PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrDIOVAN-HCT®

valsartan and hydrochlorothiazide tablets

Tablets, 80mg/12.5mg, 160mg/12.5mg, 160 mg/25 mg

320mg/12.5mg and 320mg/25mg tablets, Oral

Angiotensin II AT1 Receptor Blocker and Diuretic

Novartis Pharmaceuticals Canada Inc.

700 Saint-Hubert St., Suite 100

Montreal, Quebec

H2Y 0C1

www.novartis.ca

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RECENT MAJOR LABEL CHANGES

7 WARNINGS AND PRECAUTIONS, Driving and Operating Machinery	1/2023
7 WARNINGS AND PRECAUTIONS, Ophthalmologic	1/2023
7 WARNINGS AND PRECAUTIONS, Respiratory	1/2023
9.1 Serious Drug Interactions	1/2023

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

DIOVAN-HCT® (valsartan and hydrochlorothiazide tablets) is indicated for:

- the treatment of mild to moderate essential hypertension in patients for whom combination therapy is appropriate.

DIOVAN-HCT is not indicated for initial therapy (see 4 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 DIOVAN-HCT may be more convenient in the management of patients. If during maintenance therapy dosage adjustment is necessary it is advisable to use the individual drugs.

1.1 Pediatrics (< 18 years of age):

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

1.2 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.

2 CONTRAINDICATIONS

- DIOVAN-HCT is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container (see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING).
- Because of the hydrochlorothiazide component, it is also contraindicated in patients with anuria, severe progressive renal disease and if increasing azotemia and oliguria occur during treatment.
- Patients who are hypersensitive to other sulfonamide-derived drugs.
- DIOVAN-HCT is also contraindicated in pregnant and nursing women (see 7.1.2 Breast-feeding).
- 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 7 WARNINGS AND PRECAUTION-Cardiovascular- Dual Blockade of the Renin-Angiotensin System (RAS) and Renal and 9.4 Drug-Drug Interactions-Dual Blockade of the Renin-Angiotensin-System (RAS) with ARBs, ACEIs, or aliskiren)

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions
• Pregnancy: **angiotensin receptor (AT_1) blockers (ARB)** can cause injury to or even death of the developing fetus. When pregnancy is detected, DIOVAN-HCT should be discontinued as soon as possible (see 2 CONTRAINDICATIONS and 7.1 Special Populations).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

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

- **Hepatic Impairment**

No initial dosage adjustment in valsartan is required in patients with mild to moderate hepatic impairment. Due to the hydrochlorothiazide component, DIOVAN-HCT is not recommended in patients with severe hepatic impairment (see 7 Warnings and Precautions). Because thiazide diuretics may precipitate hepatic coma, care should be exercised when administering a fixed combination product containing hydrochlorothiazide (see 7 WARNINGS AND PRECAUTIONS). Due to the valsartan component, DIOVAN-HCT should be used with particular caution in patients with biliary obstructive disorders (see 2 Contraindications and 7 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/1.73m^2). Due to the hydrochlorothiazide component, DIOVAN-HCT is contraindicated in patients with severe renal impairment (creatinine clearance < 30 mL/min/1.73m^2) and with anuria (see 2 Contraindications) and should be used with caution in patients with severe renal impairment (GFR <30 mL/min/1.73m^2) (see 7 Warnings and precautions and 10.3 Pharmacokinetics).

- **Elderly**

No dosage adjustment is usually necessary however see 7 WARNINGS AND PRECAUTIONS.

4.2 Recommended Dose and Dosage Adjustment

Once the patient has been stabilized on the individual components as described below, DIOVAN-HCT tablet, 80mg/12.5mg, 160mg/12.5mg, 160 mg/25, 320mg/12.5mg, or 320mg/25mg once daily may be substituted if the doses on which the patient was stabilized are the same as those in the fixed combination (see 1 INDICATIONS and 7 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.

DIOVAN-HCT may be administered with or without food, however it should be taken consistently with respect to food intake.

- **Valsartan monotherapy**

The recommended starting dose of DIOVAN is 80 mg once daily. The antihypertensive effect is present within 2 weeks and maximal reduction is usually attained within 4 weeks following initiation of therapy. In patients whose blood pressure is not adequately controlled, the daily dose may be increased to a maximum of 320 mg or a thiazide diuretic added.

- **Diuretic-Treated Patients**

In patients receiving diuretics, valsartan therapy should be initiated with caution, since these patients may be volume-depleted and thus more likely to experience hypotension following initiation of additional anti-hypertensive therapy. Whenever possible, all diuretics should be discontinued two to three days prior to the administration of DIOVAN-HCT to reduce the likelihood of hypotension (see 7 WARNINGS AND PRECAUTIONS and 9 DRUG INTERACTIONS). If this is not possible because of the patient's condition, DIOVAN-HCT should be administered with caution and the blood pressure monitored closely. Thereafter, the dosage should be adjusted according to the individual response of the patient.

4.5 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.

5 OVERDOSAGE

No specific information is available on the treatment of overdosage with DIOVAN-HCT. Treatment is symptomatic and supportive.

For management of a suspected drug overdose, contact your regional poison control centre.

Valsartan

Limited data are available in regard to overdosage with DIOVAN (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.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Tablets: 80mg/12.5mg 160mg/12.5mg 160mg/25mg 320mg/12.5mg 320mg/25mg valsartan and hydrochlorothiazide	Colloidal silicon dioxide, crospovidone, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, talc, and titanium dioxide. Additional nonmedicinal ingredients for: DIOVAN-HCT 80/12.5 mg tablets: red iron oxide and yellow iron oxide. DIOVAN-HCT 160/12.5 mg tablets: red iron oxide. DIOVAN-HCT 160/25 mg tablets: black iron oxide, red iron oxide and yellow iron oxide. DIOVAN-HCT 320/12.5 mg tablets: black iron oxide and red iron oxide. DIOVAN-HCT 320/25 mg tablets: yellow iron oxide.

Description

DIOVAN-HCT tablets, 80mg/12.5mg: Each light orange, ovaloid, film-coated tablet imprinted with HGH on one side and CG on the other. These are supplied in cartons containing 2 blister strips of 14 tablets.

DIOVAN-HCT tablets, 160mg/12.5mg: Each dark red, ovaloid, film-coated tablet imprinted with HHH on one side and CG on the other. These are supplied in cartons containing 2 blister strips of 14 tablets.

DIOVAN-HCT tablets, 160mg/25mg: Each brown, ovaloid, film-coated tablet imprinted with HXH on one side and NVR on the other. These are supplied in cartons containing 2 blister strips of 14 tablets.

DIOVAN-HCT tablets, 320mg/12.5mg: Each pink, ovaloid, film coated tablet imprinted with "NVR" on one side and "HIL" on the other. These are supplied in cartons containing 2 blister strips of 14 tablets.

DIOVAN-HCT tablets, 320mg/25mg: Each yellow, ovaloid, film coated tablet imprinted with "NVR" on one side and "CTI" on the other. These are supplied in cartons containing 2 blister strips of 14 tablets.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

General

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. DIOVAN-HCT should be immediately discontinued in patients who develop angioedema, and DIOVAN-HCT should not be re-administered.

If laryngeal stridor or angioedema of the face, extremities, lips, tongue, or glottis occurs, DIOVAN-HCT 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 8.5 Post Market Adverse Reactions).

Patients with a known hypersensitivity (anaphylaxis) or angioedema to ARBs should not be treated with DIOVAN-HCT (see 8.5 Post Market Adverse Reactions).

Carcinogenesis and Mutagenesis

Non-melanoma skin cancer

An increased risk of non-melanoma skin cancer (NMSC) [basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) of the skin] after hydrochlorothiazide therapy was reported in some epidemiological studies. The risk may be higher with increasing cumulative use. The certainty of the evidence was assessed by Health Canada (see 8.5 Post Market Adverse Reactions). The photosensitizing action of hydrochlorothiazide may be a possible mechanism for NMSC (see 16 NON-CLINICAL TOXICOLOGY, Carcinogenicity – Hydrochlorothiazide).

Patients taking hydrochlorothiazide should be informed of the potential risk of NMSC. They should be advised to regularly check their skin for new lesions as well as changes to existing ones, and to promptly report any suspicious skin lesions. Patients should also be advised to limit exposure to sunlight, to avoid the use of indoor tanning equipment, and to use adequate

protection (e.g. a broad spectrum sunscreen with a SPF of 30 or higher, clothing, and a hat) when exposed to sunlight or UV light to minimize the risk of skin cancer.

Alternatives to hydrochlorothiazide may be considered for patients who are at a particularly high risk for NMSC (e.g., light coloured skin, known personal or family history of skin cancer, ongoing immunosuppressive therapy, etc.) (see 8.5 Post Market Adverse Reactions).

Photosensitivity

Photosensitivity reactions have been reported with the use of thiazide diuretics.

If photosensitivity reactions occur during treatment with hydrochlorothiazide-containing drugs, treatment should be stopped.

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<60ml/min/1.73m^2). Therefore, the use of DIOVAN-HCT in combination with aliskiren-containing drugs is contraindicated in these patients. Co-administration of ARBs, including DIOVAN-HCT, 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.

Driving and Operating Machinery

Exercise caution when driving or operating a vehicle or potentially dangerous machinery.

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 2 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, DIOVAN-HCT should not be used (not recommended) in patients with severe hepatic impairment (see 4 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 10.3 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

Choroidal Effusion, Acute Myopia and Secondary Angle-Closure Glaucoma

Hydrochlorothiazide, a sulfonamide, can cause an idiosyncratic reaction, resulting in choroidal effusion, acute transient myopia and/or acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity, blurred vision 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 8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data). 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 9 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 DIOVAN-HCT 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/1.73m^2). Because of the hydrochlorothiazide component, DIOVAN-HCT (valsartan and hydrochlorothiazide) should not be used in patients with severe renal impairment (GFR<30 mL/min/1.73m^2). Thiazide diuretics may precipitate azotemia in patients with chronic kidney disease (see 2 CONTRAINDICATIONS). They are ineffective as monotherapy in severe renal impairment (GFR<30 mL/min/1.73m^2) (see 4 DOSAGE AND ADMINISTRATION-renal impairment, and 10.3 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 2 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 2 CONTRAINDICATIONS and 9.4 Drug-Drug Interactions-Dual Blockade of the Renin-Angiotensin-System (RAS) with ARBs, ACEIs, or aliskiren-containing drugs).

Respiratory

Acute Respiratory Distress

Severe cases of acute respiratory toxicity, including acute respiratory distress syndrome (ARDS), have been reported after taking hydrochlorothiazide. Pulmonary edema typically develops within minutes to hours after hydrochlorothiazide intake. At the onset, symptoms can include dyspnea, fever, pulmonary deterioration and hypotension. If diagnosis of ARDS is suspected, DIOVAN-HCT should be withdrawn, and appropriate treatment should be given. DIOVAN-HCT must not be administered to patients who previously experienced ARDS following intake of hydrochlorothiazide or another thiazide diuretic.

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.

7.1 Special Populations

7.1.1 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, DIOVAN-HCT 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.

7.1.2 Breast-feeding

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.

7.1.3 Pediatrics

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

7.1.4 Geriatrics

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.

8 ADVERSE REACTIONS

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

DIOVAN-HCT has been evaluated for safety in more than 7616 patients treated for essential hypertension. Of these, 4372 were treated with DIOVAN-HCT 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 DIOVAN-HCT and placebo, respectively. The most common AEs resulting in discontinuation of therapy with DIOVAN-HCT were dizziness and headache.

The most common serious AEs with DIOVAN-HCT were myocardial infarction and chest pain.

The following table is based on double-blind, active or placebo-controlled trials in patients treated with DIOVAN-HCT at doses of 80mg/12.5mg, 80mg/25mg, 160mg/12.5mg, 160mg/25mg, 320mg/12.5mg and 320mg/25mg, DIOVAN at doses of 80mg, 160mg, and 320 mg, and HCT at doses of 12.5mg and 25mg (see14 CLINICAL TRIALS). The table includes all AEs

with an incidence of 1% or greater in either the DIOVAN-HCT, DIOVAN monotherapy, HCT monotherapy, or placebo group, irrespective of causal relationship to study drug.

Table 2 - Occurrence of adverse events during double-blind controlled trials in patients treated with DIOVAN-HCT at doses of 80mg/12.5mg, 80mg/25mg, 160mg/12.5mg, 160mg/25mg, 320mg/12.5mg and 320mg/25mg.

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

Musculoskeletal and connective tissue disorders				
Back pain	52 (1.2)	37 (1.5)	11 (2.1)	7 (2.7)
Arthralgia	44 (1.0)	25 (1.0)	8 (1.5)	3 (1.1)
Myalgia	25 (0.6)	15 (0.6)	6 (1.1)	1 (0.4)
Pain in extremity	21 (0.5)	10 (0.4)	11 (2.1)	0 (0.0)
Muscle cramp	18 (0.4)	3 (0.1)	10 (1.9)	3 (1.1)
Nervous system disorders				
Headache	161 (3.7)	126 (5.1)	54 (10.1)	38 (14.5)
Dizziness	153 (3.5)	49 (2.0)	27 (5.0)	10 (3.8)
Somnolence	11 (0.3)	8 (0.3)	1 (0.2)	3 (1.1)
Hypoaesthesia	10 (0.2)	5 (0.2)	2 (0.4)	4 (1.5)
Sinus headache	4 (0.1)	7 (0.3)	3 (0.6)	3 (1.1)
Migraine	2 (0.0)	7 (0.3)	0 (0.0)	4 (1.5)
Psychiatric disorders				
Insomnia	16 (0.4)	12 (0.5)	3 (0.6)	3 (1.1)
Renal and urinary disorders				
Pollakiuria	30 (0.7)	11 (0.4)	8 (1.5)	2 (0.8)
Respiratory, thoracic and mediastinal disorders				
Cough	52 (1.2)	37 (1.5)	11 (2.1)	2 (0.8)
Pharyngolaryngeal pain	30 (0.7)	12 (0.5)	6 (1.1)	1 (0.4)
Sinus congestion	19 (0.4)	7 (0.3)	12 (2.2)	3 (1.1)
Nasal congestion	16 (0.4)	14 (0.6)	7 (1.3)	0 (0.0)
Skin and subcutaneous tissue disorders				
Rash	11 (0.3)	10 (0.4)	6 (1.1)	1 (0.4)

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

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

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

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

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

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

8.3 Less Common Clinical Trial Adverse Reactions

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

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

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

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 DIOVAN-HCT and 0.4% and 6.3%, respectively, of patients given placebo in controlled clinical trials. Uric acid increase of > 50% was observed most frequently with valsartan/HCTZ 320/25mg (5.5%), followed by valsartan/HCTZ 320/12.5mg (2.8%), HCTZ 25mg (2.0%), valsartan 320mg (1.7%), and HCTZ 12.5mg (0.8%) compared to placebo (1.6%).

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

Neutropenia: Neutropenia was observed in 0.1% of patients treated with DIOVAN-HCT and 0.4% of patients treated with placebo.

8.5 Post-Market Adverse Reactions

Other adverse reactions reported in post-marketing use of DIOVAN 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.

Non-melanoma skin cancer: Some pharmacoepidemiological studies have suggested a higher risk of squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) of the skin with increasing use of hydrochlorothiazide. A systematic review and meta-analysis undertaken by Health Canada suggested, with important uncertainty, that the use of hydrochlorothiazide for several years (>3 years) could lead to:

- 122 additional cases (95% CI, from 112 to 133 additional cases) of SCC per 1000 treated patients compared with non-use of hydrochlorothiazide (meta-analysis of 3 observational studies);
- 31 additional cases (95% CI, from 24 to 37 additional cases) of BCC per 1000 treated patients compared with non-use of hydrochlorothiazide (meta-analysis of 2 observational studies).

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 DIOVAN-HCT. It is unknown whether these effects were causally related to the therapy.

Cases of dehydration, dizziness postural, hypoesthesia, prutitus 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.

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

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 <60 ml/min/1.73m^2) is contraindicated. (See 9.4 Drug-Drug Interactions-Dual Blockade of the Renin-Angiotensin-System (RAS) with ARBs, ACEIs, or aliskiren)

9.4 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 3 – Established or Potential Drug-Drug Interactions for valsartan

Proper Name	Source of evidence	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.	Monitor serum potassium level.

Proper Name	Source of evidence	Effect	Clinical comment
		Since valsartan decreases the production of aldosterone, potassium-sparing diuretics or potassium supplements should be given only for documented hypokalemia and with frequent monitoring of serum potassium. Potassium-containing salt substitutes should also be used with caution.	
Lithium	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 DIOVAN-HCT.	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 NSAIDs may lead to an increased risk of worsening of renal function.	Monitoring of renal function is recommended when initiating or modifying the treatment in patients on valsartan who are taking NSAIDs concomitantly.
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.

Proper Name	Source of evidence	Effect	Clinical comment
Dual blockade of the Renin-Angiotensin-System (RAS) with ARBs, ACEIs, or aliskiren-containing drugs	CT	See WARNINGS AND PRECAUTIONS-Cardiovascular-Dual Blockade of the Renin-Angiotensin System (RAS).	

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

Table 4 – Established or Potential Drug-Drug Interactions for hydrochlorothiazide

Proper Name	Source of evidence	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 channel blockers, ACEI, ARB, and direct renin inhibitors).	
Antineoplastic drugs, including cyclophosphami	C	Concomitant use of thiazide diuretics may reduce renal excretion of cytotoxic agents and	Hematological status should be closely

Proper Name	Source of evidence	Effect	Clinical comment
de and methotrexate		enhance their myelosuppressive effects.	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	Concomitant administration of hydrochlorothiazide and digoxin requires caution. Monitor electrolytes and digoxin levels closely.

Proper Name	Source of evidence	Effect	Clinical comment
		of digoxin toxicity, which may lead to fatal arrhythmic events.	Supplement potassium or adjust doses of digoxin or thiazide, as required.
Drugs that alter GI motility, i.e., anti-cholinergic 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 co-administration of hydrochlorothiazide and allopurinol may increase the incidence of hypersensitivity reactions to allopurinol.	Dosage adjustment of gout medications may be required.
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 synergetically aggravated by concomitant administration of kaliuretic diuretics, corticosteroids, ACTH, amphotericin, carbenoxolone, penicillin G, salicylic acid derivatives or antiarrhythmics, β2-agonists, pseudoephedrine, ephedrine, chloroquine, and antibiotics.	Monitoring of serum electrolyte balance is recommended. Simultaneous administration of potassium supplements may be necessary.
Nonsteroidal anti-inflammatory drugs (NSAID)	CT	NSAID-related retention of sodium and water antagonises the diuretic and antihypertensive effects of thiazides.	If combination use is necessary, monitor renal function, serum potassium, and blood pressure closely.

Proper Name	Source of evidence	Effect	Clinical comment
		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.	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

9.5 Drug-Food Interactions

DIOVAN-HCT may be administered with or without food, however it should be taken consistently with respect to food intake (see 4 DOSAGE AND ADMINISTRATION).

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

DIOVAN-HCT (valsartan and hydrochlorothiazide) combines the actions of valsartan, an orally active angiotensin II AT_1 receptor blocker, and that of a diuretic, hydrochlorothiazide.

10.1 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.

10.2 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 DIOVAN-HCT 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 DIOVAN-HCT 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 DIOVAN-HCT had no clinically significant effect on heart rate.

10.3 Pharmacokinetics

Valsartan

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

Absorption: 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.

Elimination: 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.

Elimination: 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.

- **Sex:** 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 7 WARNINGS AND PRECAUTIONS, and 4 DOSAGE AND ADMINISTRATION). DIOVAN-HCT should be used with particular caution in patients with biliary obstructive disorders. Because of hydrochlorothiazide, DIOVAN-HCT is not recommended in patients with severe hepatic impairment (see 7 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, DIOVAN-HCT is not recommended for use in patients with severe renal impairment (creatinine clearance < 30 mL/min).
  Valsartan is not removed from plasma by dialysis.

11 STORAGE, STABILITY AND DISPOSAL

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

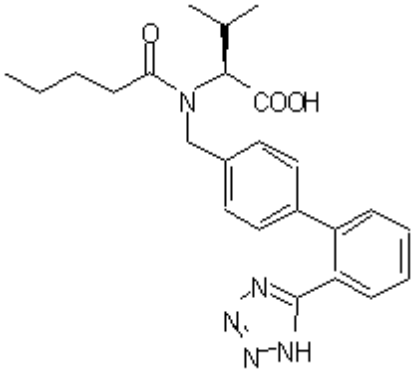
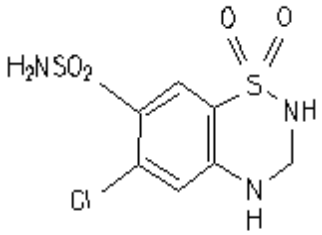
12 SPECIAL HANDLING INSTRUCTIONS

Not applicable.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper Names:	
valsartan	hydrochlorothiazide
Chemical Names:	
(*S*)-*N*-valeryl-*N*-{[2'-(1H-tetrazol-5-yl) biphenyl-4-yl] methyl}-valine	6-chloro-3,4-dihydro-2*H*-1,2,4-benzothiazidine-7-sulfonamide 1,1-dioxide
Molecular formulae:	
$C_{24}H_{29}N_5O_3$	$C_7H_8ClN_3O_4S_2$
Molecular mass:	
435.5	297.74
Structural formula:	
	
Physicochemical properties:	
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.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Hypertension

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.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

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.

General 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: ↑ urea NOEL = 60 mg/kg.
Marmoset	Gavage	14 day	60, 200, 600	High dose group: Vomiting and mild to moderate ↑ in urea NOEL = 200 mg/kg.

Species	Route	Duration	Dose mg/kg	Major findings
Rat	Intra-venous	14 day	10, 30, 100	No adverse findings. NOAEL = 100 mg/kg.
Marmoset	Intra-venous	14 day	6, 20, 60	No adverse findings. NOAEL = 60 mg/kg.
Rat	Gavage	91 day	60, 200, 600	Mid & High dose groups: ↑ urea High dose group: Renal tubular hyperplasia, glomerular arteriolar hypertrophy. Anemia with regenerative response. NOEL = 60 mg/kg.
Marmoset	Gavage	91 day	30, 60, 200, 600□400	Plasma urea & creatinine ↑ from 200 mg/kg. Nephropathy at 200 & 600 mg/kg. Alk. Phos. ↑ at 400 mg/kg. Anemia from 200 mg/kg. Hypertrophy of glomerular arteriole at 400 mg/kg. Adrenal cortex hypertrophy from 200 mg/kg in F. Cachexia including 3 deaths at 600 mg/kg. One death at 200 mg/kg. One death at 400 mg/kg during the recovery period. NOEL = 60 mg/kg.
Rat	Gavage	12 months	20, 60, 200	Mid dose group: ↑ urea at 60 mg/kg High dose group: anemia & renal arteriolar hypertrophy. NOAEL = 20 mg/kg.
Marmoset	Gavage	12 months	12, 40, 120	Mid & High dose groups: ↑ in urea and creatinine NOAEL = 12 mg/kg.

NOEL No observable effect level.

NOAEL No observable adverse effect level.

Valsartan and hydrochlorothiazide

The combination of valsartan/hydrochlorothiazide was evaluated for toxicity in the rat and marmoset for up to 6 months. Treatment-related findings were mainly related to the exaggerated pharmacological effects of valsartan and/or hydrochlorothiazide and consisted of reduction in red cells parameters, alterations in electrolyte and water concentrations in the

body, hypertrophy of the juxtaglomerular apparatus and renal tubular changes. The marmoset was a much more sensitive species in which there was an approximate 10-fold potentiation of blood pressure reduction with the combination of valsartan and hydrochlorothiazide as compared to valsartan alone. Hydrochlorothiazide alone had no effect on the blood pressure of marmosets. This potentiation has not been seen in the human subject; the effect of valsartan and hydrochlorothiazide is additive.

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

Marmoset	Gavage	6 months	3.0 10.0 30.0	0.93 3.125 9.325	No adverse findings NOAEL=10.0:3.125

NOAEL: No Observed Adverse Effect Level

NOEL: No Observed Effect Level

Carcinogenicity:

Valsartan

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

Hydrochlorothiazide

According to the experimental data available, hydrochlorothiazide revealed inconsistent evidence of carcinogenic activity in rats and mice with conflicting evidence of hepatic adenoma in male mice at the highest dose and adrenal pheocytochroma in one rat study but not in another. Current evidence is inadequate to draw a clear conclusion for a carcinogenic effect of hydrochlorothiazide in animals.

The mutagenic potential was assessed in a series of *in vitro* and *in vivo* test systems. While some positive results were obtained *in vitro*, all *in vivo* studies provided negative results. Hydrochlorothiazide enhanced the UVA-induced formation of pyrimidine dimers *in vitro* and in the skin of mice following oral treatment. It is therefore concluded that there is no relevant mutagenic potential *in vivo*, although hydrochlorothiazide could enhance the genotoxic effects of UVA light. This mechanism of photosensitization could be associated with a higher risk for non-melanoma skin cancer.

Genotoxicity:

Mutagenicity

Valsartan

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

In vitro

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

In-vivo

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

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

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

Reproductive and Developmental Toxicology:

Valsartan

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

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 $\geq$ 200 mg/kg/days and in rabbits at doses of $\geq$ 10 mg/kg/day. In a peri- and postnatal development toxicity

(segment III) study, the offsprings 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 7.1.1 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: ↓ in field motor activity in F; no effect on fertility, reproductive performance in F_0 & F_1 and on F_1 development. No effect on kidney development.

Segment II

Species	Route	Duration of dosing	Dose mg/kg	Major Findings
Mouse	Gavage	Day 6 to 15	60, 200, 600	All dose groups: No embryotoxicity, fetotoxicity or teratogenicity.
Rat	Gavage	Day 6 to 15	60, 200, 600	Mid & High dose groups:↓ maternal body weight gain High dose group: ↓ fetal weights All dose groups: No embryotoxicity, fetotoxicity or teratogenicity
Rabbit[1]	Drench	Day 6 to 18	2.5, 15, 30, 45, 50, 150	Litter losses and deaths at 15 mg/kg and above. One litter loss (1/5) at 2.5 mg/kg.
Rabbit	Gavage	Day 6 to 18 Day 7 to 19	2, 5, 10	Mid dose group: ↑ incidence of low fetal weights Mid & High dose groups: Litter loss and abortion All dose groups: No teratogenicity.

1. Range Finding

Segment III

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

+ - Number of days post-parturition

Valsartan and hydrochorothiazide

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

Segment II

Species	Route	Duration	Dose (mg/kg)		Major Findings
			Valsartan	HCTZ	
Rat	Gavage	Day 6 to 15	50.0 200.0 600.0	15.6 62.5 187.5 187.5	All dose groups: Maternal & fetal toxicty, ↓ food consumption, body weight & weight gain Mid dose & High dose groups: Maternal deaths (3/26 & 11/26), salivation and stool changes and ↓ fetal weight No embryotoxicity or teratogenicity.
Rat	Gavage	Day 6 to 15	10.0 25.0 100.0	3.1 7.8 31.3 31.3	High dose group:↓ food consumption and weight gain No evidence of embryo- & feto-toxicity or embryotoxicity NOEL (maternal): 25.0:7.8 mg/kg NOEL (fetal): 100:31.3 mg/kg
Rabbit	Gavage	Day 7 to 19	1.0 3.0 10.0	0.3 0.9 3.1 3.1	All dose groups: Slightly ↓ food consumption Mid dose group: Maternal death (1/18) High dose group: ↑ no. of late resorptions, total resorptions, mean & % post implantation loss; slight ↓ in no. of live fetuses. No evidence of teratogenecity NOAEL (fetal): 3.0:0.9 mg/kg

Mouse	Gavage	Day 6 to 15	50 200 600	15.6 62.5 187.5 187.5	No maternal effects, embryo-, fetotoxicity or teratogenicity. NOAEL (fetal & Maternal): 600.0:187.5 mg/kg

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrDIOVAN-HCT®

valsartan and hydrochlorothiazide tablets

Read this carefully before you start taking **DIOVAN-HCT®** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **DIOVAN-HCT.**

Serious Warnings and Precautions

Pregnancy: Angiotensin receptor blockers (ARBs), such as valsartan in DIOVAN-HCT, can cause harm or even death to your unborn baby. Therefore, DIOVAN-HCT should not be taken during pregnancy. If you become pregnant or think you are pregnant, stop taking DIOVAN-HCT right away and tell your healthcare professional.

What is DIOVAN-HCT used for?

DIOVAN-HCT is used in adults to treat mild to moderate essential hypertension (high blood pressure).

How does DIOVAN-HCT work?

DIOVAN-HCT is a combination tablet of two medicinal ingredients, valsartan and hydrochlorothiazide. Valsartan is an angiotensin receptor blocker (ARB) that helps relax blood vessels. This makes it easier for your heart to pump blood around your body. While hydrochlorothiazide is a diuretic or “water pill” that increases urination. These work together to lower high blood pressure.

What are the ingredients in DIOVAN-HCT?

Medicinal ingredients: Valsartan and hydrochlorothiazide

Non-medicinal ingredients: Colloidal silicon dioxide, crospovidone, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, talc, and titanium dioxide.

In addition, the tablets also contain:

- 80 mg/12.5 mg tablets: red iron oxide and yellow iron oxide
- 160 mg/12.5 mg tablets: red iron oxide
- 160 mg/25 mg tablets: black iron oxide, red iron oxide and yellow iron oxide
- 320 mg/12.5 mg tablets: black iron oxide and red iron oxide
- 320 mg/25mg tablets: yellow iron oxide

DIOVAN-HCT comes in the following dosage forms:

Tablets:

- 80 mg valsartan/12.5 mg hydrochlorothiazide (light orange)
- 160 mg valsartan/12.5 mg hydrochlorothiazide (dark red)
- 160 mg valsartan/25 mg hydrochlorothiazide (brown)
- 320 mg valsartan/12.5 mg hydrochlorothiazide (pink)
- 320 mg valsartan/25 mg hydrochlorothiazide (yellow)

Do not use DIOVAN-HCT if:

- you are allergic to valsartan, hydrochlorothiazide or to any other ingredients in DIOVAN-HCT.
- Have one of the following rare hereditary diseases:
    - Galactose intolerance;
    - Lapp lactase deficiency; or
    - Glucose-galactose malabsorption

  Because lactose is a non-medicinal ingredient in DIOVAN-HCT.
- you are allergic to any sulfonamide-derived medicines (also known as "sulfa drugs"). Most of them have a medicinal ingredient that ends in "**-MIDE**". Ask your healthcare professional if you are not sure what sulfonamide-derived medicines are.
- you have anuria (difficulty urinating or producing no urine).
- you have severe kidney problems.
- during treatment with DIOVAN-HCT you have:
    - oliguria (low urine output); or
    - progressive azotemia (high levels of nitrogen in the blood).
- you have electrolyte disturbances such as:
    - hyponatremia (low level of sodium in the blood); or
    - hypercalcemia (high level of calcium in the blood).
- you have a medical condition that involves a low level of potassium in the blood.
- you have gout or kidney stones due to high levels of uric acid in the blood.
- you are pregnant or planning to become pregnant.
- you are breastfeeding or planning to breastfeed.
- you are taking medicines that contain aliskiren (such as RASILEZ) that help lower blood pressure **and** you have diabetes or kidney disease.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take DIOVAN-HCT. **Talk about any health conditions or problems you may have, including if you:**

- are taking other medicines, including:

    - medicines used to lower high blood pressure such as angiotensin-converting enzyme (ACE) inhibitors, diuretics ("water pills") and medicines containing aliskiren;
    - medicines that increase the level of potassium in the blood such as a salt substitute that contains potassium, potassium supplements, potassium-sparing diuretics (a type of "water pill"), heparin (used to treat and prevent blood clots), etc.
- ever had an allergic reaction, which may involve swelling of the hands, feet, or ankles, face, lips, tongue, throat, or sudden difficulty breathing or swallowing (angioedema), when taking other medicines, including:
    - medicines used to treat high blood pressure such as ACE inhibitors and angiotensin receptor blockers (ARBs);
    - penicillin (used to treat bacterial infections).
- have or have had heart problems (e.g., heart failure, narrowing of an artery or a heart valve).
- have or have had problems that affect the blood flow and blood vessels in the brain (e.g., stroke).
- have diabetes.
- have liver problems. This includes if you suffer from a medical condition that involves a blockage of the bile ducts (tubes that carry bile from the liver and gallbladder to the small intestine).
- have kidney problems.
- are undergoing dialysis (a procedure to remove waste products and excess fluid from the blood when the kidneys stop working properly).
- are dehydrated or suffer from excessive vomiting, diarrhea, or sweating.
- are on a low-salt diet.
- have lupus erythematosus (an autoimmune disease).
- have a history of allergies or bronchial asthma.
- are planning to have surgery or anesthesia.
- have been told by a healthcare professional that you have hyperuricemia (high levels of uric acid in the blood) and are at risk of gout (a type of arthritis that causes joint pain).
- have edema (swelling caused by excess fluid in body tissues) in hot weather.
- are at a higher risk of developing skin cancer. You may be at a higher risk if you have light skin colour, have a personal or family history of skin cancer, or if you are taking medicines that suppress your immune system.
- have had breathing or lung problems (including inflammation or fluid in the lungs) in the past following the use of medication containing hydrochlorothiazide. If you experience any severe shortness of breath or difficulty breathing after taking DIOVAN-HCT, stop the medication and seek medical attention immediately.

Other warnings you should know about:

DIOVAN-HCT can cause the following:

- **Angioedema** (swelling of tissue under the skin): Treatment with valsartan, a component of DIOVAN-HCT, can cause angioedema. This can be life-threatening. Your healthcare professional will monitor your health for signs of angioedema. If you notice swelling on your body or have difficulty swallowing or breathing, stop taking DIOVAN-HCT and tell your healthcare professional right away.
- **Skin cancer:** Hydrochlorothiazide in DIOVAN-HCT may increase the risk of developing skin cancer such as non-melanoma skin cancer (NMSC), squamous cell carcinoma (SCC), and basal cell carcinoma (BCC). The risk is higher if you have been taking DIOVAN-HCT for many years (more than 3) or at a high dose. While taking DIOVAN-HCT:
    - you should regularly check your skin for new lesions (e.g., a lump, bump, sore, or patch). These are more likely to occur in areas that are more exposed to the sun (e.g., face, ears, hands, shoulders, upper chest, and back).
    - you should limit your exposure to the sun, avoid indoor tanning, and use sun protection when going outside. This includes using sunscreen (SPF 30 or higher), wearing protective clothing, and wearing a hat.
    - tell your healthcare professional right away if you get more sensitive to the sun or UV light, or if you develop an unexpected lesion.
- **Photosensitivity:** You may become sensitive to the sun while taking DIOVAN-HCT. Exposure to sunlight should be reduced until you know how you respond. Tell your healthcare professional if you notice any photosensitivity. They may decide to stop your treatment with DIOVAN-HCT.
- **Hypotension** (low blood pressure): Treatment with DIOVAN-HCT can cause hypotension, in some cases even after the first dose. Your healthcare professional may monitor your health and adjust your dose as needed. Tell your healthcare professional, if you notice an increase in sweating, feel dehydrated, are vomiting, or have diarrhea.
- **Fluid or electrolyte imbalance:** Hydrochlorothiazide in DIOVAN-HCT can cause fluid or electrolyte imbalances such as:
    - hypokalemia (low level of potassium in the blood),
    - hyponatremia (low level of sodium in the blood),
    - hypochloremic alkalosis (low level of chloride in the blood),
    - hyperuricemia (high uric acid levels in the blood), and
    - acute gout (a type of arthritis that causes joint pain).

  Tell your healthcare professional if you notice any signs or symptoms related to fluid or electrolyte imbalances.
- **Eye problems:** Hydrochlorothiazide in DIOVAN-HCT can cause sudden eye disorders:
    - **Choroidal effusion** (an abnormal build-up of liquid in your eye that may result in vision changes),
    - **Myopia** (sudden nearsightedness or blurred vision), and

- **Glaucoma** (an increased pressure in your eye). If left untreated, it may lead to permanent vision loss.

If your vision changes, stop taking DIOVAN-HCT and seek immediate medical help. These eye disorders are related and can develop within hours to weeks of starting DIOVAN-HCT.

- **Kidney problems:** Treatment with DIOVAN-HCT can cause kidney problems resulting in decreased urine, progressive azotemia (high levels of nitrogen in the blood), kidney failure or even death. Your healthcare professional will closely monitor your kidneys before and during your treatment. They may decide to reduce or stop your treatment.

See the **Serious side effects and what to do about them table**, below, for more information on these and other serious side effects.

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

Driving and using machines: DIOVAN-HCT can decrease your blood pressure causing light-headedness, dizziness, and fainting. These can occur more often after your first dose, and when your dose is increased. Before you drive or do tasks that require special attention, wait until you know how you respond to DIOVAN-HCT.

Check-ups and testing:

- You may have regular visits with your healthcare professional, before, during and after your treatment. These tests may be used to monitor the health of your kidneys and liver, your blood pressure and the profile of your blood.
- Your healthcare professional may stop your treatment with DIOVAN-HCT before performing tests to assess the health of your parathyroid glands.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Serious Drug Interactions
Do not use DIOVAN-HCT if you take: • medicines that contain aliskiren that are used to lower blood pressure and you have diabetes or kidney disease.

The following may interact with DIOVAN-HCT:

- other medicines used to lower high blood pressure such as guanethidine, methyldopa, ACE inhibitors, ARBs, beta blockers, vasodilators, calcium channel blockers and direct renin inhibitors.

- medicines known as diuretics (“water pill”) such as potassium-sparing diuretic and potassium-retaining diuretics (e.g., spironolactone, triamterene, or amiloride).
- medicines that increase the potassium in the blood such as a salt substitute that contains potassium, potassium supplements, and a potassium-sparing diuretic (a type of “water pill”).
- medicines used to treat and prevent blood clots such as heparin.
- non-steroidal anti-inflammatory drugs (NSAIDs) that are used to reduce pain and swelling such as ibuprofen, naproxen, celecoxib, indomethacin, and acetylsalicylic acid (aspirin).
- medicines used to treat bacterial infections such as trimethoprim-sulfamethoxazole, rifampin, and penicillin.
- medicines used to treat fungal infections such as amphotericin B.
- medicines used to treat bipolar disorder such as lithium.
- medicines used to suppress the immune system such as cyclosporine.
- medicines used to treat HIV/AIDS such as ritonavir.
- medicines used to help with sleep such as barbiturates.
- medicines used to help reduce intense pain such as narcotics.
- medicines used to treat Parkinson’s Disease such as amantadine.
- medicines used to treat diabetes (antidiabetics) such as insulin and oral hypoglycemic agents (used to lower glucose levels in the blood).
- medicines used to treat cancer such as cyclophosphamide and methotrexate.
- medicines used to lower cholesterol such as bile acid resins (e.g., cholestyramine).
- vitamins and mineral supplements such as calcium or vitamin D.
- medicines used to treat epilepsy such as carbamazepine and topiramate.
- medicines known as corticosteroids that are used to treat joint pain, swelling, and other conditions.
- medicines used to treat West Syndrome such as adrenocorticotropic hormone (ACTH).
- medicines used to treat low blood sugar such as diazoxide.
- medicines used to treat heart conditions such as digoxin.
- medicines that change the speed of bowel movements such as atropine, metoclopramide, and domperidone.
- medicines used to treat gout (a type of arthritis that causes joint pain) such as allopurinol, probenecid, uricosurics, and xanthine oxidase inhibitors.
- medicines used to treat acid peptic disease such as carbenoxolone.
- medicines used to treat an abnormal heartbeat.
- medicines known as sympathomimetic agents that reduce nasal congestion such as cough and cold medicines, or are used to treat asthma.
- medicines used to prevent and treat malaria such as chloroquine.
- medicines that have the potential to increase your blood pressure such as norepinephrine.

- medicines used to treat depression (antidepressants) such as selective serotonin re-uptake inhibitors (e.g., citalopram, escitalopram, and sertraline).
- medicines used to relieve muscle spasms such as tubocurare.
- medicines known as anesthetics that block pain during surgery or certain medical procedures.
- medicines that slow down brain activity such as sedatives.
- alcohol.

How to take DIOVAN-HCT:

- DIOVAN-HCT is not for initial therapy.
- You must be stabilized on valsartan and hydrochlorothiazide before taking DIOVAN-HCT. If your dosage matches the dosages in DIOVAN-HCT, your healthcare professional may prescribe DIOVAN-HCT (instead of each medicinal ingredient as a separate pill).
- Your healthcare professional will decide the dose and length of DIOVAN-HCT for you. They may start with a low dose and slowly adjust the dose as needed. Take DIOVAN-HCT exactly as prescribed by your healthcare professional.
- DIOVAN-HCT can be taken with or without food, but it should be taken the same way each day. If DIOVAN-HCT causes upset stomach, take it with food or milk.
- It is recommended that you take your daily dose at about the same time every day, preferably in the morning.
- Your healthcare professional will monitor your health throughout your treatment and may interrupt, reduce or stop your dose.

Usual dose:

- Your healthcare professional will decide the best dose for you.
- The maximum daily dose is 320 mg valsartan and 25 mg hydrochlorothiazide.

Overdose:

Signs of an overdose with DIOVAN-HCT may include:

- low blood pressure that can lead to shock (rapid breathing, pale skin, cold and sweaty skin), decreased consciousness or a rapid heartbeat.
- low electrolyte levels in the blood, which may cause you to feel weak, dizzy, confused, tired, have cramps, vomit.
- dehydration.

If you think you, or a person you are caring for, have taken too much DIOVAN-HCT, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you have forgotten to take your dose during the day, skip the missed dose and take your next dose at the usual time. Do not double the doses.

What are possible side effects from using DIOVAN-HCT?

These are not all the possible side effects you may have when taking DIOVAN-HCT. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- dizziness, difficulty in maintaining your balance while standing, motion sickness, fainting
- diarrhea, constipation, nausea, vomiting, gas, indigestion, decreased appetite, stomach flu or discomfort, dry mouth, toothache
- upper respiratory tract infection, runny or stuffy nose, cough, throat pain, bronchitis (inflammation of the lining of your lungs)
- fatigue, lack of energy
- pain or swelling of the hands, arms, legs or feet
- burning or prickling sensation of the skin, numbness, itchy skin
- bladder infection, frequent urination during the day
- sexual difficulties, impotence, decreased sexual desire
- problems with sleeping, anxiety
- headache
- fever
- feeling dehydrated
- back or neck pain
- sprains and strains, muscle spasm
- ringing in the ears, ear pain
- pink eye
- excessive sweating
- nosebleed
- changes in taste

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON			
Allergic reaction / Angioedema: rash, hives, swelling of the face, lips, tongue or throat,			✓

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
difficulty swallowing or breathing, effect on the eyes, itching, fever, wheezing, drop in blood pressure, or feeling sick to your stomach and throwing up			
Hypotension (low blood pressure): dizziness, fainting, light-headedness (may occur when you go from lying or sitting to standing up), blurred vision, nausea, vomiting, or fatigue	✓		
Decreased or increased levels of potassium in the blood: irregular heartbeats, muscle weakness, generally feeling unwell, muscle spasms, cramping, constipation, feeling of skipped heart beats or palpitations, fatigue, tingling, or numbness		✓	
Non-melanoma skin cancer: lump or discoloured patch on the skin that stays after a few weeks and slowly changes; lumps can be red/pink, firm and sometimes turn into ulcers; and cancerous patches are usually flat and scaly		✓	
UNCOMMON			
Kidney problems: increased or decreased urination, nausea, vomiting, swelling of extremities, fatigue, fever, thirst, dry skin, irritability, dark urine, blood in the urine, rash, weight gain (from retaining fluid), loss of appetite, abnormal blood test results, or mental status changes (drowsiness, confusion, coma)		✓	
Liver problems: yellowing of the skin or eyes (jaundice), dark urine, abdominal pain or swelling, nausea, vomiting, loss of appetite, or unusual tiredness		✓	
Hyperglycemia (high blood sugar): frequent urination, thirst, and hunger, dry skin, headache, blurred vision, or fatigue	✓		
Electrolyte Imbalance: weakness, drowsiness, muscle pain or cramps, irregular heartbeat		✓	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Myocardial infarction (heart attack): pressure or squeezing pain between the shoulder blades, in the chest, jaw, left arm or upper abdomen, shortness of breath, dizziness, fatigue, light-headedness, clammy skin, sweating, indigestion, anxiety, feeling faint, palpitations, or possible irregular heartbeat			✓
Abdominal pain		✓	
RARE			
Rhabdomyolysis (breakdown of damaged muscle): muscle tenderness, weakness, red-brown (tea-coloured) urine		✓	
Decreased White Blood Cells: infections, fatigue, fever, aches, pains, and flu-like symptoms		✓	
Decreased Platelets: bruising, bleeding, fatigue and weakness		✓	
Arrhythmia (abnormal heart rhythms): rapid, slow or irregular heartbeat		✓	
Increased levels of uric acid in the blood: swelling, redness in the joints, sudden and intense attacks of joint pain (gout attack)		✓	
Photosensitivity (sensitivity to sunlight): itchy, red skin when exposed to sunlight			✓
Depression (sad mood that won't go away)**:** difficulty sleeping or sleeping too much, changes in appetite or weight, feelings of worthlessness, guilt, regret, helplessness or hopelessness, withdrawal from social situations, family, gatherings and activities with friends, reduced libido (sex drive) and thoughts of death or suicide. If you have a history of depression, your depression may become worse			✓
VERY RARE			
Necrotizing vasculitis: Inflammation of vessels with or without pain	✓		

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Acute respiratory distress (inflammation of lung tissue or excess fluid in the lungs): severe shortness of breath or difficulty breathing, fever, weakness, and confusion			✓
Bone marrow failure, aplastic anemia (body fails to produce enough new blood cells): weakness, bruising and frequent infections	✓		
Worsening or activation of lupus: fatigue, fever, joint pain, stiffness and swelling, rash on the face that covers the cheeks and the bridge of the nose or rashes elsewhere on the body, skin lesions, shortness of breath, chest pain, dry eyes, headaches, confusion and memory loss		✓	
UNKNOWN FREQUENCY			
Eye disorders: • **Myopia:** sudden near sightedness or blurred vision • **Glaucoma:** increased pressure in your eyes, eye pain, decrease in vision • **Choroidal effusion:** (build-up of liquid in your eye): blind spots, eye pain, or blurred vision			✓
Serious skin reactions: raised red or purple skin patches, possibly with blister or crust in the center, possibly swollen lips, mild itching or burning; blisters of different sizes; skin redness, blistering and/or peeling of the skin and/or inside of the lips, eyes, mouth, nasal passages or genitals, can be accompanied with fever, chills, headache, cough, body aches or swollen glands.			✓
Anemia (decreased number of red blood cells): fatigue, loss of energy, weakness, shortness of breath, irregular heartbeats, or pale complexion		✓	
Pancreatitis (inflammation of the pancreas): upper abdominal pain that lasts and gets		✓	

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
worse when you lie down, nausea, vomiting, fever, rapid heartbeat, or tenderness when touching the abdomen			

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

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

Storage:

- Store at room temperature (15°C-30°C). Protect from moisture.
- Do not take DIOVAN-HCT past the expiry date shown on the pack.
- Keep out of reach and sight of children.

If you want more information about DIOVAN-HCT:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website http://www.novartis.ca, or by calling 1-800-363-8883.

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