PRODUCT MONOGRAPH

[Pr]pms-VALSARTAN-HCTZ

Valsartan and Hydrochlorothiazide Tablets, USP
80 mg/12.5 mg, 160 mg/12.5 mg, 160 mg/25 mg, 320 mg/12.5 mg & 320 mg/25 mg

Angiotensin II AT_1 Receptor Blocker and Diuretic

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[Pr]pms-VALSARTAN-HCTZ
Valsartan and Hydrochlorothiazide Tablets, USP

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All nonmedicinal Ingredients
Oral	Tablets: 80 mg/12.5 mg 160 mg/12.5 mg 160 mg/25 mg 320 mg/12.5 mg 320 mg/25 mg	Colloidal Silicon Dioxide, Crospovidone, Magnesium Stearate, Powdered Cellulose, Sodium Lauryl Sulfate The coating of the tablets contains **80 mg/12.5 mg:** Hypromellose, Iron Oxide Red, Iron Oxide Yellow, Polyethylene Glycol and Titanium Dioxide. **160 mg/12.5 mg:** Hypromellose, Iron Oxide Red, Polyethylene Glycol and Titanium Dioxide. **160 mg/25 mg:** Hypromellose, Iron Oxide Black, Iron Oxide red, Iron Oxide Yellow, Polyethylene Glycol and Titanium Dioxide. **320 mg/12.5 mg:** Hypromellose, Iron Oxide Black, Iron Oxide Red, Polyethylene Glycol and Titanium Dioxide. **320 mg/25 mg:** FD & C Yellow # 6 Aluminum Lake, Hypromellose, Iron Oxide Yellow, Polyethylene Glycol and Titanium Dioxide.

INDICATIONS AND CLINICAL USE

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

pms-VALSARTAN-HCTZ 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 pms-VALSARTAN-HCTZ 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 pms-VALSARTAN-HCTZ in children and adolescents (below the age of 18 years) have not been established and use in this age group is not recommended.

CONTRAINDICATIONS

- pms-VALSARTAN-HCTZ (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 occurs during treatment.

- Patients who are hypersensitive to other sulfonamide-derived drugs.

- pms-VALSARTAN-HCTZ is also contraindicated in pregnant and nursing women (see WARNINGS AND PRECAUTIONS, Special Populations, Nursing Women).

- Thiazide diuretics are contraindicated in patients with hyponatremia, hypercalcemia, symptomatic hyperuricemia, and conditions involving enhanced potassium loss.

- Concomitant use of angiotensin receptor antagonists (ARBs) - including 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 <60mL/min/1.73m^2) is contraindicated (see WARNINGS AND PRECAUTION, General, 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)

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, pms-VALSARTAN-HCTZ should be discontinued as soon as possible (see CONTRAINDICATIONS and 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. pms-VALSARTAN-HCTZ should be immediately discontinued in patients who develop angioedema, and pms-VALSARTAN-HCTZ should not be re-administered.

If laryngeal stridor or angioedema of the face, extremities, lips, tongue, or glottis occurs, pms-VALSARTAN-HCTZ 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 pms-VALSARTAN-HCTZ (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.

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.

Dual Blockade of the Renin-Angiotensin System (RAS)

There is evidence that co-administration of angiotensin receptor antagonists (ARBs), including 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/1.73m^2). Therefore, the use of pms-VALSARTAN-HCTZ in combination with aliskiren-containing drugs is contraindicated in these patients. Co-administration of ARBs, including pms-VALSARTAN-HCTZ, 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.

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, pms-VALSARTAN-HCTZ 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 Myopia and Secondary Angle-Closure Glaucoma
Hydrochlorothiazide, a sulfonamide, can cause 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 weeks of drug initiation. Untreated acute-angle-closure glaucoma can lead to permanent vision loss.

The primary treatment is to discontinue hydrochlorothiazide as rapidly as possible. Prompt medical or surgical treatments 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

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.

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

Some patients with heart failure have developed increases in blood urea nitrogen, serum creatinine, and potassium. These effects are more likely to occur in patients with pre-existing renal impairment. Dosage reduction and/or discontinuation of pms-VALSARTAN-HCTZ 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.

No dosage adjustment is required for patients with mild to moderate renal impairment (GFR ≥30 mL/min). Because of the hydrochlorothiazide component, pms-VALSARTAN-HCTZ (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 (see CONTRAINDICATIONS). 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 (see CONTRAINDICATIONS).

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

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, pms-VALSARTAN-HCTZ (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 pms-VALSARTAN-HCTZ 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 hydrochlorothiazide at doses of 12.5mg and 25mg (see CLINICAL TRIALS). The table includes all AEs with an incidence of 1% or greater in 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 (HCTZ) 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	HCTZ 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)

	Valsartan/ HCTZ N = 4372	Valsartan N = 2447	HCTZ N = 535	Placebo N = 262
	n (%)	**n (%)**	**n (%)**	**n (%)**
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 320 mg/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 25 mg (9.7%), followed by HCTZ 12.5 mg (6.3%), valsartan/HCTZ 320/25 mg (4.5%), valsartan 320/12.5 mg (3.8%), and valsartan 320 mg (2.0%) compared to placebo (3.1%). Also some patients showed serum potassium increase >20 % but no dose relationship could be demonstrated.

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 320/25 mg (5.5%), followed by valsartan/HCTZ 320/12.5 mg (2.8%), HCTZ 25 mg (2.0%), valsartan 320 mg (1.7%), and HCTZ 12.5 mg (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 in post-marketing use of valsartan alone include: anaphylaxis (very rarely), angioedema (involving swelling of the face, lips and/or tongue), dermatitis bullous (frequency unknown), 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 tablets. It is unknown whether these effects were causally related to the therapy.

Cases of dehydration, dizziness postural, hypoesthesia, pruritus and rhinitis, leucopenia, abdominal pain upper, bronchitis acute, epistaxis, gastroenteritis, hyperhidrosis, neck pain, otitis media, paraesthesia, ligament sprain, hypersensitivity/allergic reactions including serum sickness, non-cardiogenic pulmonary oedema and libido decreased have also been reported.

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

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.

DRUG INTERACTIONS

Drug-Drug Interactions

Table 2: Established or Potential Drug-Drug Interactions for Valsartan

Proper Name	Ref.	Effect	Clinical comment
Agents Increasing Serum Potassium	T	Concomitant use of potassium-sparing diuretics (e.g., spironolactone, triamterene, amiloride), or other drugs that can increase potassium levels (e.g., heparin, non-steroidal anti-inflammatory [NSAID] drugs, trimethoprim-sulfamethoxazole), potassium supplements, or salt substitutes containing potassium, may lead to increases in serum potassium. Concomitant thiazide diuretic use may attenuate any effect that valsartan may have on serum potassium. Since valsartan decreases the production of aldosterone, potassium-sparing diuretics or potassium supplements should be given only for documented hypokalemia and with frequent monitoring of serum potassium. Potassium-containing salt substitutes should also be used with caution.	Monitor serum potassium level.
Lithium	CT, C	Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors, angiotensin II receptor antagonists or thiazides. Since renal clearance of lithium is reduced by thiazides, the risk of lithium toxicity may presumably be increased further with valsartan and hydrochlorothiazide.	Careful monitoring of serum lithium concentrations is recommended during concomitant use.
Non-Steroidal Anti-Inflammatory (NSAID) Drugs, including Selective Cyclooxygenase-2 Inhibitors (COX-2 Inhibitors)	CT	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	Monitoring of renal function is recommended when initiating or modifying the treatment in patients on valsartan who are taking NSAIDs concomitantly.

Proper Name	Ref.	Effect	Clinical comment
		NSAIDs may lead to an increased risk of worsening of renal function.	
OATP1B1 and MRP2 Transporters	T	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.	Monitor blood pressure as per routine.
Warfarin	CT	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).	Interaction is not clinically relevant. Monitor PT as per routine.
Dual blockade of the Renin-Angiotensin-System (RAS) with ARBs, ACEIs, or aliskiren-containing drugs	CT	See WARNINGS AND PRECAUTIONS, General, Dual Blockade of the Renin-Angiotensin System (RAS).	

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

Table 3: Established or Potential Drug-Drug Interactions for Hydrochlorothiazide

Proper Name	Ref.	Effect	Clinical comment
Alcohol, barbiturates, or narcotics	C	Potentiation of orthostatic hypotension may occur.	Avoid alcohol, barbiturates or narcotics, especially with initiation of therapy.
Amantadine	C	Co-administration of thiazide diuretics (including hydrochlorothiazide) may increase the risk of adverse effects caused by amantadine.	Monitor for adverse effects of amantadine.
Amphotericin B	T	Amphotericin B increases the risk of hypokalemia induced by thiazide diuretics	Monitor serum potassium level.
Antidiabetic agents (e.g. insulin and oral hypoglycemic agents)	CT	Thiazide-induced hyperglycemia may compromise blood sugar control. Depletion of serum potassium augments glucose intolerance.	Monitor glycemic control, supplement potassium if necessary, to maintain appropriate serum potassium levels, and adjust diabetes medications as required.
Antihypertensive drugs	CT	Hydrochlorothiazide may potentiate the action of other antihypertensive drugs (e.g. guanethidine, methyldopa, beta-blockers, vasodilators, calcium	

Proper Name	Ref.	Effect	Clinical comment
		channel blockers, ACEI, ARB, and direct renin inhibitors).	
Antineoplastic drugs, including cyclophosphamide and methotrexate	C	Concomitant use of thiazide diuretics may reduce renal excretion of cytotoxic agents and enhance their myelosuppressive effects.	Hematological status should be closely monitored in patients receiving this combination. Dose adjustment of cytotoxic agents may be required.
Bile acid sequestrants, eg. cholestyramine	CT	Bile acid sequestrants bind thiazide diuretics in the gut and impair gastrointestinal absorption by 43-85%. Administration of thiazide 4 hours after a bile acid sequestrant reduced absorption of hydrochlorothiazide by 30-35%.	Give thiazide 2-4 hours before or 6 hours after the bile acid sequestrant. Maintain a consistent sequence of administration. Monitor blood pressure, and increase dose of thiazide, if necessary.
Calcium and vitamin D supplements	C	Thiazides decrease renal excretion of calcium and increase calcium release from bone.	Monitor serum calcium, especially with concomitant use of high doses of calcium supplements. Dose reduction or withdrawal of calcium and/or vitamin D supplements may be necessary.
Carbamazepine	C	Carbamazepine may cause clinically significant hyponatremia. Concomitant use with thiazide diuretics may potentiate hyponatremia.	Monitor serum sodium levels. Use with caution.
Corticosteroids, and adrenocorticotropic hormone (ACTH)	T	Intensified electrolyte depletion, particularly hypokalemia, may occur.	Monitor serum potassium, and adjust medications, as required.
Cyclosporine	C	Concomitant treatment with *cyclosporine* may increase the risk of hyperuricemia and gout-type complications.	Monitor serum uric acid.
Diazoxide	C	Thiazide diuretics may enhance the hyperglycemic effect of diazoxide.	Monitor serum glucose.
Digoxin	CT	Thiazide-induced electrolyte disturbances, i.e. hypokalemia, hypomagnesemia, increase the risk of digoxin toxicity, which may lead to fatal arrhythmic events.	Concomitant administration of hydrochlorothiazide and digoxin requires caution. Monitor electrolytes and digoxin levels closely. Supplement potassium or adjust doses of digoxin or thiazide, as required.
Drugs that alter GI motility, i.e., anticholinergic agents, such as atropine and prokinetic agents, such as metoclopramide, domperidone	CT, T	Bioavailability of thiazide diuretics may be increased by anticholinergic agents due to a decrease in gastrointestinal motility and gastric emptying. Conversely, prokinetic drugs may decrease the bioavailability of thiazide diuretics.	Dose adjustment of thiazide may be required.
Gout medications (allopurinol, uricosurics, xanthine oxidase inhibitors)	T, RCS	Thiazide-induced hyperuricemia may compromise control of gout by allopurinol and probenecid. The	Dosage adjustment of gout medications may be required.

Proper Name	Ref.	Effect	Clinical comment
		co-administration of hydrochlorothiazide and allopurinol may increase the incidence of hypersensitivity reactions to allopurinol.	
Lithium	CT	Thiazide diuretics reduce the renal clearance of lithium and add a high risk of lithium toxicity.	Concomitant use of thiazide diuretics with lithium is generally not recommended. If such use is deemed necessary, reduce lithium dose by 50% and monitor lithium levels closely.
Medicinal products affecting serum potassium level	CT, C	The hypokalemic effect of diuretics may be synergistically 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.
Nonsteroidal anti-inflammatory drugs (NSAID)	CT	NSAID-related retention of sodium and water antagonises the diuretic and antihypertensive effects of thiazides. NSAID-induced inhibition of renal prostaglandins leading to decreases of renal blood flow, along with thiazide-induced decreases in GFR may lead to acute renal failure. Patients with heart failure may be at particular risk.	If combination use is necessary, monitor renal function, serum potassium, and blood pressure closely. Dose adjustments may be required.
Pressor amines (e.g. norepinephrine)	T	Hydrochlorothiazide may reduce the response to pressor amines such as norepinephrine.	The clinical significance of this effect is not sufficient to preclude their use.
Selective serotonin reuptake inhibitors (SSRIs, e.g. citalopram, escitalopram, sertraline)	T, C	Concomitant use with thiazide diuretics may potentiate hyponatremia.	Monitor serum sodium levels. Use with caution.
Skeletal muscle relaxants of the curare family, eg., tubocurare	C	Thiazide drugs may increase the responsiveness of some skeletal muscle relaxants, such as curare derivatives	
Topiramate	CT	Additive hypokalemia. Possible thiazide-induced increase in topiramate serum concentrations.	Monitor serum potassium and topiramate levels. Use potassium supplements, or adjust topiramate dose as necessary.

Legend: C = Case Study; RCS = Retrospective Cohort Study; CT = Clinical Trial; T = Theoretical

Drug-Food Interactions

pms-VALSARTAN-HCTZ may be administered with or 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 pms-VALSARTAN-HCTZ (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, pms-VALSARTAN-HCTZ 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, pms-VALSARTAN-HCTZ 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, pms-VALSARTAN-HCTZ 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, pms-VALSARTAN-HCTZ tablet, 80 mg/12.5 mg, 160 mg/12.5 mg, 160 mg/25 mg, 320 mg/12.5 mg, or 320 mg/25 mg 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.

pms-VALSARTAN-HCTZ 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 antihypertensive therapy. Whenever possible, all diuretics should be discontinued two to three days prior to the administration of pms-VALSARTAN-HCTZ to reduce the likelihood of hypotension (see WARNINGS AND PRECAUTIONS and DRUG INTERACTIONS). If this is not possible because of the patient's condition, pms-VALSARTAN-HCTZ 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/hydrochlorothiazide. Treatment is symptomatic and supportive.

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.

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

ACTION AND CLINICAL PHARMACOLOGY

pms-VALSARTAN-HCTZ (valsartan and hydrochlorothiazide) combines the actions of valsartan, an orally active angiotensin II AT1 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 hydrochlorothiazide have 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 their 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: 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.

Distribution: Valsartan is 94-97% bound to serum protein, mainly serum albumin. The steady-state volume of distribution of valsartan after intravenous administration is about 17 L, indicating that valsartan is not distributed 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 labeled 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.

Hydrochlorothiazide

Absorption: 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.

Distribution: 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.

Metabolism: Hydrochlorothiazide is eliminated predominantly as unchanged drug.

Excretion: 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).

pms-VALSARTAN-HCTZ should be used with particular caution in patients with biliary obstructive disorders. Because of hydrochlorothiazide, pms-VALSARTAN-HCTZ is not recommended in patients with severe hepatic impairment (see Warnings and Precautions, 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, pms-VALSARTAN-HCTZ 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

Store between 15°C and 30°C. Protect from moisture and heat.

SPECIAL HANDLING INSTRUCTIONS

Not applicable.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Tablets

80 mg/12.5 mg: Each pale pink, ovaloid, coated tablet, debossed with "VSH" on one side and "081" on the other side contains 80 mg of valsartan, 12.5 mg of hydrochlorothiazide, and the following non-medicinal ingredients: Colloidal Silicon Dioxide, Crospovidone, Hypromellose, Iron Oxide Red, Iron Oxide Yellow, Magnesium Stearate, Polyethylene Glycol, Powdered Cellulose, Sodium Lauryl Sulfate and Titanium Dioxide. Available in bottles of 100 tablets and blister packs of 30.

160 mg/12.5 mg: Each dark red, ovaloid, coated tablet, debossed with "VSH" on one side and "161" on the other side contains 160 mg of valsartan, 12.5 mg of hydrochlorothiazide and the following non-medicinal ingredients: Colloidal Silicon Dioxide, Crospovidone, Hypromellose, Iron Oxide Red, Magnesium Stearate, Polyethylene Glycol, Powdered Cellulose, Sodium Lauryl Sulfate and Titanium Dioxide. Available in bottles of 100 tablets and blister packs of 30.

160 mg/25 mg: Each yellowish brown, ovaloid, coated tablet, debossed with "VSH" on one side and "162" on the other side contains 160 mg of valsartan, 25 mg of hydrochlorothiazide, and the following non-medicinal ingredients: Colloidal Silicon Dioxide, Crospovidone, Hypromellose, Iron Oxide Black, Iron Oxide Red, Iron Oxide Yellow, Magnesium Stearate, Polyethylene Glycol, Powdered Cellulose, Sodium Lauryl Sulfate and Titanium Dioxide. Available in bottles of 100 tablets and blister packs of 30.

320 mg/12.5 mg: Each pink, ovaloid, coated tablet, debossed with "VSH" on one side and "321" on the other side contains 320 mg of valsartan, 12.5 mg of hydrochlorothiazide, and the following non-medicinal ingredients: Colloidal Silicon Dioxide, Crospovidone, Hypromellose, Iron Oxide Black, Iron Oxide Red, Magnesium Stearate, Polyethylene Glycol, Powdered Cellulose, Sodium Lauryl Sulfate and Titanium Dioxide. Available in bottles of 100 tablets and blister packs of 30.

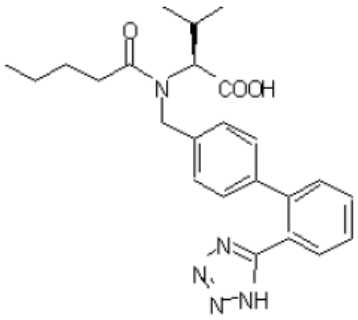
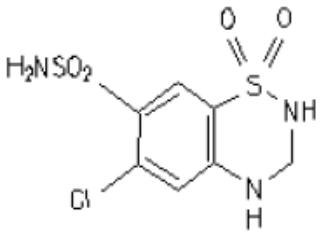
320 mg/25 mg: Each yellow, ovaloid, coated tablet, debossed with "VSH" on one side and "322" on the other side contains 320 mg of valsartan, 25 mg of hydrochlorothiazide, and the following non-medicinal ingredients: Colloidal

Silicon Dioxide, Crospovidone, FD & C Yellow # 6 Aluminum Lake, Hypromellose, Iron Oxide Yellow, Magnesium Stearate, Polyethylene Glycol, Powdered Cellulose, Sodium Lauryl Sulfate and Titanium Dioxide. Available in bottles of 100 tablets and blister packs of 30.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper Names:	
Valsartan	Hydrochlorothiazide
Chemical Names:	
(S)-*N*-valery-*N*-{ [(2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-methyl}-valine.	6-chloro-3,4-dihydro-2*H*-1,2,4-benzo- thiadiazine-7-sulfonamide 1,1-dioxide
Molecular formulae:	
$C_{24}H_{29}N_5O_3$	$C_7H_8ClN_3O_4S_2$
Molecular weights:	
428.53 g/mol	297.72 g/mol
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

Comparative Bioavailability Study

A randomized, single-dose, blinded, 2-period, 2-sequence, crossover comparative bioavailability study between pms-VALSARTAN-HCTZ 160 mg/25 mg tablets (Pharmascience Inc.) versus DIOVAN^{TM}-HCT 160 mg/25 mg tablets (Novartis Pharmaceuticals Canada Inc.) was conducted with forty-one (41) male volunteers under fasting conditions. The objective of this study was to evaluate and compare the relative bioavailability of two different fixed dose combination formulations of valsartan/ hydrochlorothiazide after a single oral dose administration under fasting conditions.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA – VALSARTAN

Valsartan data (1 x 160 mg / 25 mg tablet) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test***	**Reference†**	**% Ratio of Geometric Means**	**90% Confidence Interval**
AUC_T (ng·h/mL)	21118.6 23335.9 (47.4)	22419.7 24048.5 (37.1)	94.20	85.93-103.26
AUC_I (ng·h/mL)	22338.7 24780.3 (49.0)	23498.9 25263.5 (37.9)	95.06	86.69-104.25
C_{max} (ng/mL)	3378.4 3702.8 (45.1)	3660.5 3945.5 (37.3)	92.29	84.07-101.32
T_{max}§ (h)	3.00 (1.00-5.00)	2.50 (0.75-5.00)		
$T_{½}$€ (h)	6.07 (31.5)	5.67 (18.2)		

* pms-VALSARTAN-HCTZ 160 mg/25 mg tablets (Pharmascience Inc.)
† DIOVAN^{TM}-HCT 160 mg/25 mg tablets (Novartis Pharmaceuticals Canada Inc.) were purchased in Canada
§ Expressed as the median (range) only
€ Expressed as the arithmetic mean (CV %) only

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA – HYDROCHLOROTHIAZIDE

Hydrochlorothiazide data (1 x 160 mg / 25 mg tablet) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test***	**Reference†**	**% Ratio of Geometric Means**	**90% Confidence Interval**
AUC_T (ng·h/mL)	955.6 973.72 (20.0)	951.8 969.28 (19.1)	100.40	96.12-104.86
AUC_I (ng·h/mL)	1032.2 1053.5 (21.4)	1021.2 1041.7 (19.9)	101.08	96.76-105.58
C_{max} (ng/mL)	135.3 139.1 (23.8)	140.1 145.3 (27.6)	96.57	89.96-103.67
T_{max}§ (h)	1.67 (1.00-4.00)	1.67 (1.00-3.07)		
$T_{½}$€ (h)	10.91 (19.9)	10.98 (19.2)		

* pms-VALSARTAN-HCTZ 160 mg/25 mg tablets (Pharmascience Inc.)
† DIOVAN™-HCT 160 mg/25 mg tablets (Novartis Pharmaceuticals Canada Inc.) were purchased in Canada
§ Expressed as the median (range) only
€ Expressed as the arithmetic mean (CV %) only

Valsartan and hydrochlorothiazide

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 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.

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.

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.

Species	Route	Duration	Dose (mg/kg)	Major Findings
Rat	Gavage	14 day	60, 200, 600	Mid & High dose groups: increased urea NOEL = 60 mg/kg.

Species	Route	Duration	Dose (mg/kg)	Major Findings
Marmoset	Gavage	14 day	60, 200, 600	High dose group: Vomiting and mild to moderate increase in urea NOEL = 200 mg/kg.
Rat	Intravenous	14 day	10, 30, 100	No adverse findings. NOAEL = 100 mg/kg.
Marmoset	Intravenous	14 day	6, 20, 60	No adverse findings. NOAEL = 60 mg/kg.
Rat	Gavage	91 day	60, 200, 600	Mid & High dose groups: increased 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, 400, 600	Plasma urea & creatinine increase from 200 mg/kg. Nephropathy at 200 & 600 mg/kg. Alk. Phos. increase 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: increased 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: increase 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: Decreased 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; increase in urea. NOAEL > 600:187.5 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; Increase 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), embryotoxicity, fetotoxicity, teratogenicity in rats and mice (600 mg/kg).

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 during lactation showed a slightly reduced survival rate and a slight developmental delay (see WARNINGS AND PRECAUTIONS, Special Populations, Pregnant Women).

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: decrease 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: decreased maternal body weight gain High dose group: decreased 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: increased 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 hydrochlorothiazide:

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 toxicity, decreased food consumption, body weight & weight gain Mid dose & High dose groups: Maternal deaths (3/26 & 11/26), salivation and stool changes and decreased 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: decreased 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
Rabbit	Gavage	Day 7 to 19	1.0 3.0 10.0 --	0.3 0.9 3.1 3.1	All dose groups: Slightly decreased food consumption Mid dose group: Maternal death (1/18) High dose group: increased no. of late resorptions, total resorptions, mean & % post implantation loss; slight decrease in no. of live fetuses. No evidence of teratogenicity 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:

Valsartan has been tested for mutagenicity, clastogenicity, reproductive performance and carcinogenicity with negative results.

***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, TA 1535, 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. 9 body weight gain at ≥10 mg/kg. No carcinogenic effect
Rat	Diet	2 years	10, 50, 200	Decreased body weight gain, anemia, nephropathy at ≥ 50 mg/kg. Increased urea and creatinine, decreased total proteins and albumin at 200 mg/kg. No carcinogenic effect.

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11. DIOVAN^{TM}-HCT (Valsartan and Hydrochlorothiazide Tablets) Product Monograph (Novartis Pharmaceutical Canada Inc.), Revision date: May 12, 2015, Control No: 181891.

PART III: CONSUMER INFORMATION

[Pr]pms-VALSARTAN-HCTZ
Valsartan and Hydrochlorothiazide Tablets, USP
80 mg/12.5 mg, 160 mg/12.5 mg, 160 mg/25 mg, 320 mg/12.5 mg & 320 mg/25 mg

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

ABOUT THIS MEDICATION

What the medication is used for:
pms-VALSARTAN-HCTZ lowers high 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:
pms-VALSARTAN-HCTZ contains a combination of 2 drugs, valsartan and hydrochlorothiazide:

- Valsartan is an angiotensin receptor blocker (ARB). You can recognize an ARB because its medicinal ingredient ends in "-SARTAN". It lowers blood pressure. pms-VALSARTAN-HCTZ does this 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.

- Hydrochlorothiazide is a diuretic or "water pill" that increases urination. This lowers blood pressure.

Together valsartan and hydrochlorothiazide lower blood pressure.

This medicine does not cure high blood pressure. It helps to control it. Therefore, it is important to continue taking pms-VALSARTAN-HCTZ regularly even if you feel fine.

If you have any questions about how pms-VALSARTAN-HCTZ works or why this medicine has been prescribed for you, ask your doctor.

When it should not be used:
Do not take **pms-VALSARTAN-HCTZ** if you:

- Are allergic to valsartan, hydrochlorothiazide or to any non-medicinal ingredient in the formulation.
- Are allergic to any sulfonamide-derived drugs (sulfa drugs); most of them have a medicinal ingredient that ends in "-**MIDE**". Ask your physician or pharmacist if you are not sure what sulfonamide-derived drugs are.
- 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.
- Have difficulty urinating or produce no urine.
- 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 taking a medicine that contains aliskiren **and** you have diabetes or kidney disease.
- Are pregnant or intend to become pregnant. Taking pms-VALSARTAN-HCTZ during pregnancy can cause injury and even death to your baby.
- Are breastfeeding. pms-VALSARTAN-HCTZ passes into breast milk.
- 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 under 18 years old.

If either of these applies to you, **tell your doctor without taking pms-VALSARTAN-HCTZ.**

What the medicinal ingredients are:
Valsartan and Hydrochlorothiazide

What the nonmedicinal ingredients are:
Colloidal silicon dioxide, crospovidone, magnesium stearate, powdered cellulose and sodium lauryl sulfate. The coating of the tablets contains:
80 mg/12.5 mg: hypromellose, iron oxide red, iron oxide yellow, polyethylene glycol and titanium dioxide.
160 mg/12.5 mg: hypromellose, iron oxide red, polyethylene glycol and titanium dioxide.
160 mg/25 mg: hypromellose, iron oxide black, iron oxide red, iron oxide yellow, polyethylene glycol and titanium dioxide.
320 mg/12.5 mg: hypromellose, iron oxide black, iron oxide red, polyethylene glycol and titanium dioxide.
320 mg/25 mg: FD & C yellow # 6 Aluminum Lake, hypromellose, iron oxide yellow, polyethylene glycol and titanium dioxide.

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

What dosage forms it comes in:
Tablets: 80 mg /12.5 mg (pale pink), 160 mg/12.5 mg (dark red), 160 mg/25 mg (yellowish brown), 320 mg/12.5 mg (pink), 320 mg/25 mg (yellow).

WARNINGS AND PRECAUTIONS

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

BEFORE you use pms-VALSARTAN-HCTZ talk to your doctor, nurse, or pharmacist if you:

- Are allergic to any drug used to lower blood pressure, including angiotensin converting enzyme (ACE) inhibitors, or penicillin.
- Have narrowing of an artery or a heart valve.
- Have heart failure.
- Have diabetes, liver or kidney disease.
- Have lupus or gout.
- 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").
- Are on a low-salt diet.
- Are less than 18 years old.
- 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);
- Ever had swelling mainly of the face and throat while taking other drugs (including an ACE-inhibitor). If you get those symptoms, **stop taking pms-VALSARTAN-HCTZ and contact your doctor straight away. You should never take pms-VALSARTAN-HCTZ again;**
- 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 diarrhea, or taking high doses of a diuretic (water pill);
- Are taking a medicine that contains aliskiren used to lower high blood pressure. The combination with pms-VALSARTAN-HCTZ is not recommended.
- Are taking an angiotensin converting enzyme (ACE) inhibitor.

Hydrochlorothiazide in pms-VALSARTAN-HCTZ can cause Sudden Eye Disorders:

- **Myopia:** sudden nearsightedness or blurred vision.
- **Glaucoma:** an increased pressure in your eyes, eye pain. Untreated, it may lead to permanent vision loss.

These eye disorders are related and can develop within hours to weeks of starting pms-VALSARTAN-HCTZ.

You may become sensitive to the sun while taking pms-VALSARTAN-HCTZ. Exposure to sunlight should be minimized until you know how you respond.

You should have regular blood tests before and during treatment with pms-VALSARTAN-HCTZ. 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 pms-VALSARTAN-HCTZ 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 pms-VALSARTAN-HCTZ, contact immediately your doctor.
It is also advisable not to take pms-VALSARTAN-HCTZ during breast-feeding. The diuretic component of pms-VALSARTAN-HCTZ passes into the breast milk and may also reduce your milk supply. If you are breast-feeding, avoid using pms-VALSARTAN-HCTZ 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 pms-VALSARTAN-HCTZ during pregnancy.

Driving and using machines:
Before you perform tasks which may require special attention, wait until you know how you respond to pms-VALSARTAN-HCTZ. Dizziness, light-headedness, 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 medicines you take, including drugs prescribed by other doctors, vitamins, minerals, natural supplements, or alternative 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 pms-VALSARTAN-HCTZ, as there may be a sudden drop in blood pressure associated with general anesthesia.

The following may interact with pms-VALSARTAN-HCTZ:

- Alcohol, barbiturates (sleeping pills), or narcotics (strong pain medications). They may cause low blood pressure and dizziness when you go from lying or sitting to standing up.
- Amphotericin B, an antifungal drug.
- Anticancer drugs, including cyclophosphamide and methotrexate.
- Antidepressants, in particular selective serotonin reuptake inhibitors (SSRIs), including citalopram, escitalopram, and sertraline.
- Antidiabetic drugs, including insulin and oral medicines.
- Bile acid resins used to lower cholesterol.
- Other blood pressure lowering drugs, including ACE inhibitors or aliskiren.
- Calcium or vitamin D supplements.
- Corticosteroids used to treat joint pain and swelling.
- Digoxin, a heart medication, or other digitalis glycosides.
- Drugs that slow down or speed up bowel function, including atropine, metoclopramide, and domperidone.
- Drugs used to treat epilepsy, including carbamazepine and topiramate.
- Gout medications, including allopurinol and probenecid.
- Lithium, antipsychotics, medicines used to treat some psychological conditions such as bipolar disease.
- Nonsteroidal anti-inflammatory drugs (NSAIDs), used to reduce pain and swelling. Examples include ibuprofen, naproxen, and celecoxib.
- Skeletal muscle relaxants used to relieve muscle spasms, including tubocurare.
- Other diuretics (water pills),
- Pressor amines such as epinephrine (substances that raise blood pressure),
- Potassium-sparing agents
- Potassium supplement, salt substitutes containing potassium or other drugs that may increase potassium levels. Your doctor may monitor the levels of potassium in your blood periodically,
- Some antibiotics (rifamycin group), a drug used to protect against transplant rejection (cyclosporine) or an antiretroviral drug used to treat HIV/AIDS infection (ritonavir). These drugs may increase the effect of pms-VALSARTAN-HCTZ.
- Amantadine (medicine to treat Parkinson's disease and also used to treat or prevent certain illnesses caused by viruses),
- Anticholinergic 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)
- Cortisone-like medicines, carbenoxolone (a medicine used to treat ulceration and inflammation), antibiotics such as penicillin G, antiarrhythmics (medicines used to treat heart problems),
- Cyclosporine (a medicine used in transplantation and in autoimmune disorders)
- Warfarin (medicine to prevent blood clot)
- Diazoxide (medicine to increase blood glucose level)

Taking carbamazepine with hydrochlorothiazide (a medicinal ingredient in pms-VALSARTAN-HCTZ) 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 pms-VALSARTAN-HCTZ, so tell your physician or pharmacist if you are taking any of these.

PROPER USE OF THIS MEDICATION

Take pms-VALSARTAN-HCTZ exactly as prescribed. It is recommended to take your dose at about the same time every day.

pms-VALSARTAN-HCTZ can be taken with or without food. If pms-VALSARTAN-HCTZ causes upset stomach, take it with food or milk.

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.

If you have any questions about how long to take pms-VALSARTAN-HCTZ, talk to your doctor or your pharmacist.

Usual Adult dose:
Take pms-VALSARTAN-HCTZ as directed. Dosage must be individualized. pms-VALSARTAN-HCTZ is not for initial therapy. Once you are stabilized on both individual components of pms-VALSARTAN-HCTZ the usual dosage is one 80 mg/12.5 mg tablet once a day. In some cases, your doctor may prescribe a higher dose (e.g., the 160 mg/12.5 mg, 160 mg/25 mg, 320 mg/12.5 mg or the 320 mg/25 mg tablet).

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

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

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

Side effects may include:

- back or leg pain, muscle cramps, spasms and pain, weakness, restlessness
- dizziness, pins and needles in your fingers, headache
- constipation, diarrhea, nausea, vomiting, decreased appetite, upset stomach, enlargement of the glands in your mouth
- bleeding under the skin, rash, red patches on the skin
- drowsiness, insomnia
- reduced libido
- joint pain
- Cough
- Fatigue (unusual tiredness or weakness, sometimes sign of potassium loss)
- Upper respiratory tract infection
- Blistering skin (sign of dermatitis bullous)

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

- pms-VALSARTAN-HCTZ 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 help
		Only if severe	In all cases	
Common	*Allergic reactions:* Skin rash, skin eruption or other effect on the skin or eyes			✓
	Low Blood Pressure: Dizziness, fainting, light-headedness may occur when you go from lying or sitting to standing up.	✓		
	Decreased or increased levels of potassium in the blood: irregular heartbeats, muscle weakness and generally feeling unwell		✓	
Uncommon	*Allergic Reaction:* rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			✓
	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 appetite		✓	

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 help
		Only if severe	In all cases	
	Increased blood sugar: frequent urination, thirst, and hunger	✓		
	Electrolyte Imbalance: weakness, drowsiness, muscle pain or cramps, irregular heartbeat		✓	
	Abdominal pain		✓	
Rare	*Rhabdomyolysis*: muscle pain that you cannot explain, muscle tenderness or weakness, dark brown urine		✓	
	Decreased White Blood Cells: infections, fatigue, fever, aches, pains, and flu-like symptoms		✓	
	Decreased Platelets: bruising, bleeding, fatigue and weakness		✓	
Very rare	*Toxic Epidermal Necrolysis:* severe skin peeling, especially in mouth and eyes			✓
Unknown	*Eye disorders:* - Myopia: sudden near sightedness or blurred vision - Glaucoma: increased pressure in your eyes, eye pain			✓
	Anemia: fatigue, loss of energy, weakness, shortness of breath.		✓	
	Inflammation of the Pancreas: abdominal pain that lasts and gets worse when you lie down, nausea, vomiting		✓	
	Blistering skin reactions with symptoms such as rash, red skin, blistering of the lips, eyes or mouth, skin peeling and fever			✓
Rare or very rare	Possible signs of a blood disorder (symptoms like sore throat, fever, or chills)			✓
	Jaundice: yellow eyes or skin			✓
	Irregular heart beat		✓	
	Necrotizing vasculitis; (Inflammation of vessels	✓		

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 help
		Only if severe	In all cases	
	with or without pain)			
	Tiredness, confusion, muscle twitching, convulsions (possible symptoms of hypernatremia)			✓
	Respiratory problems including pneumonitis and pulmonary edema			✓
	Bone marrow failure, aplastic anemia: (Weakness, bruising and frequent infections)	✓		

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

HOW TO STORE IT

Store your pms-VALSARTAN-HCTZ tablets in a dry place at room temperature (15°C-30°C). Protect from moisture and heat.

Do not take pms-VALSARTAN-HCTZ 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 out of 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 Pharmascience Inc. at 1-888-550-6060.

This leaflet was prepared by
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