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equivalent amounts. Indirectly, the diuretic action of hydrochlorothiazide reduces plasma volume with consequent increases in plasma renin activity, increases in aldosterone secretion, increases in urinary potassium loss, and decreases in serum potassium. The renin-aldosterone link is mediated by angiotensin II, therefore co-administration of an angiotensin II AT_1 Receptor Blocker tends to reverse the potassium loss associated with thiazide diuretics.

Hydrochlorothiazide is useful in the treatment of hypertension. It may be used alone or as an adjunct to other antihypertensive drugs. Hydrochlorothiazide does not affect normal blood pressure.

Pharmacodynamics

Valsartan

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 heart 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).

Hydrochlorothiazide

Onset of the diuretic action following oral administration occurs in 2 hours and the peak action in about 4 hours. Diuretic activity lasts about 6-12 hours.

Valsartan-Hydrochlorothiazide

The components of valsartan and hydrochlorothiazidehave been shown to have additive effect on blood pressure reduction, reducing blood pressure to a greater degree than either component used alone.

The antihypertensive effect of valsartan and hydrochlorothiazide is sustained for a 24-hour period. In clinical studies of at least one year duration, the antihypertensive effect was maintained with continued therapy. Despite the significant decrease in blood pressure, administration of valsartan and hydrochlorothiazide had no clinically significant effect on heart rate.

Pharmacokinetics

Valsartan

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

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.

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 labeled valsartan, 83% of absorbed valsartan is excreted in the feces and 13% in the urine, mainly as unchanged compound.

Hydrochlorothiazide
The absorption of hydrochlorothiazide, after an oral dose, is rapid (T_{max} about 2 h).The increase in mean AUC is linear and dose proportional in the therapeutic range. Concomitant administration with food has been reported to both increase and decrease the systemic availability of hydrochlorothiazide compared with the fasted state. The magnitude of these effects is small and has little clinical importance. Absolute bioavailability of hydrochlorothiazide is 70 % after oral administration.

The distribution and elimination kinetics have generally been described as a bi-exponential decay function. The apparent volume of distribution is 4-8 L/kg. Circulating hydrochlorothiazide is bound to serum proteins (40-70%), mainly serum albumin. Hydrochlorothiazide also accumulates in erythrocytes at approximately 3 times the level in plasma.

Hydrochlorothiazide is eliminated predominantly as unchanged drug. Hydrochlorothiazide is eliminated from plasma with a half-life averaging 6 to 15 hours in the terminal elimination phase. There is no change in the kinetics of hydrochlorothiazide on repeated dosing, and accumulation is minimal when dosed once daily. There is more than 95 % of the absorbed dose being excreted as unchanged compound in the urine.

Hydrochlorothiazide crosses the placental but not the blood-brain barrier and is excreted in breast milk.

Valsartan- Hydrochlorothiazide

The systemic availability of hydrochlorothiazide is reduced by about 30% when co-administered with valsartan. The kinetics of valsartan are not markedly affected by the co-administration of hydrochlorothiazide. This observed interaction has no impact on the combined used of valsartan and hydrochlorothiazide.

Special Populations and Conditions

Pediatrics: The pharmacokinetics of valsartan have not been investigated in patients <18 years of age.

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).

Valsartan and hydrochlorothiazide should be used with particular caution in patients with biliary obstructive disorders. Because of hydrochlorothiazide, valsartan and hydrochlorothiazide is not recommended in patients with severe hepatic impairment (see WARNINGS AND PRECAUSIONS, Hepatic/Biliary/Pancreatic).

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.

In the patients with moderate to severe renal impairment, mean peak plasma levels and AUC values of hydrochlorothiazide are increased by 2.27 fold and 8.46 fold respectively and the mean cumulative urinary excretion rate is reduced by 35% as compared to baseline 51% of the oral dose.

As expected for a compound which is cleared almost exclusively via the kidneys, renal function has a marked effect on the kinetics of hydrochlorothiazide. Therefore, valsartan and hydrochlorothiazide is not recommended for use in patients with severe renal impairment (creatinine clearance < 30 mL/min).

Valsartan is not removed from plasma by dialysis.

STORAGE AND STABILITY

Protect from moisture. Store at 15 - 30°C.

SPECIAL HANDLING INSTRUCTIONS

Not applicable.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Availability
Ava-Valsartan HCT tablets, 80mg/12.5mg are supplied in bottles of 100 and 500 tablets and in cartons containing 2 blister strips of 15 tablets.

Ava-Valsartan HCT tablets, 160mg/12.5mg are supplied in bottles of 100 and 500 tablets and in cartons containing 2 blister strips of 15 tablets.

Ava-Valsartan HCT tablets, 160mg/25mg are supplied in bottles of 100 and 500 tablets and in cartons containing 2 blister strips of 15 tablets.

Ava-Valsartan HCT tablets, 320mg/12.5mg are supplied in cartons containing 2 blister strips of 15 tablets.

Ava-Valsartan HCT tablets, 320mg/25mg are supplied in bottles of 100 and in cartons containing 2 blister strips of 15 tablets.

Composition
Ava-Valsartan HCT Tablet, 80mg/12.5mg
Each light orange, ovaloid, film-coated tablet imprinted with HGH on one side and CG on the other contains 80 mg of valsartan and 12.5 mg of hydrochlorothiazide as the active ingredients. Each tablet contains the following non-medicinal ingredients: Colloidal silicon dioxide, crospovidone, magnesium stearate, microcrystalline cellulose. The coating contains hydroxypropyl methylcellulose, polyethylene glycol, red iron oxide, talc, titanium dioxide and yellow iron oxide.

Ava-Valsartan HCT Tablet, 160mg/12.5mg
Each dark red, ovaloid, film-coated tablet imprinted with HHH on one side and CG on the other contains 160 mg of valsartan and 12.5 mg of hydrochlorothiazide as the active ingredients. Each tablet contains the following non-medicinal ingredients: Colloidal silicon dioxide, crospovidone, magnesium stearate, microcrystalline cellulose. The coating contains hydroxypropyl methylcellulose, polyethylene glycol, red iron oxide, talc, and titanium dioxide.

Ava-Valsartan HCT Tablet, 160mg/25mg
Each brown, ovaloid, film-coated tablet imprinted with HXH on one side and NVR on the other contains 160 mg of valsartan and 25 mg of hydrochlorothiazide as the active ingredients. Each tablet contains the following non-medicinal ingredients: Colloidal silicon dioxide, crospovidone, magnesium stearate, microcrystalline cellulose. The coating contains hydroxypropyl

methylcellulose, polyethylene glycol, black iron oxide, red iron oxide, talc, and titanium dioxide and yellow iron oxide.

Ava-Valsartan HCT Tablet, 320mg/12.5mg
Each pink, ovaloid, film coated tablet imprinted with “NVR” on one side and “HIL” on the other contains 320 mg of valsartan and 12.5 mg of hydrochlorothiazide as the active ingredients. Each tablet contains the following non-medicinal ingredients: Colloidal silicon dioxide, crospovidone, magnesium stearate, microcrystalline cellulose. The coating contains hydroxypropyl methylcellulose, polyethylene glycol, red iron oxide, black iron oxide, talc, and titanium dioxide.

Ava-Valsartan HCT Tablet, 320mg/25mg
Each yellow, ovaloid, film coated tablet imprinted with “NVR” on one side and “CTI” on the other contains 320 mg of valsartan and 25 mg of hydrochlorothiazide as the active ingredients. Each tablet contains the following non-medicinal ingredients: Colloidal silicon dioxide, crospovidone, magnesium stearate, microcrystalline cellulose. The coating contains hydroxypropyl methylcellulose, polyethylene glycol, yellow iron oxide, talc, and titanium dioxide.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper Names:

valsartan	hydrochlorothiazide

Chemical Names:

(*S*)-*N*-valeryl-*N*-{[2'-(1H-tetrazol-5-yl) biphenyl-4-yl] methyl}-valine	6-chloro-3,4-dihydro-2*H*-1,2,4-benzothiazidine-7-sulfonamide 1,1-dioxide

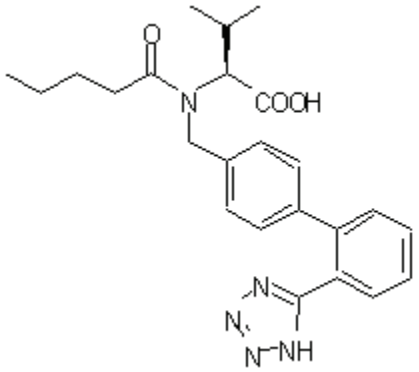
Molecular formulae:

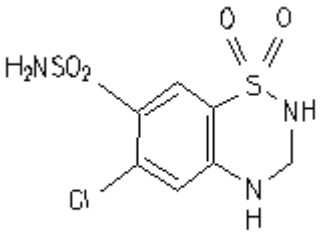
$C_{24}H_{29}N_5O_3$	$C_7H_8ClN_3O_4S_2$

Molecular weights:

435.5	297.74

Structural formulae:





Description:

Fine white to practically white, practically odourless powder. It is soluble in ethanol, methanol and slightly soluble in water.	White, or practically white, crystalline powder. It is slightly soluble in water; freely soluble in sodium hydroxide solution and dimethyl sulfoxide, sparingly soluble in methanol and ethanol; practically insoluble in diethyl ether.

CLINICAL TRIALS

In controlled clinical trials including over 7600 patients with essential hypertension, 4372 patients were exposed to valsartan (80, 160 and 320 mg) and concomitant hydrochlorothiazide (12.5 and 25 mg). Two randomized, double-blind factorial trials compared various combinations of 80/12.5 mg, 80/25 mg, 160/12.5 mg, 160/25 mg, 320/12.5 mg and 320/25 mg with their respective components and placebo. The combination of valsartan and hydrochlorothiazide resulted in additive placebo-adjusted decreases in systolic and diastolic blood pressure at trough of 14-21/8-11 mmHg at 80/12.5 mg to 320/25 mg, compared to 7- 10/4-5 mmHg for valsartan 80 mg to 320 mg and 5-11/2-5 mmHg for hydrochlorothiazide 12.5 mg to 25 mg, alone.

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

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

In one year open label follow up study (without placebo control) the effect of the combination of valsartan and hydrochlorothiazide was maintained. The antihypertensive effect was independent of age or gender. The overall response to the combination was similar for black and non-black patients.

There was essentially no change in heart rate in patients treated with the combination of valsartan and hydrochlorothiazide in controlled trials.

DETAILED PHARMACOLOGY

Pharmacodynamics

The *in vitro* data support that valsartan is a specific antagonist of the AT_1 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 AT_1 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 AT_1 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 AT_2 receptor. The role of the AT_2 receptor is currently unknown. No untoward effects were noted in preclinical or clinical studies that might suggest an AT_2 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 AT_1 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.

TOXICOLOGY

Acute Toxicity
Valsartan

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

Valsartan and hydrochlorothiazide

Species	Route	Dose (mg/kg)		Major Findings
		valsartan	HCTZ	
Rat	Gavage	1524	476	No adverse findings. Approximate LD_{50} > 1524.0:476.0 mg/kg
Marmoset	Gavage	320.0 761.9	100.0 238.1	No adverse findings Approximate LD_{50} > 761.9:238.1 mg/kg

Long-Term Toxicity

Valsartan

In toxicity studies conducted in several animal species, the main preclinical safety findings involving the kidney and related effects, are attributed to the pharmacological action of the compound.

Species	Route	Duration	Dose mg/kg	Major findings
Rat	Gavage	14 day	60, 200, 600	Mid & High dose groups: ↑ urea NOEL = 60 mg/kg.
Marmoset	Gavage	14 day	60, 200, 600	High dose group: Vomiting and mild to moderate ↑ in urea 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	Mid & High dose groups: ↑ urea High dose group: 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	Mid dose group: ↑ urea at 60 mg/kg High dose group: anemia & renal arteriolar hypertrophy. NOAEL = 20 mg/kg.
Marmoset	Gavage	12 months	12, 40, 120	Mid & High dose groups: ↑ in urea and creatinine NOAEL = 12 mg/kg.

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

Valsartan and hydrochlorothiazide

The combination of valsartan/hydrochlorothiazide was evaluated for toxicity in the rat and marmoset for up to 6 months. Treatment-related findings were mainly related to the exaggerated pharmacological effects of valsartan and/or hydrochlorothiazide and consisted of reduction in red cells parameters, alterations in electrolyte and water concentrations in the body, hypertrophy of the juxtaglomerular apparatus and renal tubular changes. The marmoset was a much more sensitive species in which there was an approximate 10-fold potentiation of blood pressure reduction with the combination of valsartan and hydrochlorothiazide as compared to valsartan alone. Hydrochlorothiazide alone had no effect on the blood pressure of marmosets. This potentiation has not been seen in the human subject; the effect of valsartan and hydrochlorothiazide is additive.

Species	Route	Duration	Dose (mg/kg)		Major findings
			valsartan	HCTZ	
Marmoset	Gavage	14 days	-- -- --	100 300 1000	No adverse findings. All groups: ↓ Plasma Na^+ and K^+
Rat	Gavage	1 month	50.0 200.0 600.0 --	15.625 62.5 187.5 187.5	All groups: Pharmacological dose-related findings; ↑ in urea. NOAEL > 600.0:187.5 mg/kg
Marmoset	Gavage	1 month	30.0 120.0 400.0 --	9.375 37.5 125 125	High dose group: Early death of all 3 F. High dose and HCTZ groups: Renal changes including tubular basophilia Low and mid dose groups: Minor pharmacological dose-related changes. NOAEL = 30.0:9.375 mg/kg
Rat	Gavage	6 months	30.0 100.0 300.0 --	9.375 31.25 93.75 93.75	All groups: Pharmacological dose-related findings; ↑ urea. High dose group: Changes in plasma lipid parameters. NOAEL = 100.0:31.25 mg/kg
Marmoset	Gavage	6 months	30.0 60.0 120.0 240.0→120.0	9.375 18.75 37.5 75.0→37.5 75.0	All dose levels (not HCTZ): Deaths associated with renal changes related to severe pharmacological effects. HCTZ: Minor effects. NOAEL not identified.
Marmoset	Gavage	6 months	3.0 10.0 30.0	0.93 3.125 9.325	No adverse findings NOAEL=10.0:3.125

NOAEL: No Observed Adverse Effect Level
NOEL: No Observed Effect Level

Reproduction and Teratology

Valsartan

In reproductive studies in rats, mice and rabbits, only minor effects were noted. In rabbits there was evidence of low fetal weights, litter loss and abortion, but no teratogenicity at 5 and 10 mg/kg. Rabbits are extremely susceptible to compounds acting on the RAAS so this finding is not unexpected. There was also a slightly reduced postnatal F_1 survival and development together with reduced maternal bodyweight gain in rats at 600 mg/kg. Otherwise, there was no effect at the highest doses tested on fertility, reproductive performance in rats (200 mg/kg), embryotoxcity, fetotoxicity, teratogenicity in rats and mice (600 mg/kg).

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	High dose: ↓ in field motor activity 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

Species	Route	Duration of dosing	Dose mg/kg	Major Findings
Mouse	Gavage	Day 6 to 15	60, 200, 600	All dose groups: No embryotoxicity, fetotoxicity or teratogenicity.
Rat	Gavage	Day 6 to 15	60, 200, 600	Mid & High dose groups:↓ maternal body weight gain High dose group: ↓ fetal weights All dose groups: No embryotoxicity, fetotoxicity or teratogenicity
Rabbit[1]	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	Mid dose group: ↑ incidence of low fetal weights Mid & High dose groups: Litter loss and abortion All dose groups: No teratogenicity.

[1] Range Finding

Segment III

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

+ - Number of days post-parturition

Valsartan and hydrochorothiazide

Reproductive studies with the combination of valsartan/hydrochlorothiazide were conducted in rats, mice and rabbits. In all 3 species, there was no evidence of teratogenicity. In rats, there were maternal changes, mainly decreased food consumption, bodyweight or bodyweight gain at 50:115.6 mg/kg and above and deaths at 200:62.5 mg/kg and above. Fetotoxicity was seen at 262.5 mg/kg and above. This was considered to be related to the maternal toxicity. No effects were noted in mice at 600:187.5 mg/kg. Rabbits showed similar effects to those of valsartan alone at equivalent doses.

Segment II

Species	Route	Duration	Dose (mg/kg)		Major Findings
			Valsartan	HCTZ	
Rat	Gavage	Day 6 to 15	50.0 200.0 600.0	15.6 62.5 187.5 187.5	All dose groups: Maternal & fetal toxicty, ↓ food consumption, body weight & weight gain Mid dose & High dose groups: Maternal deaths (3/26 & 11/26), salivation and stool changes and ↓ fetal weight No embryotoxicity or teratogenicity.
Rat	Gavage	Day 6 to 15	10.0 25.0 100.0	3.1 7.8 31.3 31.3	High dose group:↓ food consumption and weight gain No evidence of embryo- & feto-toxicity or embryotoxicity NOEL (maternal): 25.0:7.8 mg/kg NOEL (fetal): 100:31.3 mg/kg

Species	Route	Duration	Dose (mg/kg)		Major Findings
			Valsartan	HCTZ	
Rabbit	Gavage	Day 7 to 19	1.0 3.0 10.0	0.3 0.9 3.1 3.1	All dose groups: Slightly ↓ food consumption Mid dose group: Maternal death (1/18) High dose group: ↑ no. of late resorptions, total resorptions, mean & % post implantation loss; slight ↓ in no. of live fetuses. No evidence of teratogenecity NOAEL (fetal): 3.0:0.9 mg/kg
Mouse	Gavage	Day 6 to 15	50 200 600	15.6 62.5 187.5 187.5	No maternal effects, embryo-, fetotoxicity or teratogenicity. NOAEL (fetal & Maternal): 600.0:187.5 mg/kg

Mutagenicity

Valsartan

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

In vitro

Test	System	mcg/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

Valsartan

Species	Route	Duration	Dose (mg/kg)	Major Findings
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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PART III: CONSUMER INFORMATION

[Pr]Ava-Valsartan HCT
Valsartan and hydrochlorothiazide tablets

This leaflet is part III of a three-part "Product Monograph" published when Ava-Valsartan HCT 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 HCT. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
Ava-Valsartan HCT is a combination of an angiotensin II AT_1 receptor blocker (valsartan) and a diuretic (hydrochlorothiazide). Valsartan and hydrochlorothiazide work together to lower your blood pressure.

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:
The valsartan ingredient in Ava-Valsartan HCT lowers blood pressure by specifically blocking angiotensin II. 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. Valsartan works by blocking the effect of angiotensin II. As a result, blood pressure is lowered. The hydrochlorothiazide ingredient in Ava-Valsartan HCT works by making your kidneys pass more water and salt. Together valsartan and hydrochlorothiazide lower blood pressure.

When it should not be used:
You should not take Ava-Valsartan HCT if you:
- are allergic to valsartan, hydrochlorothiazide or to any other component of this product;
- are allergic to any sulfonamide-derived drugs (ask your physician or pharmacist if you are not sure what sulfonamide-derived drugs are);
- suffer from severe kidney disease with being unable to produce urine (anuria)
- suffer from severe liver disease with destruction of the small bile ducts within the liver (biliary cirrhosis) leading to the builds up bile in the liver (cholestasis)
- are pregnant or planning to become pregnant (See WARNINGS AND PRECAUTIONS below);
- have serious kidney disease;
- have a too low level of potassium or sodium or if you have a too high level of calcium in your blood despite treatment;
- have uric acid crystals in the joints (gout);
- are pregnant;
- are under 18 years old.

What the medicinal ingredients are:
Valsartan and hydrochlorothiazide.

What the nonmedicinal ingredients are:
Ava-Valsartan HCT 80/12.5 mg tablets: Colloidal silicon dioxide, crospovidone, magnesium stearate, microcrystalline cellulose, hydroxypropyl methylcellulose, polyethylene glycol, red iron oxide, talc, titanium dioxide and yellow iron oxide.

The other strengths also contain:

Ava-Valsartan HCT 160/25 mg: Black iron oxide

Ava-Valsartan HCT 320/12.5 mg: Black iron oxide

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:
Tablet; valsartan/hydrochlorothiazide 80 mg/12.5 mg, 160 mg/12.5 mg, 160 mg/25 mg, 320 mg/12.5 mg, 320 mg/25 mg.

WARNINGS AND PRECAUTIONS

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

BEFORE you use Ava-Valsartan HCT talk to your doctor or pharmacist if you:
- suffer from liver or kidney disorders;
- suffer from diabetes (high blood sugar in your blood);
- have fever, rash, and joint pain, which may be signs of lupus erythematosus (or a history of this disease);
- have low levels of potassium in your blood (with or without symptoms such as muscle weakness, muscle spasms, abnormal heart rhythm);
- have low levels of sodium in your blood (with or without symptoms such as tiredness, confusion, muscle twitching, convulsions);
- have high levels of calcium in your blood (with or without symptoms such as nausea, vomiting, constipation, stomach pain, frequent urination, thirst, muscle weakness and twitching);
- have high levels of uric acid in the blood;
- are suffering from allergy or asthma
- have high levels of cholesterol or triglycerides in your blood;
- are suffering from vomiting or diarrhoea, or taking high doses of a diuretic (water pill);
- experience a decrease in vision or eye pain. These could be symptoms of an increase of pressure in your eye and can happen within hours to weeks of taking Ava-Valsartan HCT. This can lead to permanent vision impairment, if not treated.

You should have regular blood tests before and during treatment with Ava-Valsartan HCT. These will monitor the amount of

electrolytes (such as potassium, sodium, calcium or magnesium) in your blood and may also monitor your kidney function

You are pregnant, breast-feeding or thinking of becoming pregnant?

Taking Ava-Valsartan HCT 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 HCT, contact immediately your doctor.

It is also advisable not to take Ava-Valsartan HCT during breast-feeding. The diuretic component of Ava-Valsartan HCT passes into the breast milk and may also reduce your milk supply. If you are breast-feeding, avoid using Ava-Valsartan HCT unless recommended by your doctor.

Similar medicines were associated with serious harm to fetuses when they were taken during pregnancy. 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 HCT during pregnancy.

Like many other medicines used to treat high blood pressure, Ava-Valsartan HCT may rarely cause effects such as dizziness or fainting in some patients. 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 HCT.

INTERACTIONS WITH THIS MEDICATION

Tell your doctor or pharmacist about any medicines you are taking or have recently taken, including prescription medications, over-the-counter medications or natural health products (herbal medicines).

Certain medicines tend to increase your blood pressure, for example, non prescription preparations for appetite control, asthma, colds, coughs, hay fever and sinus problems.

Before surgery and general anesthesia (even at the dentist's office), tell the physician or dentist that you are taking Ava-Valsartan HCT, as there may be a sudden drop in blood pressure associated with general anesthesia.

It is especially important for your physician and pharmacist to know if you are taking other drugs, such as:

- digoxin or other digitalis glycosides (a heart medicine),
- other diuretics (water pills),
- pressor amines such as epinephrine (substances that raise blood pressure),
- other medicines used to lower blood pressure,
- potassium-sparing agents,
- potassium supplement or salt substitutes containing potassium. Your doctor may monitor the levels of potassium in your blood,
- vitamin D and calcium salts,
- amantadine (medicine to treat Parkinson's disease and also used to treat or prevent certain illnesses caused by viruses),
- certain cancer medicines,
- anticholonergic agents (medicines used to treat a variety of disorders such as gastrointestinal cramps, urinary bladder spasm, asthma, motion sickness, muscular spasms, Parkinson's disease and as an aid to anaesthesia),
- lithium, antidepressants, antipsychotics, medicines used to treat some mental conditions,
- antiepileptics, such as carbamazepine (medicines used to treat convulsions),
- medicines used to relieve pain or inflammation, especially non-steroidal anti-inflammatory agents (NSAIDS) including Cox-2 selective inhibitors,
- cortisone-like medicines, steroids, carbenoxolone (a medicine used to treat ulceration and inflammation), antibiotics such as penicillin G, amphothericine, antiarrhythmics (medicines used to treat heart problems),
- steroids,
- cholestyramine, colestipol or other resins (medicines used mainly to treat high levels of lipids in the blood),
- insulin or antidiabetic medicines taken by mouth (medicines used to treat high levels of sugar in your blood),
- muscle relaxant drugs (medicines used during operations),
- allopurinol (medicine used to treat gout),
- cyclosporine (a medicine used in transplantation and in autoimmune disorders),
- barbiturates, narcotics (medicines with sleep-inducing properties) and alcohol,
- warfarin (medicine to prevent blood clot),
- diazoxide (medicine to increase blood glucose level).

Taking carbamazepine with hydrochlorothiazide (a medicinal ingredient in Ava-Valsartan HCT) may cause a low sodium level in the blood. Symptoms of low sodium level in the blood may include: nausea, vomiting, headache, muscular cramps or weakness, and general uneasiness. As it worsens, confusion, decreased consciousness, convulsions (fits), or coma may occur. Tell your doctor if this happens to you.

Sedatives, tranquilizers, narcotics, alcohol and analgesics may increase the blood-pressure lowering effect of Ava-Valsartan HCT, so tell your physician or pharmacist if you are taking any of these.

PROPER USE OF THIS MEDICATION

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 HCT as directed.

Usual dose:

Take Ava-Valsartan HCT as directed. Dosage must be individualized. Ava-Valsartan HCT is not for initial therapy. Once you are stabilized on both individual components of Ava-

Valsartan HCT the usual dosage is one 80 mg/12.5mg tablet once a day. In some cases, your doctor may prescribe a higher dose (e.g., the 160mg/12.5mg, 160 mg/25 mg, 320mg/12.5mg or the 320mg/25mg tablet).

You can take Ava-Valsartan HCT with or without food, but it should be taken the same way each day.

Overdose:
If you experience severe dizziness and/or fainting, contact your doctor immediately so that medical attention may be given promptly.

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 completely forgotten to take your dose during the day, carry on with the next one at the usual time. Do not double doses.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, Ava-Valsartan HCT may cause unwanted reactions, or side effects. Most patients do not experience side effects from Ava-Valsartan HCT, however, some patients may experience dizziness.

Possible side effects are:
Headache; dizziness or light-headedness when getting up from a lying or sitting position; fainting; stomach upset; unusual tiredness or weakness (sometimes sign of potassium loss), loss of appetite; skin rash or itching; increased sensitivity of the skin to sunlight, muscle pain; difficulty in achieving erection or loss of interest in sex, vomiting; nausea; diarrhea; pain in the back or stomach; constipation; pain in the joints; cold and flu-like symptoms, dry cough; vertigo (feeling of spinning); rash; sleep disturbance.; blurred vision, blistering rash.

If any of these affect you severely, tell your doctor.

Other possible side effects from spontaneous reporting are:
Muscle spasm, fever (pyrexia), weakness (asthenia)

If any of these affect you severely, tell your doctor.

If you notice any other effects not listed above, check with your doctor.

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 mediate attention**
	Only if severe	**In all cases**	

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**
Common	*Allergic reactions* Skin rash, skin eruption or other effect on the skin or eyes			✓
Uncommon	Low Blood Pressure (hypotension): Fainting, dizziness, blurred vision			✓
	Severe 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, severely decreased urine output)			✓
	Rhabdomyoly-sis (symptoms like Muscle tenderness or weakness, generalized weakness)		✓	
	Abdominal pain		✓	
Rare or very rare	Possible signs of a blood disorder (symptoms like sore throat, fever, or chills)			✓
	Jaundice: Yellow eyes or skin			✓
	Thrombocyto-penia: (numbness or tingling in the hands, feet, or lips; unusual bleeding or bruising)		✓	
	Irregular heart beat		✓	
	Pancreatitis (severe upper stomach pain, vomiting and fever)	✓		
	Necrotizing vasculitis; (Inflammation of vessels with or without pain)	✓		
	Respiratory problems including pneumonitis and pulmonary edema:			✓
	Bone marrow failure, aplastic anemia: (Weakness, bruising and frequent infections)	✓		

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**
	Glaucoma: (Decrease in vision or pain in your eyes due to high pressure)			✓
	Erythematic multiforme: rash, red skin, blistering of the lips, eyes or mouth, skin peeling, fever			✓

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

HOW TO STORE IT

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

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

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

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.

Keep this medicine out of the reach and sight 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