PRODUCT MONOGRAPH

PrTEVA-IRBESARTAN/HCTZ

(irbesartan/hydrochlorothiazide)

tablets 150/12.5 mg, 300/12.5 mg and 300/25 mg

Teva Standard

Angiotensin II AT_1 Receptor Blocker / Diuretic

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Table of Contents

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form/Strength	Non Medicinal Ingredients
Oral	Tablets/ 150/12.5 mg 300/12.5 mg 300/25 mg	colloidal anhydrous silica, croscarmellose sodium, magnesium stearate, microcrystalline cellulose, poloxamer, povidone, pregelatinized starch and film-coating containing the following: **150/12.5 mg and 300/12.5 mg**: hypromellose, iron oxide black, iron oxide red, iron oxide yellow, macrogol and titanium dioxide. **300/25 mg:** FD&C Blue # 2, hypromellose, iron oxide black, iron oxide red, macrogol and titanium dioxide.

INDICATIONS AND CLINICAL USE

TEVA-IRBESARTAN/HCTZ (irbesartan/hydrochlorothiazide) is indicated:

- For the treatment of essential hypertension in patients for whom combination therapy is appropriate (see DOSAGE AND ADMINISTRATION).

- As initial therapy in patients with severe essential hypertension (Sitting DBP ≥ 110 mmHg) for whom the benefit of a prompt blood pressure reduction exceeds the risk of initiating combination therapy in these patients (see CLINICAL TRIALS and DOSAGE AND ADMINISTRATION).

TEVA-IRBESARTAN /HCTZ is not indicated as initial therapy in patients with mild to moderate essential hypertension.

Geriatrics (> 65 years of age): In clinical studies, no overall differences in safety or efficacy were observed between patients >65 years of age and younger patients (See WARNINGS AND PRECAUTIONS- Special populations)**.**

Pediatrics (< 18 years of age): The safety and efficacy of irbesartan/hydrochlorothiazide in patients <18 years of age have not been established (See WARNINGS AND PRECAUTIONS- Special populations).

CONTRAINDICATIONS

TEVA-IRBESARTAN /HCTZ (irbesartan/hydrochlorothiazide) is contraindicated in:

- Patients who are hypersensitive to this drug or any ingredient in the formulation. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the Product Monograph.
- Patients who are hypersensitive to other sulphonamide-derived drugs, because of the hydrochlorothiazide component.
- Patients with anuria.
- Pregnant women (see WARNINGS AND PRECAUTIONS, Special Populations, Pregnant Women.)
- Nursing women (see WARNINGS AND PRECAUTIONS, Special Populations, Nursing Women.)
- Combination with aliskiren-containing drugs in patients with diabetes mellitus (type 1 or type2) or moderate to severe renal impairment (GFR <60 ml/min/1.73m^2) (see WARNINGS AND PRECAUTIONS, Renal - Renal Impairment, and DRUG INTERACTIONS, Dual Blockade of the Renin-Angiotensin-System (RAS) with ARBs, ACE inhibitors or aliskiren containing drugs).
- Combination with angiotensin converting enzyme (ACE) inhibitors in patients with diabetic nephropathy (see WARNINGS AND PRECAUTIONS, Renal - Renal Impairment, and DRUG INTERACTIONS, Dual Blockade of the Renin-Angiotensin-System (RAS) with ARBs, ACE inhibitors or aliskiren-containing drugs) .

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

When used in pregnancy, angiotensin receptor (AT_1) blockers (ARB) can cause injury and even death of the developing fetus. When pregnancy is detected, TEVA-IRBESARTAN /HCTZ should be discontinued as soon as possible. (see WARNINGS AND PRECAUTIONS- Special Populations).

General

The effect of irbesartan on the ability to drive and use machinery has not been studied, but based on its pharmacodynamic properties, irbesartan is unlikely to affect this ability. When driving vehicles or operating machinery, it should be taken into account that occasionally dizziness or weariness may occur during treatment of hypertension.

Cardiovascular

Hypotension
Occasionally, symptomatic hypotension has occurred after administration of irbesartan, 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 (see DOSAGE AND ADMINISTRATION). 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 particular risk of decreased coronary perfusion when treated with vasodilators because they do not develop as much afterload reduction.

Dual Blockade of the Renin-Angiotensin System (RAS)
There is evidence that co-administration of angiotensin receptor antagonists (ARBs), such as the irbesartan component of TEVA-IRBESARTAN /HCTZ, or of angiotensin converting enzyme (ACE) inhibitors with aliskiren increases the risk of hypotension, syncope, stroke, hyperkalemia and deterioration of renal function, including renal failure, in patients with diabetes mellitus (type 1 or type 2) and/or moderate to severe renal impairment (GFR < 60 ml/min/1.73m$_2$). Therefore, the use of TEVA-IRBESARTAN /HCTZ in combination with aliskiren-containing drugs is contraindicated in these patients (see CONTRAINDICATIONS).

The use of TEVA-IRBESARTAN /HCTZ in combination with an ACE inhibitor is contraindicated in patients with diabetic nephropathy (see CONTRAINDICATIONS).

Further, co-administration of ARBs, including the irbesartan component of TEVA-IRBESARTAN /HCTZ, with other agents blocking the RAS, such as ACE inhibitors or aliskiren-containing drugs, is generally not recommended in other patients, since such treatment has been associated with an increased incidence of severe hypotension, renal failure, and hyperkalemia.

Endocrine and Metabolism
Thiazides, including hydrochlorothiazide, can cause fluid or electrolyte imbalance (hypokalemia, hyponatremia and hypochloremic alkalosis). Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals.

Calcium excretion is decreased by thiazides which may cause intermittent and slight elevation of serum calcium. If calcium or a calcium sparing drug (e.g., vitamin D therapy) is prescribed,

serum calcium levels should be monitored and calcium dosage adjusted accordingly. Marked hypercalcemia suggests the possibility of hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Thiazides have been shown to increase the urinary excretion of magnesium, which may result in hypomagnesemia.

Hyperuricemia may occur, and an acute attack of gout may be precipitated in certain patients receiving thiazide therapy.

Insulin requirements in diabetic patients may be altered and latent diabetes mellitus may become manifest during thiazide diuretic therapy.

Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.

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

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

Immune

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

Systemic Lupus Erythematosus
Thiazide diuretics have been reported to cause exacerbation or activation of systemic lupus erythematosus.

Ophthalmic

Acute Myopia and Secondary Acute Angle-Closure Glaucoma

Hydrochlorothiazide, a sulfonamide, can cause an idiosyncratic reaction, resulting in acute transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue drug intake 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

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 impairment the diuretic should be discontinued.

Renal Impairment

As a consequence of inhibiting the renin-angiotensin-aldosterone system (RAAS), changes in renal function have been seen in susceptible individuals. In patients whose renal function may depend on the activity of the (RAAS), 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 use of ARBs including the irbesartan component of TEVA-IRBESARTAN /HCTZ – or of the ACE inhibitors with aliskiren-containing drugs is contraindicated in patients with moderate to severe renal impairment (GFR < 60 ml/min/1.73m$_2$). (See CONTRAINDICATIONS and DRUG INTERACTIONS, Dual Blockade of the Renin-Angiotensin-System (RAS) with ARBs, ACE inhibitors, or aliskiren-containing drugs).

The use of ARBs including the irbesartan component of TEVA-IRBESARTAN /HCTZ in combination with an ACE inhibitor is contraindicated in patients with diabetic nephropathy due to risk of hyperkalemia, hypotension and renal impairment (see CONTRAINDICATIONS and DRUG INTERACTIONS, Dual Blockade of the Renin-Angiotensin-System (RAS)).

Use of irbesartan should include appropriate assessment of renal function.

Thiazides should be used with caution.

Because of the hydrochlorothiazide component, TEVA-IRBESARTAN /HCTZ (irbesartan/hydrochlorothiazide) is not recommended in patients with severe renal impairment (creatinine clearance ≤ 30 mL/min).

Special Populations

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

The use of ARB is contraindicated during pregnancy. Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE 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 ARBs 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).

Infants with histories of *in utero* exposure to an 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 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. Irbesartan is not removed by hemodialysis.

Thiazides cross the placental barrier and appear in cord blood. The routine use of diuretics 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 reactions that have occurred in adults. Diuretics do not prevent development of toxemia of pregnancy and there is no satisfactory evidence that they are useful in the treatment of toxemia.

Nursing Women

It is not known whether irbesartan is excreted in human milk, but significant levels of radioactivity have been found in the milk of lactating rats. Thiazides appear in human milk. Thiazides in high doses causing intense diuresis can inhibit the milk production.

Because many drugs are excreted in human milk and because of their potential for affecting the nursing infant adversely, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatrics (< 18 years of age)

Safety and effectiveness have not been established.

Geriatrics(> 65 years of age)

Of the 2650 hypertensive patients receiving irbesartan/hydrochlorothiazide in clinical studies, 618 patients were $\geq$ 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.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Irbesartan/hydrochlorothiazide was evaluated for safety in 2746 patients with essential hypertension including 968 patients for 1 ≥ year.

The most commonly reported adverse events (AEs) (occurring in ≥ 10% of patients treated with irbesartan/hydrochlorothiazide) was headache (11.0%), which occurred at a significantly higher incidence in the placebo group (16.1%).

The AEs most frequently resulting in clinical intervention (discontinuation of irbesartan/hydrochlorothiazide) were due to dizziness (0.7%) and headache (0.7%). The AE of hypotension is more likely to occur in volume depleted patients (See Warnings and Precautions related to Cardiovascular under Hypotension).

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

Clinical Trial Adverse Drug Reactions

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

Hypertension

In placebo-controlled clinical trials, therapy was discontinued due to a clinical or laboratory AE in 3.6% of patients treated with irbesartan/hydrochlorothiazide, versus 6.8% of patients given placebo.

AEs regardless of drug relationship, occurring in ≥1% of the irbesartan/ hydrochlorothiazide patients in placebo-controlled clinical trials include the following:

Table 1: Adverse events regardless of drug relationship, occurring in ≥1% of the irbesartan/hydrochlorothiazide patients in placebo-controlled clinical trials

	Irbesartan/ HCTZ n = 898 (%)	Irbesartan n = 400 (%)	HCTZ n = 380 (%)	Placebo n = 236 (%)
Cardiovascular				
Edema	3.1	1.5	1.6	2.5
Tachycardia	1.2	0.5	0.5	0.4
Dermatologic				
Rash	1.2	1.8	3.2	1.7
Gastrointestinal				
Nausea/vomiting	3.2	1.5	2.4	0.4
Dyspepsia	2.1	0.3	1.6	0.8
Diarrhea	2.1	2.8	1.1	3.4
Abdominal Pain	1.7	1.5	1.6	0.8
General				
Fatigue	6.5	4.0	3.2	3.0
Influenza	2.8	2.0	1.8	1.3
Chest Pain	1.8	1.5	1.6	1.3
Immunology	1.1	0.5	0.5	0
Allergy				
Musculoskeletal				
Musculoskeletal Pain	6.5	6.0	9.7	4.7
Muscle Cramp	1.0	0.8	2.1	1.3
Nervous System				
Headache	11.0	9.3	11.6	16.1
Dizziness	7.6	5.5	4.7	4.2
Orthostatic Dizziness	1.1	1.0	0.8	0.4
Anxiety / Nervousness	1.0	1.0	0.5	1.7
Renal/Genitourinary				
Urination abnormal	1.9	0.5	2.1	0.8
Urinary Tract Infection	1.6	1.5	2.4	2.5

	Irbesartan/ HCTZ n = 898 (%)	Irbesartan n = 400 (%)	HCTZ n = 380 (%)	Placebo n = 236 (%)
Respiratory				
URTI	5.6	8.3	7.1	5.5
Sinus disorder	2.9	4.5	3.2	4.7
Cough	2.2	2.3	2.6	3.0
Pharyngitis	2.1	2.3	2.9	1.7
Rhinitis	1.9	2.0	1.6	2.5

Severe Hypertension

In a clinical study in patients with severe hypertension (SeDBP ≥110 mmHg), the overall pattern of AEs reported through seven weeks of follow-up was similar in patients treated with irbesartan/hydrochlorothiazide as initial therapy and in patients treated with irbesartan as initial therapy.

Table 2: Most common adverse events regardless of drug relationship, occurring in ≥1% of the irbesartan/hydrochlorothiazide patients with Severe Hypertension in controlled clinical trial

	Number (%) of Subjects Irbesartan/HCTZ N = 468	**Number (%) of Subjects Irbesartan N= 227**
Headache	19 (4.1)	15 (6.6)
Dizziness	16 (3.4)	9 (4.0)
Nasopharyngitis	8 (1.7)	10 (4.4)
Bronchitis	6 (1.3)	6 (2.6)
Fatigue	6 (1.3)	1 (0.4)
Upper Respiratory Tract Infection	6 (1.3)	4 (1.8)
Erectile Dysfunction	5 (1.1)	0
Nausea	5 (1.1)	5 (2.2)
Diarrhea	4 (0.9)	3 (1.3)
Sinusitis	4 (0.9)	3 (1.3)
Cough	3 (0.6)	4 (1.8)
Muscle Spasms	2 (0.4)	3 (1.3)

The incidence of the pre-specified AEs was: 0% reported cases of syncope in either treatment group; 0.6% and 0% cases of hypotension, 3.6% and 4.0% cases of dizziness, 4.3% and 6.6% cases of headache, 0.2% and 0% cases of hyperkalemia, and 0.6% and 0.4% cases of hypokalemia reported in the group treated with irbesartan/hydrochlorothiazide and the group treated with irbesartan, respectively.

The rate of discontinuation due to AEs was 1.9% and 2.2% in the group treated with irbesartan/hydrochlorothiazide and the group treated with irbesartan, respectively.

Irbesartan Alone

In addition, the following potentially important events occurred in < 1% of patients receiving irbesartan, regardless of drug relationship:

Body as a Whole: chills, facial edema, fever upper extremity edema;

Cardiovascular: angina pectoris, arrhythmic/conduction disorder, cardiac murmur,cardio-respiratory arrest, flushing heart failure, hypertension, hypertensive crisis, myocardial infarction, syncope;

Dermatologic: dermatitis, ecchymosis, erythema, erythema face, photosensitivity pruritus, urticaria;

Endocrine: gout, libido disorder, sexual dysfunction;

Gastrointestinal: abdominal distention, constipation, flatulence, gastroenteritis, hepatitis;

Musculoskeletal: arthritis, bursitis, extremity swelling, joint stiffness, muscle cramp, muscular weakness, musculoskeletal chest pain, musculoskeletal trauma, myalgia,;

Nervous System: cerebrovascular accident, depression, emotional disturbances, numbness, paresthesia, sleep disturbance, somnolence, transient ischemic attack, tremor, vertigo;

Renal/Genitourinary: abnormal urination,prostate disorder;

Respiratory: congestion, dyspnea, epistaxis, pulmonary congestion, tracheobronchitis, wheezing;

Special Senses: conjunctivitis, ear infection, ear pain, hearing impaired, taste disturbance, visual disturbance.

Hydrochlorothiazide alone

Other adverse events that have been reported with hydrochlorothiazide, without regard to causality, are listed below:

Body as a Whole*:* weakness;

Digestive: cramping, gastric irritation, jaundice (intrahepatic cholestatic jaundice), pancreatitis, sialadenitis;

Hematologic: agranulocytosis, aplastic anemia, hemolytic anemia, leukopenia, thrombocytopenia
Hypersensitivity: anaphylactic reactions, fever, necrotizing angiitis (vasculitis and cutaneous vasculitis), photosensitivity, purpura, respiratory distress including pneumonitis and pulmonary edema, urticaria;
Metabolic: glycosuria, hyperglycemia, hyperuricemia;

Musculoskeletal: muscle spasm;

Nervous System/Psychiatric: restlessness;

Renal: interstitial nephritis, renal dysfunction, renal failure;

Skin: erythema multiforme including Stevens-Johnson syndrome, exfoliative dermatitis including toxic epidermal necrolysis;

Special Senses: transient blurred vision, xanthopsia.

Abnormal Hematologic and Clinical Chemistry Findings

Irbesartan/hydrochlorothiazide

Liver Function Tests: Occasional elevations of liver enzymes and/or serum bilirubin have occurred. In patients with essential hypertension treated with irbesartan/hydrochlorothiazide alone, one patient was discontinued due to elevated liver enzymes.

Creatinine, Blood Urea Nitrogen: Minor increases in blood urea nitrogen (BUN) or serum creatinine were observed in 2.3% of patient. No patient was discontinued due to increased BUN. One patient was discontinued due to a minor increase in serum creatinine.

IRBESARTAN

Liver Function Tests: In placebo-controlled trials, elevations of aspartate aminotransferase (AST) and alanine transaminase (ALT) ≥3X upper limit of normal (ULN) occurred in 0.1% and 0.2%, respectively, of irbesartan treated patients compared to 0.3% and 0.3%, respectively, of patients receiving placebo. In patients treated with irbesartan for a mean duration of >1 year, the cumulative incidence of AST and/or ALT elevations ≥ 3X ULN was 0.4%.

Hyperkalemia: In placebo-controlled trials, greater than a 10% increase in serum potassium was observed in 0.4% of irbesartan treated patients compared to 0.5% of patients receiving placebo.

Creatinine, Blood Urea Nitrogen: Minor increases in (BUN) or serum creatinine were observed in less than 0.7% of patients with essential hypertension treated with irbesartan alone versus 0.9% on placebo.

Hemoglobin: Mean decreases in hemoglobin of 0.16g/dL were observed in patients receiving irbesartan. No patients were discontinued due to anemia.

Neutropenia: Neutropenia (<1000 cells/mm^3) was observed in 0.3% of irbesartan treated patients compared to 0.5% of patients receiving placebo.

In clinical trials, the following were noted to occur with an incidence of < 1%, regardless of drug relationship: anemia, increased creatinine phosphokinase (CPK), lymphocytopenia, thrombocytopenia.

Post-Market Adverse Drug Reactions
The following adverse reactions were reported in post-marketing use:

Angioedema (involving swelling of the face, lips, and/or tongue) has been reported rarely.

Anaphylactic reactions; asthenia; elevated liver function tests; hepatobiliary disorders (acute hepatitis, cholestatic or cytolytic hepatitis); impaired renal function including cases of renal failure in patients at risk (see WARNINGS AND PRECAUTIONS – Renal - Renal Impairment); jaundice; myalgia; syncope.

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

Other adverse reactions reported with the use of hydrochlorothiazide alone include: agranulocytosis, anorexia, bone marrow depression, gastric irritation, interstitial nephritis, leucopenia, necrotizing angiitis (vasculitis, cutaneous vasculitis), pancreatitis, respiratory distress (including pneumonitis and pulmonary oedema), sialadenitis, tinnitus, toxic epidermal necrolysis, xanthopsia.

DRUG INTERACTIONS

Overview

Irbesartan does not substantially induce or inhibit the following isoenzymes: CYP 1A1, 1A2, 2A6, 2B6, 2D6, 2E1. There was no induction or inhibition of CYP 3A4.

Drug-Drug Interactions

Table 3- Established or Potential Drug-Drug Interactions

Proper Name	Ref.	Effect	Clinical comment
Alcohol, barbiturates, or narcotics	C	Potentiation of orthostatic hypotension may occur.	Avoid alcohol, barbiturates or narcotics, especially with initiation of therapy.
Agents increasing Serum Potassium	RCS	Based on experience with the use of other drugs that affect the renin-angiotensin system, concomitant use of irbesartan with potassium-sparing diuretics, potassium supplements salt substitutes containing potassium or other potassium-raising medicinal products may lead to increases in serum potassium, sometimes severe. Such co-administration requires close monitoring of serum potassium. Concomitant	

		thiazide diuretic use may attenuate any effect that irbesartan may have on serum potassium .	
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 See also: Dual Blockade of the Renin-Angiotensin-System (RAS) with ARBs , ACE inhibitors or aliskiren-containing drugs.	CT	Hydrochlorothiazide may potentiate the action of other antihypertensive drugs (e.g. guanethidine, methyldopa, betablockers, vasodilators, calcium channel blockers, diuretics, ACE inhibitors, ARB, and direct renin inhibitors).	Thiazides, including hydrochlorothiazide, can cause fluid or electrolyte imbalance (hypokalemia, hyponatremia and hypochloremic alkalosis). Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals.
Antineoplastic drugs, including cyclophosphamide and methotrexate	C	Concomitant use of thiazide diuretics may reduce renal excretion of cytotoxic agents and enhance their myelosuppressive effects.	Hematological status should be closely monitored in patients receiving this combination. Dose adjustment of cytotoxic agents may be required.
Beta-blockers	C	The hyperglycaemic effect of beta-blockers may be enhanced by thiazides.	
Bile acid sequestrants, e.g., 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 hydrochlorothaizide 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	C	Thiazides decrease renal	Monitor serum calcium,

supplements		excretion of calcium and increase calcium release from bone.	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. If possible, another class of diuretics should be used.
Corticosteroids, and adrenocorticotropic hormone (ACTH)	T	Intensified electrolyte depletion, particularly hypokalemia, may occur.	Monitor serum potassium, and adjust medications, as required.
Diazoxide	C	The hyperglycaemic effect of diazoxide may be enhanced by thiazides.	
Dual Blockade of the Renin-Angiotensin-System (RAS) with ARBs , ACE inhibitors or aliskiren-containing drugs		Dual Blockade of the Renin-Angiotensin-System (RAS) with ARBs , ACE inhibitors or aliskiren-containing drugs is contraindicated in patients with diabetes and/or moderate to severe renal impairment, and is generally not recommended in other patients, since such treatment has been associated with an increased incidence of severe hypotension, renal failure, and hyperkalemia. Dual Blockade of the Renin-Angiotensin-System (RAS) with ARBs and ACE inhibitors is contraindicated in patients with diabetic nephropathy and is generally not recommended in other patients, since such treatment has been associated with an increased incidence of severe hypotension,	See CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS, Dual Blockade of the Renin-Angiotensin-System (RAS).
Digoxin	CT	When irbesartan was administered as 150 mg once daily under steady-state	Concomitant administration of hydrochlorothiazide and

		conditions, no effect was seen on the pharmacokinetics of digoxin at steady-state. Thiazide-induced electrolyte disturbances, i.e. hypokalemia, hypomagnesemia, increase the risk of digoxin toxicity, which may lead to fatal arrhythmic events.	digoxin requires caution. Monitor electrolytes and digoxin levels closely. Supplement potassium or adjust doses of digoxin or thiazide, as required.
Drugs that alter GI motility, i.e., anticholinergic agents, such as atropine and prokinetic agents, such as metoclopramide, domperidone	CT, T	Bioavailability of thiazide diuretics may be increased by anticholinergic agents due to a decrease in gastrointestinal motility and gastric emptying. Conversely, prokinetic drugs may decrease the bioavailability of thiazide diuretics.	Dose adjustment of thiazide may be required.
Gout medications (allopurinol, uricosurics, xanthine oxidase inhibitors)	T, RCS	Thiazide-induced hyperuricemia may compromise control of gout by allopurinol and probenecid. The 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. As with other drugs which eliminate sodium, lithium clearance may be reduced in the presence of irbesartan. Increases in serum lithium concentrations and lithium toxicity have been reported with concomitant use of irbesartan and lithium.	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. Serum lithium levels should be monitored carefully if lithium salts are to be administered with irbesartan.
Nonsteroidal antiinflammatory		In patients who are elderly, volume-depleted (including	Monitor renal function periodically in patients

drugs (NSAID) (including selective COX-2 inhibitors)		those on diuretic therapy), or with compromised renal function, coadministration of NSAIDs, including selective COX-2 inhibitors, with ARBs, including irbesartan, may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible. The antihypertensive effect of ARBs, including irbesartan, may be attenuated by NSAIDs including selective COX-2 inhibitors. In some patients, the administration of a NSAID agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics.	receiving irbesartan and NSAID therapy. When irbesartan/hydrochlorothiazide and NSAID are used concomitantly, the patient should be observed closely to determine if the desired effect is obtained.
Pressor Amines (e.g., Norepinephrine)	CT	In the presence of diuretics, possible decreased response to pressor amines may be seen but 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, e.g., 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.
Warfarin	CT	When irbesartan was administered as 300 mg once	

		daily under steady-state conditions, no pharmacodynamic effect on PT was demonstrated in subjects stabilized on warfarin.	

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

Drug-Food Interactions
No statistically significant effects of food were observed on the C_{max}, $AUC_{(inf)}$ or $T_{1/2}$ of irbesartan or on the AUC(inf) or $T_{1/2}$ of hydrochlorothiazide. In the fasted and fed states, Tmax increased from 1 to 2 hours for irbesartan and from 1.5 to 3.5 hours for hydrochlorothiazide. The C_{max} for hydrochlorothiazide decreased 21% in the fed state relative to the fasted state. None of these changes were considered to be clinically significant.

Drug-Herb Interactions
There have been no clinical studies to assess the possible interaction of any herbal products and irbesartan/hydrochlorothiazide.

DOSAGE AND ADMINISTRATION

Dosing Considerations

- Dosage must be individualized.
- The fixed combination is not for initial therapy except for severe hypertension.
- The dose of TEVA-IRBESARTAN /HCTZ (irbesartan/hydrochlorothiazide) should be determined by the titration of the individual components.
- Use of TEVA-IRBESARTAN /HCTZ with patients with liver impairment is not advisable.
- Dosage adjustment may be required in hemodialysis patients (see Recommended Dose and Dosage Adjustment - Adjustment in Renal Insufficiency).

Recommended Dose and Dosage Adjustment
Once the patient has been stabilized on the individual components as described below, either one tablet of TEVA-IRBESARTAN /HCTZ 150/12.5 mg, 300/12.5 mg or 300/25 mg once daily may be substituted if the doses on which the patient was stabilized are the same as those in the fixed combination.

TEVA-IRBESARTAN /HCTZ may be administered with or without food, however it should be taken consistently with respect to food intake.

Irbesartan Monotherapy

The recommended dose of irbesartan is 150 mg once daily. In patients whose blood pressure is not adequately controlled, the daily dose may be increased to 300 mg.

SEVERE HYPERTENSION (Sitting DBP ≥ 110 mmHg)

The starting dose of TEVA-IRBESARTAN /HCTZ for initial treatment of severe hypertension is one tablet of TEVA-IRBESARTAN /HCTZ 150/12.5 mg once daily (see INDICATIONS AND CLINICAL USE and CLINICAL TRIALS: Severe Hypertension). The dosage may be increased after 2 - 4 weeks of therapy to a maximum of one 300/25 mg tablet once daily. TEVA-IRBESARTAN /HCTZ is not recommended as initial therapy in patients with intravascular volume depletion **(see WARNINGS AND PRECAUTIONS: Hypotension).**

DOSE ADJUSTMENT IN SPECIAL POPULATION

Diuretic Treated Patients
In patients receiving diuretics, irbesartan therapy should be initiated with caution, since these patients may be volume-depleted and thus more likely to experience hypotension following initiation of additional antihypertensive therapy. Whenever possible, all diuretics should be discontinued 2 - 3 days prior to the administration of irbesartan to reduce the likelihood of hypotension (see WARNINGS AND PRECAUTIONS – Cardiovascular: Hypotension, and DRUG INTERACTIONS). If this is not possible because of the patient's condition, irbesartan should be administered with caution and the blood pressure monitored closely. The recommended starting dose of irbesartan is 75 mg once daily in hypovolemic patients (see WARNINGS AND PRECAUTIONS – Cardiovascular: Hypotension). Thereafter, the dosage should be adjusted according to the individual response of the patient.

Geriatrics
No initial dosage adjustment in irbesartan is necessary for most elderly patients. Appropriate caution should nevertheless be used when prescribing to the elderly, as increased vulnerability to drug effect is possible in this patient population. [See WARNINGS AND PRECAUTIONS – Special Populations - Geriatrics].

Hepatic Insufficiency
No initial dosage adjustment in irbesartan is generally necessary in patients with mild to moderate hepatic impairment. Since thiazide diuretics may precipitate hepatic coma, the use of a fixed combination product such as TEVA-IRBESARTAN /HCTZ is not advisable.

Renal Insufficiency
No initial dosage adjustment in irbesartan is generally necessary in patients with renal impairment, although due to the apparent greater sensitivity of hemodialysis patients, an initial dose of 75 mg is recommended in this group of patients.

The usual regimens of therapy with TEVA-IRBESARTAN /HCTZ may be followed as long as the patient's creatinine clearance is > 30mL/min. In patients with more severe renal impairment, loop diuretics are preferred to thiazides so TEVA-IRBESARTAN /HCTZ is not recommended.

Missed Dose
Patients should be instructed to take TEVA-IRBESARTAN /HCTZ at the next scheduled dose and not take two doses at the same time if they miss a dose.

OVERDOSAGE

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

No specific information is available on the treatment of overdosage with TEVA-IRBESARTAN /HCTZ (irbesartan/hydrochlorothiazide). The patient should be closely monitored, and the treatment should be symptomatic and supportive, including fluid and electrolyte replacement.

Irbesartan
No data or very little data available in regard to overdosage in humans.

The most likely manifestations of overdosage would be hypotension and/or tachycardia; bradycardia might also occur in this setting. Irbesartan is not removed by hemodialysis.

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

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

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Irbesartan/hydrochlorothiazide combines the actions of irbesartan, an angiotensin II AT_1 receptor blocker (ARB), and that of a thiazide diuretic, hydrochlorothiazide.

Irbesartan

Irbesartan antagonizes angiotensin II by blocking AT_1 receptors.

Angiotensin II is the primary vasoactive hormone in the renin-angiotensin system (RAS). Its effects include vasoconstriction and the stimulation of aldosterone secretion by the adrenal cortex.

Irbesartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking in a non-competitive manner the binding of angiotensin II to the AT_1

receptor found in many tissues. Irbesartan has no agonist activity at the AT_1 receptor. AT_2 receptors have been found in many tissues, but to date they have not been associated with cardiovascular homeostasis. Irbesartan has essentially no affinity for the AT_2 receptors.

Irbesartan does not inhibit ACE, also known as kininase II, the enzyme that converts angiotensin I to angiotensin II and degrades bradykinin, nor does it affect renin or other hormone receptors or ion channels involved in cardiovascular regulation of blood pressure and sodium homeostasis.

Hydrochlorothiazide

Hydrochlorothiazide is a thiazide diuretic. Thiazides affect the renal tubular mechanisms 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, so coadministration of an ARB tends to reverse the potassium loss associated with these diuretics.

The mechanism of the antihypertensive effect of thiazides is not fully understood.

Pharmacodynamics

Irbesartan

In healthy subjects, single oral doses of irbesartan ≤ 300 mg produced dose-dependent inhibition of the pressor effect of angiotensin II infusions. The inhibition was complete (100%) 4 hours following oral doses of 150 mg or 300 mg. Partial inhibition of 40% and 60% was still present 24 hours post-dose with 150 mg and 300 mg irbesartan respectively.

In hypertensive patients, angiotensin II receptor inhibition following chronic administration of irbesartan caused a 1.5-2 fold rise in angiotensin II plasma concentration and a 2-3 fold increase in plasma renin levels. Aldosterone plasma concentrations generally declined following irbesartan administration, however serum potassium levels were not significantly affected at recommended doses.

During clinical trials, minimal incremental blood pressure response was observed at doses > 300 mg.

The blood pressure lowering effect of irbesartan was apparent after the first dose and substantially present within 1-2 weeks, with the maximal effect occurring by 4-6 weeks. In long-term studies, the effect of irbesartan appeared to be maintained for more than one year. There was essentially no change in average heart rate in patients treated with irbesartan in controlled trials.

There was no rebound effect after withdrawal of irbesartan.

Black hypertensive patients had a smaller blood pressure response to irbesartan monotherapy than caucasians.

There was no significant difference in blood pressure response based on age and gender.

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

Irbesartan/Hydrochlorothiazide
The components of irbesartan/hydrochlorothiazide were shown to have an additive effect on blood pressure reduction, reducing blood pressure to a greater degree than either component alone.

The blood pressure lowering effect of irbesartan in combination with hydrochlorothiazide was apparent after the first dose and substantially present within 1-2 weeks, with the maximal effect occurring by 6-8 weeks. In long-term follow-up studies, the effect of irbesartan/hydrochlorothiazide was maintained for >1 year.

Pharmacokinetics

Table 4: Pharmacokinetic Parameters for Irbersartan

Irbesartan	**T_{max} (h)**	**t½ (h)**	**Clearance (mL/minute**	**Volume of distribution**
Single dose mean	1.5-2	11-15	Plasma 157 -176 Renal 3.0 – 3.5	53 -93

Table 5: Pharmacokinetic Parameters for hydrochlorothiazide

Hydrochlorothiazide	**T_{max} (h)**	**t½ (h)**	**Clearance (mL/minute)**	**Volume of distribution (L/kg)**
Single dose mean	1.5-2	5-15	Plasma 192-343 Predominantly Renal (unchanged)	1.5-4.2

Irbesartan

Absorption
Irbesartan is an orally active agent. The oral absorption of irbesartan is rapid and complete with an average absolute bioavailability of 60% - 80%. Following oral administration, peak plasma concentrations are attained at 1.5-2 hours after dosing. Steady-state concentrations are achieved within 3 days.

Distribution
The average volume of distribution of irbesartan is 53-93 litres.

Irbesartan is approximately 96% protein-bound in the plasma, primarily to albumin and α_1-acid glycoprotein.

Metabolism
Irbesartan is metabolized via glucuronide conjugation, and oxidation by the cytochrome P-450 system.

Excretion
Irbesartan and its metabolites are excreted by both biliary and renal routes. Following either oral or intravenous administration of ^{14}C-labeled irbesartan, about 20% of radioactivity is recovered in the urine and the remainder in the feces. Less than 2% of the dose is excreted in urine as unchanged irbesartan. Irbesartan exhibits linear pharmacokinetics over the therapeutic dose range with an average terminal elimination half-life of 11-15 hours.

Total plasma and renal clearances are in the range of 157 - 176 and 3.0 - 3.5 mL/minute, respectively.

Hydrochlorothiazide

Absorption
Hydrochlorothiazide is rapidly absorbed from the gastrointestinal tract. The bioavailability is approximately 65 - 70%.

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

Metabolism
Hydrochlorothiazide is not metabolized.

Excretion
Hydrochlorothiazide is eliminated rapidly by the kidney. At least 61% of the oral dose is eliminated unchanged within 24 hours. The plasma half life has been observed to vary from 5.6 and 14.8 hours.

Special Populations and Conditions

Geriatrics
In subjects > 65 years, irbesartan elimination half-life was not significantly altered, but AUC and C_{MAX} values were about 20 - 50% greater than those of young subjects.

Renal Insufficiency

The mean AUC and C_{max} of irbesartan were not altered in patients with any degree of renal impairment, including patients on hemodialysis. However, a wide variance was seen in patients with severe renal impairment.

Hepatic Insufficiency
The pharmacokinetics of irbesartan following repeated oral administration were not significantly affected in patients with mild to moderate cirrhosis of the liver. No data is available in patients with severe liver disease.

STORAGE AND STABILITY

TEVA-IRBESARTAN /HCTZ (irbesartan/hydrochlorothiazide) tablets can be stored between 15 and 30°C.

DOSAGE FORMS, COMPOSITION AND PACKAGING

TEVA-IRBESARTAN /HCTZ (irbesartan/hydrochlorothiazide) 150/12.5 mg tablets are light pink to pink, film coated, capsule shaped tablet. One side of the tablet debossed with the number "93". The other side of the tablet debossed with the number "7238".

TEVA-IRBESARTAN /HCTZ (irbesartan/hydrochlorothiazide) 300/12.5 mg tablets are light pink to pink, film coated, capsule shaped tablet. One side of the tablet debossed with the number "93". The other side of the tablet debossed with the number "7239".

TEVA-IRBESARTAN /HCTZ (irbesartan/hydrochlorothiazide) 300/25 mg tablets are pink to dark pink, film coated, capsule shaped tablet. One side of the tablet debossed with the number "93". The other side of the tablet debossed with the number "7469".

Active ingredients: irbesartan and hydrochlorothiazide. Non-medicinal ingredients: colloidal anhydrous silica, croscarmellose sodium, magnesium stearate, microcrystalline cellulose, poloxamer, povidone, pregelatinized starch and film-coating containing the following:

150/12.5 mg and 300/12.5 mg:
hypromellose, iron oxide black, iron oxide red, iron oxide yellow, macrogol and titanium dioxide.

300/25 mg:
FD&C Blue # 2, hypromellose, iron oxide black, iron oxide red, macrogol and titanium dioxide.

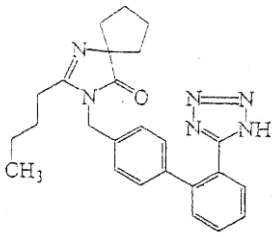
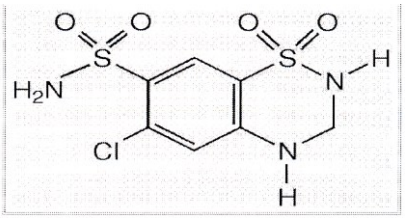
TEVA-IRBESARTAN /HCTZ 150/12.5, 300/12.5 and 300/25 mg tablets are available in bottles of 100 tablets.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: Irbesartan/hydrochlorothiazide

	Irbesartan	Hydrochlorothiazide
Chemical Name	2-butyl-3-[2'-(1 *H* –tetrazol-5-yl) [1, 1'-diphenyl]-4-yl]methyl]-1,3-diazaspiro[4,4] non-1-en-4-one.	6-chloro-3,4-dihydro- 2*H* -1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide.
Molecular Formula	$C_{25}H_{28}N_6O$	$C_7H_8ClN_3O_4S_2$
Structural Formula		
Molecular Weight	428.5	297.7
Physicochemical Properties	Irbesartan is a white to off-white crystalline powder. It is a nonpolar compound with a partition coefficient (octano/water) of 10.1 at pH of 7.4. Irbesartan is slightly soluble in alcohol and methylene chloride and practically insoluble in water.	Hydrochlorothiazide is a white, or practically white, crystalline powder. It is slightly soluble in water and freely soluble in sodium hydroxide solution.

CLINICAL TRIALS

COMPARATIVE BIOAVAILABILITY DATA

The data presented below is for a comparative, blinded, single-dose bioavailability study (N = 24) in healthy male volunteers under fasting conditions between TEVA-IRBESARTAN /HCTZ (irbesartan/hydrochlorothiazide) 300 mg/25 mg Tablets and Avalide® (irbesartan/hydrochlorothiazide) 300 mg/25 mg Tablets (Sanofi-Aventis Canada Inc.). The pharmacokinetic data calculated for the two irbesartan/hydrochlorothiazide formulations are tabulated below:

Irbesartan (1 x 300 mg/25 mg Irbesartan/Hydrochlorothiazide Tablet) From measured data **Geometric Mean Arithmetic Mean (CV %)**				
Parameter	Test*	Reference†	% Ratio of Geometric Means	Confidence Interval, 90%
AUC_T (ng*h/mL)	21475.93 23136.49 (44)	22453.99 23747.01 (35)	95.64	86.74 - 105.47
AUC_I (ng*h/mL)	22048.55 23675.73 (43)	23203.59 24680.79 (37)	95.02	86.34 - 104.58
C_{max} (ng/mL)	4095.12 4442.08 (46)	3560.87 3744.17 (32)	115.00	101.09 - 130.84
T_{max}§ (h)	1.39 (63)	1.33 (68)		
$T_{½}$§ (h)	13.40 (45)	13.65 (45)		

* TEVA-IRBESARTAN/HCTZ 300 mg/25 mg Tablets (Teva Canada Limited, Canada)

† Avalide® 300 mg/25 mg Tablets (Sanofi-Aventis Canada Inc.) were purchased in Canada.

§ Expressed as the arithmetic mean (CV%) only

Hydrochlorothiazide (1 x 300 mg/25 mg Irbesartan/Hydrochlorothiazide Tablet) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	Confidence Interval, 90%
AUC_T (ng*h/mL)	1270.430 1287.907 (17)	1279.846 1303.957 (19)	99.26	94.68 - 104.07
AUC_I (ng*h/mL)	1289.533 1306.773 (17)	1301.895 1325.506 (19)	99.05	94.59 - 103.72
C_{max} (ng/mL)	198.934 205.750 (27)	214.901 223.408 (25)	92.57	85.46 - 100.28
T_{max}§ (h)	1.65 (37)	1.46 (37)		
$T_{½}$§ (h)	10.88 (10)	10.87 (8)		

* TEVA-IRBESARTAN/HCTZ 300 mg/25 mg Tablets (Teva Canada Limited, Canada)

† Avalide® 300 mg/25 mg Tablets (Sanofi-Aventis Canada Inc.) were purchased in Canada.

§ Expressed as the arithmetic mean (CV%) only

Irbesartan-Hydrochlorothiazide
The antihypertensive effects of irbesartan/hydrochlorothiazide tablets were examined in 4 placebo-controlled studies of 8–12 weeks in patients with mild-moderate hypertension. These trials included 1914 patients randomized to fixed doses of irbesartan (37.5 to 300 mg) and concomitant hydrochlorothiazide (6.25 - 25 mg). One factorial study compared all combinations of irbesartan (37.5, 100 and 300 mg or placebo) and hydrochlorothiazide (6.25, 12.5, and 25 mg or placebo). The irbesartan-hydrochlorothiazide combinations of 75/12.5 mg and 150/12.5 mg were compared to their individual components and placebo in a separate study. A third study investigated the ambulatory blood pressure responses to irbesartan-hydrochlorothiazide (75/12.5 mg and 150/12.5 mg) and placebo after 8 weeks of dosing. Another trial investigated the effects of the addition of irbesartan (75 mg) in patients not controlled on hydrochlorothiazide (25 mg) alone.

In controlled trials, the addition of irbesartan 150–300 mg to hydrochlorothiazide doses of 6.25, 12.5 or 25 mg produced further dose-related reductions in blood pressure of 8–10/3–6 mmHg, comparable to those achieved with the same monotherapy dose of irbesartan. The addition of hydrochlorothiazide to irbesartan produced further dose related reductions in blood pressure at trough (24 hours post-dose) of 5–6/2–3 mmHg (12.5 mg) and 7–11/4–5 mmHg (25 mg), also comparable to effects achieved with hydrochlorothiazide alone. Once-daily dosing with 150 mg irbesartan and 12.5 mg hydrochlorothiazide, 300 mg irbesartan and 12.5 mg hydrochlorothiazide, or 300 mg irbesartan and 25 mg hydrochlorothiazide produced mean placebo-adjusted blood pressure reductions at trough (24 hours post-dosing) of about 13–15/7–9, 14/9–12, and 19–21/11–12 mmHg, respectively. Peak effects occurred at 3–6 hours, with the trough-to peak ratios >65%.

In another study, irbesartan (75–150 mg) or placebo was added on a background of 25 mg hydrochlorothiazide in patients not adequately controlled (SeDBP 93–120 mmHg) on hydrochlorothiazide (25 mg) alone. The addition of irbesartan (75–150 mg) gave an additive effect (systolic/diastolic) at trough (24 hours post-dosing) of 11/7 mmHg.

There was no difference in response for men and women or in patients over or under 65 years of age. Black patients had a larger response to hydrochlorothiazide than non-black patients and a smaller response to irbesartan. The overall response to the combination was similar for black and non-black patients.

Severe Hypertension

The efficacy of irbesartan/hydrochlorothiazide as initial therapy for severe hypertension (defined as a mean seated diastolic blood pressure (SeDBP) ≥110 mmHg confirmed on 2 separate occasions off all antihypertensive therapy) was studied in a 7-week, double-blind, randomized, multicenter study. Patients were randomized to either irbesartan and hydrochlorothiazide (150/12.5 mg) or to irbesartan (150 mg) once daily and followed for blood pressure response. These initial study regimens were increased at 1 week to irbesartan 300 mg/HCTZ 25 mg or to irbesartan 300 mg, respectively. The primary endpoint was a comparison at 5 weeks of the proportion of patients who achieved through SeDBP <90 mmHg. An additional supportive

endpoint compared the proportion of subjects in each treatment group whose blood pressure was controlled, defined as simultaneous SeDBP <90 mmHg and (SeSBP) <140 mmHg.

Study demographics and trial design

The study randomized 697 patients, in a 2:1 ratio to receive either combination therapy (irbesartan plus HCTZ, N=468) or irbesartan monotherapy (N=229), and included 296 (42%) females, 101 (14%) blacks, and 92 (13%) ≥65 years of age. The mean age was 52 years. The mean blood pressure at baseline for the total population was 172/113 mmHg.

Table 6 - Summary of patient demographics for clinical trial with irbesartan/ hydrochlorothiazide in subjects with severe hypertension

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age in years (Range)	Gender
CV131176	Multicenter, randomized, double-blind, active controlled , 7-week, parallel group study	Oral administration of irbesartan /HCTZ 150/12.5 mg or irbesartan 150 mg increased at one week to irbesartan /HCTZ 300/25 mg or to irbesartan 300 mg.	697 Irbesartan: 229 Irbesartan/HCTZ: 468	52.5 (23.0 - 83.0)	Male 57.5% Female 42.5%

Study results

The study results are summarized in table 7.

After 5 weeks of therapy, the mean SeDBP was 4.7 mmHg lower (p≤0.0001) and the mean SeSBP was 9.7 mmHg lower (p<0.0001) in the group treated with irbesartan/hydrochlorothiazide than in the group treated with irbesartan. Mean reductions from baseline for SeDBP and SeSBP at trough were 24.0 mmHg and 30.8 mmHg for irbesartan/hydrochlorothiazide-treated patients and 19.3 mmHg and 21.1 mmHg for irbesartan-treated patients, respectively. A greater proportion of patients on irbesartan/hydrochlorothiazide achieved a diastolic blood pressure <90 mmHg (47.2% for irbesartan/hydrochlorothiazide, 33.2% for irbesartan; p=0.0005) and a greater proportion of the patients on irbesartan/hydrochlorothiazide achieved simultaneous control of SeSBP <140 mmHg and SeDBP <90 mmHg (34.6% versus 19.2%; p<0.0001). Similar results were seen when the patients were grouped according to gender, race or age (<65 years, ≥65 years). The proportions of subjects with controlled SeDBP, as well as with simultaneous SeDBP/SeSBP control, at each week of the double-blind period were consistently larger and statistically significantly greater for irbesartan/hydrochlorothiazide-treated patients than for irbesartan-treated patients.

Table 7 - Results at week 5 of study with irbesartan/hydrochlorothiazide in subjects with severe hypertension

Endpoints	irbesartan /HCTZ 150/12.5 mg force titrated to 300/25 mg	Irbesartan 150 mg force titrated to 300 mg	p value
Primary Endpoint: Proportion of subjects in each treatment group whose SeDBP was controlled (SeDBP < 90 mmHg).	47.2%	33.2%	0.0005
Other Endpoints:			
▪ Proportion of subjects whose BP was controlled (simultaneous SeDBP <90 mmHg and SeSBP <140 mmHg)	34.6%	19.2%	< 0.0001
▪ Mean changes from baseline in trough			
SeDBP	-24.0	-19.3	< 0.0001
SeSBP	-30.8	-21.1	< 0.0001

DETAILED PHARMACOLOGY

Pharmacokinetics

Irbesartan

Following either oral or intravenous administration of ^{14}C-labeled irbesartan, > 80% of the circulating plasma radioactivity was attributable to unchanged irbesartan. The primary circulating metabolite was the inactive irbesartan glucuronide (approximately 6%). The remaining oxidative metabolites did not add appreciably to the pharmacologic activity.

In vitro studies of irbesartan indicated that the oxidation of irbesartan was primarily by cytochrome P-450 isoenzyme CYP 2C9. Metabolism of irbesartan by CYP 3A4 was negligible. Irbesartan was neither metabolized, nor does it substantially induce or inhibit the following isoenzymes: CYP 1A1, 1A2, 2A6, 2B6, 2D6, 2E1. There was no induction or inhibition of CYP 3A4.

Hydrochlorothiazide

Hydrochlorothiazide was not metabolized but is eliminated rapidly by the kidney. The plasma half-life was observed to vary between 5.6 and 14.8 hours when the plasma levels could be followed for at least 24 hours. At least 61 percent of the oral dose was eliminated unchanged within 24 hours.

TOXICOLOGY

Acute Toxicity

Irbesartan

Table 8: Acute Toxicity for Irbesartan

Species	Sex (N)	Route	LD50 (mg/kg)
Mouse	M (5) F (5)	PO	> 2000
Rat	M (5) F (5)	PO	> 2000
Mouse	M (5) F (5)	IV	> 50
Rat	M (5) F (5)	IV	> 50
Mouse	M (5) F (5)	IP	200 - 2000
Rat	M (5) F (5)	IP	200 - 2000

After single administration, toxicity was slight and no target organ was identified. Very few toxic effects, characterized by pilo-erection and/or somnolence were noted at 2000 mg/kg by the oral route, 200 mg/kg by the intraperitoneal route and 50 mg/kg by the intravenous route. Acute oral toxicity studies with Irbesartan in mice and rats indicated acute lethal doses were in excess of 2000 mg/kg, about 25 - 50 fold the maximum human dose (300 mg) on a mg/m^2 basis, respectively.

Irbesartan - hydrochlorothiazide

Table 9: Acute Toxicity for Irbesartan – hydrochlorothiazide

Species	Sex (N)	Route	LD50 (mg/kg)		
			Irbesartan	HCTZ	Irbesartan/ HCTZ
Mouse	M (5) F (5)	PO	> 2000	> 4000	> 2000/4000
Rat	M (5)	PO	> 3000	> 500	> 3000/500

No mortality occurred following administration of the irbesartan/hydrochlorothiazide combination up to and including the highest dose of irbesartan:hydrochlorothiazide (2000/4000 mg/kg in mice or 3000/500 mg/kg in rats). No treatment-related clinical signs and body weight

changes were observed. At necropsy, performed at the end of the 14-day observation period, pathologic examinations did not reveal any treatment-induced changes.

Subacute and Chronic Toxicity

Irbesartan

Table 10: Subacute and Chronic Toxicity Irbesartan

Species/ Strain	Sex (N/Dose)	Dose (mg/kg/day)	Route	Time	Effects
SUBACUTE TOXICITY					
Rat	M (10) F (10)	0, 30 , 70 , 150	PO	4 weeks	• Irbesartan only induced slight decrease in hemoglobin levels (at 150 mg/kg) and slight increase in glucose (≥30 mg/kg), urea (≥ 70 mg/kg), creatinine and K^+ levels (at 150 mg/kg), and slight decrease in Na^+ and Cl^- urinary concentrations and excretions (≥30 mg/kg).
Rat	M (10) F (10)	0, 0.8 , 2 , 5	IV	16 days	• Very slight increase in Na^+ and Cl^- plasma levels (≥0.8 mg/kg/day in males) • Very slight increase in K^+ plasma levels, in ASAT and slight decrease in kidney relative weight at 5 mg/kg/day in males.
Monkey	M (3) F (3)	0 , 10, 30 , 90	PO	4 weeks	• Dose-related hyperplasia of the juxtaglomerular apparatus (from 30 mg/kg/day upwards).
Monkey	M (3) F (3)	0 , 250 , 500 , 1000	PO	4 weeks	• ≥250 mg/kg/day: changes in the kidney (hyperplasia of the juxtaglomerular apparatus), heart (myocardial fibrosis) and erythrocytes parameters (slight anemia). • At 500 mg/kg/day: increased platelet count, fibrogen and neutrophil levels and at 1000 mg/kg/day, health deterioration were also noted. • One animal receiving 250 mg/kg/day presented the most severe heart lesions and marked electrocardiographic modifications on D1 and D29. However, pre-existing lesions could not be excluded.
Monkey	M (3) F (3)	0 , 0.8 , 2 , 5	IV	2 weeks	• Irbesartan induced only a slight hyperplasia of the juxtaglomerular apparatus in 2/3 females receiving 5 mg/kg/day. • One high-dose animal presented a marked heart hypertrophy with marked ECG changes on D1 and D10 suggesting that it was a preexisting lesion.

Species/ Strain	Sex (N/Dose)	Dose (mg/kg/day)	Route	Time	Effects
Rat	M (20) - F (20) [main study] M (10) - F (10) [reversibility study for control and high dose groups] M (5) - F (5) [toxicokinetics study]	0 , 10 , 30 , 90	PO	26 weeks	• Slight reduction of the body weight gain in males at 90 mg/kg/day (- 6 to - 8%). • Other changes can be considered to be of pharmacological origin for some of them and have no clear toxicological significance for all of them. • The no-observed adverse effect dose was considered to be 30 mg/kg/day.
CHRONIC TOXICITY					
Rat	M (20) - F (20) [main study] M (10) - F (10) [reversibility study for control and high dose groups] M (5) - F (5) [toxicokinetics study]	0 , 0 , 250 , 500, 1000	PO	26 weeks	• Slight reduction of body weight gain without any dose-relationship reversible. • Changes in hematology and blood biochemistry parameters demonstrating an effect on red blood cells and on the renal function, likely associated with the pharmacological activity of irbesartan and reversible. • Hyperplasia/hypertrophy of the juxtaglomerular apparatus in males (≥250 mg/kg/day) and in females (≥ 500 mg/kg/day) partially reversible.
Monkey	M (5) - F (5) [main study] M (3) - F (3) [reversibility study for control and high dose groups)]	0, 10, 30, 90	PO	6 months	• Dose-related hyperplasia of juxtaglomerular apparatus in all treated animals partially reversible at the end of treatment. • Slight dose-related decrease in weight gain from the 30 mg/kg/day dose level upwards and slight anemia from 10 mg/kg/day upwards, both reversible on cessation of treatment.
Monkey	M (5) F (5)	0, 20, 100, 500	PO	52 weeks	• Irbesartan was well tolerated and most of the changes observed were considered to be due to the pharmacological activity of the drug: • Dose-related decrease in blood pressure at doses ≥ 20 mg/kg/day associated with necrosis of the tip of the tail likely due to a decrease in blood flow at 500 mg/kg/day. • Dose-related hyperplasia / hypertrophy of the juxtaglomerular apparatus in all treated animals with degenerative kidney changes at 500 mg/kg/day. • Slight decrease in body weight gain and erythrocyte parameters at doses ≥ 100 mg/kg/day.

After repeated oral administrations at dose levels up to 1000 mg/kg per day, most of the treatment-related effects noted in all species are linked to the pharmacological activity of irbesartan. The kidney can be considered as the primary target organ: hyperplasia/hypertrophy of the juxtaglomerular apparatus which was observed in all species, is a direct consequence of the interaction with the renin-angiotensin system. Irbesartan also induced some hematology (slight decrease in erythrocyte parameters) and blood biochemistry variations (slight increase in urea, creatinine, phosphorus, potassium and calcium levels) likely due to a disturbance in the renal blood flow, and a slight decrease in heart weight which could result from a decrease in cardiac work load due to decreased peripheral vascular resistance. At high doses (> 500 mg/kg per day), degenerative changes of the kidney were noted which could be secondary to prolonged hypotensive effects.

Subacute and Chronic Toxicity (Cont'd)
Irbesartan/hydrochlorothiazide

Table 11: Subacute and Chronic Toxicity Irbesartan/hydrochlorothiazide

Species / Strain	Sex (N/Dose)	Dose (mg/kg/day)	Route	Time	Effects
Rat	M (20) F (20)	0*/0**, 10/10, 90/90 90/0, 0/90	PO	6 months	• Exposure to HCTZ was greater when administered in combination with irbesartan, than when given alone. • Body weight gains in the high dose group (90/90 mg/kg) were slightly decreased in females and moderately decreased in males. • Hemoglobin, hematocrit, and erythrocyte counts were slightly decreased in females given the high dose combination (90/90). • In the high dose combination, serum urea nitrogen and alkaline phosphatase (males) were slightly elevated; serum potassium and calcium (Week 12) were slightly decreased in males; serum cholesterol and triglycerides were slightly to moderately decreased. • In the low dose combination, serum cholesterol, triglycerides and potassium were slightly decreased. • Slight increases in urine pH; urine protein concentrations markedly lower in high dose combination group. • Decreased heart weights in males and females at 10/10, 99/90 and 90/0. • Decreased liver weights in males. • Juxtaglomerular-cell hypertrophy/hyperplasia. • Increased urine output. • Increased kidney weights in females. • At necropsy, discoloration of the glandular stomach correlated with focal coagulative necrosis or ulceration of the mucosa were noted in all treated groups with an incidence slightly greater in rats given the high-dose combination.
Monkey	M (20) F (20)	0*/0**, 10/10, 90/90 0/90, 90/0	PO	6 months	• Exposure to HCTZ was approximately 60% greater when administered in combination with irbesartan than when administered alone. • Body weights of males in the high dose combination group (90/90) were mildly decreased. • Mean hemoglobin, hematocrit and erythrocyte values were mildly to moderately decreased at the high dose combination (90/90). • Moderate increases in BUN; mild to moderate increases in creatinine values; mean sodium, potassium, and chloride values were mildly to moderately decreased. • Mild to moderate juxtaglomerular apparatus, hypertrophy/hyperplasia [all treated with irbesartan either alone or in combination]

* Irbesartan
** Hydrochlorothiazide

Reproduction and Teratology

Irbesartan

Fertility and reproductive performance were not affected in studies of male and female rats even at oral doses of irbesartan causing pronounced toxicity (up to 650 mg/kg/day). No significant effects on the number of corpora lutea, implants, or live fetuses were observed. Irbesartan did not affect survival, development, or reproduction of offspring except for a slight decrease of body weight gain during lactation which was reversible after weaning.

In a study of rats receiving maternally toxic doses of irbesartan (650 mg/kg/day), transient effects were observed in fetuses. These effects included increased incidences of renal pelvic cavitation at doses ≥50 mg/kg/day and subcutaneous edema at doses ≥180 mg/kg/day. Slight decreases in body weight gain were noted (prior to weaning) in offspring of females receiving irbesartan at doses ≥ 50 mg/kg/day. In rabbits, maternally toxic doses of irbesartan (30 mg/kg/day) were associated with maternal mortality and abortion. Surviving females receiving this dose had a slight increase in early resorption. However, no teratogenic effect was observed. Radioactivity was present in the rat and rabbit fetus during late gestation and in rat milk following oral doses of radiolabeled irbesartan. These findings are attributed to drug exposure in late gestation and during lactation.

Irbesartan/hydrochlorothiazide

In a Segment II teratology study carried out in rats, a dose of the combination irbesartan/hydrochlorothiazide up to 150/150mg/day/kg did not show any teratogenic potential. There was decreased foetal body weight in the litters of dams given 150/150 mg/kg/day.

Carcinogenicity and Mutagenicity

Irbesartan
No evidence of carcinogenicity was observed when irbesartan was administered at doses of up to 500/1000 mg/kg/day (males/females, respectively) in rats and 1000 mg/kg/day in mice for 2 years. These doses provided systemic exposures of 3.6 - 24.9 times (rats) and 3.8 - 6.2 times (mice) the exposures in humans receiving 300 mg daily.

Irbesartan was not mutagenic in a battery of *in vitro* tests (Ames microbial test, rat hepatocyte DNA repair test, V79 mammalian cell forward gene mutation assay). Irbesartan was negative in several tests for induction of chromosomal aberrations (*in vitro* - human lymphocyte assay; *in vivo* – mouse micronucleus study).

Irbesartan/hydrochlorothiazide
No carcinogenicity studies have been conducted with the irbesartan/hydrochlorothiazide combination.

Irbesartan/hydrochlorothiazide was not mutagenic in standard *in vitro* tests (Ames microbial test and Chinese hamster mammalian-cell forward gene-mutation assay).

Irbesartan/hydrochlorothiazide was negative in tests for induction of chromosomal aberrations (*in vitro* - human lymphocyte assay; *in vivo* - mouse micronucleus study).

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PART III: CONSUMER INFORMATION

PrTEVA-IRBESARTAN/HCTZ

(irbesartan/hydrochlorothiazide) tablets

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

ABOUT THIS MEDICATION

What the medication is used for:

TEVA-IRBESARTAN/HCTZ lowers high blood pressure.

What it does:

TEVA-IRBESARTAN/HCTZ is a combination of 2 drugs, irbesartan and hydrochlorothiazide.

- Irbesartan is an angiotensin receptor blocker (ARB). You can recognize an ARB because its medicinal ingredient ends in "SARTAN". It lowers blood pressure.
- Hydrochlorothiazide is a diuretic or "water pill" that increases urination. This lowers blood pressure.

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

When it should not be used:

Do not take TEVA-IRBESARTAN/HCTZ:

- Are allergic to irbesartan or hydrochlorothiazide or to any non-medicinal ingredient in the formulation.
- Are allergic to any sulfonamide-derived drugs (sulfa drugs); most of them have a medicinal ingredient that ends in "MIDE".
- Have experienced an allergic reaction (angioedema) with swelling of the hands, feet, or ankles, face, lips, tongue,throat, or sudden difficulty breathing or swallowing to any ARB (any drug in the same class as irbesartan). Be sure to tell your doctor, nurse, or pharmacist that this has happened to you.
- Have difficulty urinating or produce no urine.
- Have diabetes or kidney disease and are already taking:
    - a blood pressure-lowering medicine that contains aliskiren (such as RASILEZ®)
    - an angiotensin converting enzyme (ACE) inhibitor. You can recognize ACE inhibitors because their medicinal ingredient ends in '-PRIL'
- Are pregnant or intend to become pregnant. Taking TEVA-IRBESARTAN/HCTZ during pregnancy can cause injury and even death to your baby.
- Are breast feeding. TEVA-IRBESARTAN/HCTZ passes into breast milk.

TEVA-IRBESARTAN/HCTZ is not recommended for use in children and adolescents (under the age of 18 years).

What the medicinal ingredients are:

Irbesartan and hydrochlorothiazide.

What the nonmedicinal ingredients are:

colloidal anhydrous silica, croscarmellose sodium, magnesium stearate, microcrystalline cellulose, poloxamer, povidone, pregelatinized starch.

150/12.5 mg and 300/12.5 mg tablets also contain as film coating: hypromellose, iron oxide black, iron oxide red, iron oxide yellow, macrogol and titanium dioxide.

300/25 mg tablets also contain as film coating: FD&C Blue # 2, hypromellose, iron oxide black, iron oxide red, macrogol and titanium dioxide.

What dosage forms it comes in:

TEVA-IRBESARTAN/HCTZ tablets are available in three different strengths.

Tablets which contain 150 mg of irbesartan and 12.5 mg of hydrochlorothiazide come in the form of light pink to pink, film coated, capsule shaped tablet. One side of the tablet debossed with the number "93". The other side of the tablet debossed with the number "7238".

The next strength contains 300 mg of irbesartan and 12.5 mg of hydrochlorothiazide. These come in a similar form and colour, light pink to pink, film coated, capsule shaped tablet. One side of the tablet debossed with the number "93". The other side of the tablet debossed with the number "7239".

The highest strength tablets contain 300 mg of irbesartan and 25 mg of hydrochlorothiazide. These tablets come in the form of pink to dark pink, film coated, capsule shaped tablet. One side of the tablet debossed with the number "93". The other side of the tablet debossed with the number "7469".

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions-Pregnancy

TEVA-IRBESARTAN/HCTZ should not to be used during pregnancy. If you discover that you are pregnant while taking TEVA-IRBESARTAN/HCTZ stop the medication and contact your doctor, nurse or pharmacist as soon as possible.

BEFORE you use TEVA-IRBESARTAN/HCTZ tell your doctor or pharmacist if you:

- Are allergic to any drug used to lower blood pressure, including angiotensin converting enzyme (ACE) inhibitors, or penicillin.
- Have narrowing of an artery or a heart valve.

- Have had a heart attack or stroke.
- Have heart failure.
- Have diabetes, liver or kidney disease.
- Have gout, or lupus erythematosus
- Are on dialysis
- Are dehydrated or suffer from excessive vomiting, diarrhea or sweating.
- Are taking a salt substitute that contains potassium, potassium supplements, or a potassium-sparing diuretic (a specific kind of "water pill" that makes your body keep potassium).
- Are on a low-salt diet.
- Are taking a medicine that contains aliskiren, such as RASILEZ ®, used to lower high blood pressure. The combination with TEVA-IRBESARTAN/HCTZ is not recommended.
- Are taking an angiotensin converting enzyme (ACE) inhibitor. The combination with TEVA-IRBESARTAN/HCTZ is not recommended.
- Are less than 18 years old.

Hydrochlorothiazide in TEVA-IRBESARTAN/HCTZ can cause Sudden Eye Disorders:

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

These eye disorders are related and can develop within hours to weeks of starting TEVA-IRBESARTAN/HCTZ.

You may become sensitive to the sun while taking TEVA IRBESARTAN/HCTZ. Exposure to sunlight should be minimized until you know how you respond.

Before surgery and general anesthesia (even at the dentist's office), tell the doctor or dentist that you are taking TEVA IRBESARTAN/HCTZ, as there may be a sudden fall in blood pressure associated with general anesthesia.

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

INTERACTIONS WITH THIS MEDICATION

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

The following may interact with TEVA-IRBESARTAN/HCTZ:

- Adrenocorticotropic hormone (ACTH) used to treat West Syndrome.
- Alcohol, barbiturates (sleeping pills), or narcotics (strong pain medications). They may cause low blood pressure and dizziness when you go from lying or sitting to standing up.
- Amphotericin B, an antifungal drug
- Anticancer drugs, including cyclophosphamide and methotrexate.
- Antidepressants, in particular selective serotonin reuptake inhibitors (SSRIs), including citalopram, escitalopram, and sertraline.
- Antidiabetic drugs, including insulin and oral medicines.
- Bile acid resins used to lower cholesterol.
- Blood pressure-lowering drugs, including diuretics ("water pills"), aliskiren-containing products (e.g. RASILEZ ®), or angiotensin converting enzyme (ACE) inhibitors.
- Calcium or vitamin D supplements.
- Corticosteroids used to treat joint pain and swelling and other conditions.
- Digoxin, a heart medication.
- Drugs that slow down or speed up bowel function, including atropine, metoclopramide, and domperidone.
- Drugs used to treat epilepsy, including carbamazepine and topiramate.
- Gout medications, including allopurinol and probenecid.
- Hyperglycemic agent, such as diazoxide.
- Lithium used to treat bipolar disease.
- Nonsteroidal anti-inflammatory drugs (NSAIDs), used to reduce pain and swelling. Examples include ibuprofen, naproxen, and celecoxib.
- Potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes.
- Pressor amines such as norepinephrine.
- Skeletal muscle relaxants used to relieve muscle spasms, including tubocurare.
- Warfarin

PROPER USE OF THIS MEDICATION

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

TEVA-IRBESARTAN/HCTZ can be taken with or without food but it should be taken the same way each day. If TEVA-IRBESARTAN/HCTZ causes upset stomach, take it with food or milk.

Usual Adult dose:
Patients should be individually titrated for each component separately.
Usual maintenance dose is: 1 tablet daily.

Overdose:

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

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

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Side effects may include:

- back or leg pain, muscle cramps, spasms and pain, weakness, restlessness
- dizziness, pins and needles in your fingers, headache and fatigue
- constipation, diarrhea, nausea, vomiting, decreased appetite, upset stomach, enlargement of the glands in your mouth, bleeding under the skin, rash, red patches on the skin
- drowsiness, insomnia
- reduced libido

If any of these affects you severely, tell your doctor, nurse or pharmacist..
TEVA-IRBESARTAN/HCTZ Can cause abnormal blood test results. Your doctor will decide when to perform blood tests and will interpret the results.

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

Symptoms / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common	**Low Blood Pressure:** dizziness, fainting, lightheadedness May occur when you go from lying or sitting to standing up.	✓		
	Edema: swelling of hands, ankles or feet		✓	
	Tachycardia: increased heart beats		✓	
	Decreased or increased levels of potassium in the blood: irregular heartbeats, muscle weakness and generally feeling unwell		✓	
Uncommon	**Allergic Reaction:** rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			✓
Uncommon	**Kidney Disorder:** change in frequency of urination, nausea, vomiting, swelling of extremities, fatigue		✓	
	Liver Disorder: yellowing of the skin or eyes, dark urine, abdominal pain, nausea, vomiting, loss of appetite		✓	
	Increased blood sugar: frequent urination, thirst, and hunger	✓		
Rare	**Rhabdomyolysis :** muscle pain that you cannot explain, muscle tenderness or weakness, dark brown urine		✓	
	Decreased White Blood Cells: infections, fatigue, fever, aches, pains, and flu-like symptoms		✓	
	Decreased Platelets: bruising, bleeding, fatigue and weakness		✓	
Very rare	**Toxic Epidermal Necrolysis:** severe skin peeling, especially in mouth and eyes			✓
Unknown	**Eye disorders:** **- Myopia:** sudden near sightedness or blurred vision **- Glaucoma:** increased pressure in your eyes, eye pain			✓
	Anemia: fatigue, loss of energy, weakness, shortness of breath.		✓	
	Inflammation of the Pancreas: abdominal pain that lasts and gets worse when you lie down, nausea, vomiting		✓	

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

HOW TO STORE IT

Store TEVA-IRBESARTAN/HCTZ tablets at room temperature (15 to 30ºC).

Keep out of the reach and sight of children.

REPORTING SUSPECTED SIDE EFFECTS

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

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

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

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

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting Teva Canada Limited
at: 1-800-268-4127 ext. 1255005 (**English**)
or 1-877-777-9117 (**French**)
or druginfo@TevaCanada.com

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