PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]pms-IRBESARTAN-HCTZ

Irbesartan and Hydrochlorothiazide Tablets

Tablets, 150 mg/12.5 mg, 300 mg/12.5 mg and 300 mg/25 mg, Oral

House Standard

Angiotensin II AT_1 Receptor Blocker / Diuretic

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RECENT MAJOR LABEL CHANGES

7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism	06/2021
7 WARNINGS AND PRECAUTIONS, Ophthalmologic	06/2021
7 Warnings and Precautions, Respiratory	04/2023

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

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

- for the treatment of essential hypertension in patients for whom combination therapy is appropriate (see 4 DOSAGE AND ADMINISTRATION).
- as initial therapy in patients with severe essential hypertension (Sitting DBP $\geq$ 110 mmHg) for whom the benefit of a prompt blood pressure reduction exceeds the risk of initiating combination therapy in these patients (see 14 CLINICAL TRIALS; and 4 DOSAGE AND ADMINISTRATION).

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

1.1 Pediatrics

Pediatrics (< 18 years of age)
The safety and efficacy of irbesartan/hydrochlorothiazide in patients < 18 years of age have not been established. Therefore, Health Canada has not authorized an indication for pediatric use (see 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations).

1.2 Geriatrics

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 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations).

2 CONTRAINDICATIONS

pms-IRBESARTAN-HCTZ is contraindicated in:

- Patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see
- 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- Patients who are hypersensitive to other sulphonamide-derived drugs, because of the hydrochlorothiazide component.
- Patients with anuria.
- Pregnant women (see 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations).
- Nursing women (see 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations).

- Combination 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) (see 7 WARNINGS AND PRECAUTIONS, Renal; and 9 DRUG INTERACTIONS).
- Combination with angiotensin converting enzyme (ACE) inhibitors in patients with diabetic nephropathy (see 7 WARNINGS AND PRECAUTIONS, Renal; and 9 DRUG INTERACTIONS).
- Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption (due to lactose component of the pms-IRBESARTAN-HCTZ tablets).

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

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, pms-IRBESARTAN-HCTZ should be discontinued as soon as possible (see 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- Dosage must be individualized.
- The fixed combination is not for initial therapy except for severe hypertension.
- The dose of pms-IRBESARTAN-HCTZ (irbesartan/hydrochlorothiazide) should be determined by the titration of the individual components.
- Use pms-IRBESARTAN-HCTZ in patients with liver impairment is not advisable.
- Dosage adjustment may be required in hemodialysis patients (see 4.2 Recommended Dose and Dosage Adjustment).

4.2 Recommended Dose and Dosage Adjustment

Once the patient has been stabilized on the individual components as described below, either one tablet of irbesartan/hydrochlorothiazide 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.

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 $\geq$ 110 mmHg)

The starting dose of pms-IRBESARTAN-HCTZ for initial treatment of severe hypertension is one tablet of pms-IRBESARTAN-HCTZ 150/12.5 mg once daily (see 1 INDICATIONS; and 14 CLINICAL TRIALS). The dosage may be increased after 2 – 4 weeks of therapy to a maximum of one 300/25 mg tablet once daily. pms-IRBESARTAN-HCTZ is not recommended as initial therapy in patients with intravascular volume depletion (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular).

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 7 WARNINGS AND PRECAUTIONS Cardiovascular; and 9 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 7 WARNINGS AND PRECAUTIONS Cardiovascular). Thereafter, the dosage should be adjusted according to the individual response of the patient.

Geriatric
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 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations).

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 pms-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 pms-IRBESARTAN-HCTZ is not recommended.

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 irbesartan/hydrochlorothiazide is not advisable.

4.4 Administration

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

4.5 Missed Dose

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

5 OVERDOSAGE

No specific information is available on the treatment of overdosage with 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.

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

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength / Composition	Non-Medicinal Ingredients
Oral	Tablet / 150mg/12.5 mg 300 mg/12.5 mg 300 mg/25 mg	Colloidal Silicon Dioxide, Copovidone, Croscarmellose Sodium, Lactose Monohydrate, and Magnesium Stearate. The coating of the tablets contains:

		Hypromellose, Iron Oxide Black, Iron Oxide Red, Iron Oxide Yellow, Polyethylene Glycol, Titanium Dioxide.

150 mg/12.5 mg: Each peach, oval, biconvex, coated tablet debossed with "P" on one side and "150-12.5" on the other side, contains 150 mg of irbesartan, 12.5 mg of hydrochlorothiazide, and the following non-medicinal ingredients: Colloidal Silicon Dioxide, Copovidone, Croscarmellose Sodium, Lactose Monohydrate, Magnesium Stearate. The coating contains: Hypromellose, Iron Oxide Black, Iron Oxide Yellow, Iron Oxide Red, Polyethylene Glycol, Titanium Dioxide. Available in HDPE bottles of 100 tablets.

300 mg/12.5 mg: Each peach, biconvex, coated tablet debossed with "P" on one side and "300-12.5" on the other side, contains 300 mg of irbesartan, 12.5 mg of hydrochlorothiazide, and the following non-medicinal ingredients: Colloidal Silicon Dioxide, Copovidone, Croscarmellose Sodium, Lactose Monohydrate, Magnesium Stearate. The coating contains: Hypromellose, Iron Oxide Black, Iron Oxide Yellow, Iron Oxide Red, Polyethylene Glycol, Titanium Dioxide. Available in HDPE bottles of 100 tablets.

300 mg/25 mg: Each pink, oval, biconvex, coated tablet debossed with "P" on one side and "300-25" on the other side, contains 300 mg of irbesartan, 25 mg of hydrochlorothiazide, and the following non-medicinal ingredients: Colloidal Silicon Dioxide, Copovidone, Croscarmellose Sodium, Lactose Monohydrate, Magnesium Stearate. The coating contains: Hypromellose, Iron Oxide Black, Iron Oxide Yellow, Iron Oxide Red, Polyethylene Glycol, Titanium Dioxide. Available in HDPE bottles of 100 tablets.

7 WARNINGS AND PRECAUTIONS

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 (see 8 ADVERSE REACTIONS, 8.5Post-Market Adverse Reactions). The photosensitizing action of hydrochlorothiazide may be a possible mechanism for NMSC (see 16 NON-CLINICAL TOXICOLOGY, Carcinogenicity and Mutagenicity).

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 ADVERSE REACTIONS, 8.5Post-Market Adverse Reactions).

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 4 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 irbesartan/hydrochlorothiazide, 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 pms-IRBESARTAN-HCTZ in combination with aliskiren-containing drugs is contraindicated in these patients (see 2 CONTRAINDICATIONS).
The use of pms-IRBESARTAN-HCTZ in combination with an ACE inhibitor is contraindicated in patients with diabetic nephropathy (see 2 CONTRAINDICATIONS).

Further, co-administration of ARBs, including the irbesartan component of pms-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.

Driving and Operating Machinery

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.

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.

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

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

pms-IRBESARTAN-HCTZ may induce hypoglycemia, particularly in patients treated for diabetes. Therefore, dose adjustment of antidiabetic treatment such as repaglinide or insulin may be required (see 8 ADVERSE REACTIONS).

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

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.

Ophthalmologic

Choroidal effusion, Secondary Acute Angle-Closure Glaucoma and/or Acute Myopia

Hydrochlorothiazide is a sulfonamide. Sulfonamide or sulfonamide derivative drugs can cause an idiosyncratic reaction, which may result in choroidal effusion, secondary acute angle-closure glaucoma and/or acute transient myopia (see 8ADVERSE REACTIONS, 8.5 Post-Market Adverse Reactions). 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

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 pms-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 2 CONTRAINDICATIONS; and 9 DRUG INTERACTIONS).

The use of ARBs including the irbesartan component of pms-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 2 CONTRAINDICATIONS; and 9 DRUG INTERACTIONS).

Use of irbesartan should include appropriate assessment of renal function.

Thiazides should be used with caution.

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

Respiratory

Acute Respiratory Distress

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

Skin

Photosensitivity

Photosensitivity reactions have been reported with the use of thiazide diuretics.
If the photosensitivity reactions occur during treatment with hydrochlorothiazide drugs, treatment should be stopped.

Psoriasis

The use of pms-IRBESARTAN HCTZ in patients with psoriasis or a history of psoriasis should be carefully weighed as it may exacerbate psoriasis.

7.1 Special Populations

7.1.1. 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, pms-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 ARB 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.

7.1.2 Breast-feeding

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.

7.1.3 Pediatrics

Pediatrics (< 18 years of age)
Safety and effectiveness have not been established.

7.1.4.Geriatrics

Geriatrics (> 65 years of age)
Of the 2,650 hypertensive patients receiving irbesartan/hydrochlorothiazide in clinical studies, 618 patients were ≥ 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.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Irbesartan/hydrochlorothiazide was evaluated for safety in 2,746 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 7 WARNINGS AND PRECAUTIONS, Cardiovascular).

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

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.

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

	Irbesartan/HCTZ n = 898 (%)	Irbesartan n = 400 (%)	HCTZ n = 380 (%)	Placebo n = 236 (%)
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				
Allergy	1.1	0.5	0.5	0
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
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;

Hematologic: anemia, lymphocytopenia, thrombocytopenia;

Investigations: increased creatine phosphokinase (CPK);

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.

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

Irbesartan/Hydrochlorothiazide

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

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.

Irbesartan

Creatine Phosphokinase: In an open-label extension study, significant increases in plasma creatine phosphokinase (CPK) were commonly observed (1.6%) in irbesartan treated subjects.

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 0.16 g/dL were observed in patients receiving irbesartan. No patients were discontinued due to anemia.

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.

Liver Function Tests: In placebo-controlled trials, elevations of aspartate aminotransferase (AST) and alanine transaminase (ALT) $\geq$ 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 $\geq$ 3x ULN was 0.4%.

Neutropenia: Neutropenia (< 1,000 cells/mm^3) was observed in 0.3% of irbesartan treated patients compared to 0.5% of patients receiving placebo.

8.5 Post-Market Adverse Reactions

The following adverse reactions were reported in post-marketing use:

Related to Irbesartan + Hydrochlorothiazide

General: asthenia, syncope;

Hepatic/Biliary/Pancreatic: hepatobiliary disorders (acute hepatitis, cholestatic or cytolytic hepatitis), elevated liver function tests, jaundice;

Immune: anaphylactic reactions, anaphylactic shock, angioedema (involving swelling of the face, lips, and/or tongue) has been reported rarely;

Musculoskeletal: myalgia;

Renal: impaired renal function including cases of renal failure in patients at risk (see 7 WARNINGS AND PRECAUTIONS, Renal).

Related to Irbesartan

Endocrine and Metabolism: hypoglycemia (see 7 WARNINGS AND PRECAUTIONS);

Hematologic: anemia (cases of positive dechallenge and rechallenge have been reported post-market), thrombocytopenia (including thrombocytopenic purpura);

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

Related to Hydrochlorothiazide

Ear/Nose/Throat: tinnitus;

Gastrointestinal: anorexia, gastric irritation, sialadenitis;

Hematologic: agranulocytosis, bone marrow depression, leucopenia, thrombocytopenia;

Hepatic/Biliary/Pancreatic: pancreatitis;

Immune: necrotizing angiitis (vasculitis, cutaneous vasculitis), photosensitivity;

Ophthalmologic: eye disorders (secondary acute angle-closure glaucoma, acute myopia and choroidal effusion; *frequency unknown*), xanthopsia;

Renal: interstitial nephritis;

Respiratory: respiratory distress (including pneumonitis and pulmonary edema), Acute respiratory distress syndrome (ARDS) (see 7 WARNINGS AND PRECAUTIONS);

Skin: psoriasis (and psoriasis exacerbation), toxic epidermal necrolysis.

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 1,000 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 1,000 treated patients compared with non-use of hydrochlorothiazide (meta-analysis of 2 observational studies).

9 DRUG INTERACTIONS

9.2 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.

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

Proper / Common 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.
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	

Proper / Common Name	Source of Evidence	Effect	Clinical Comment
		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.

Proper / Common Name	Source of Evidence	Effect	Clinical Comment
Antidiabetic agents (e.g., insulin and oral antihyperglycemic agents) (e.g., repaglinide)	CT	Thiazide-induced hyperglycemia may compromise blood sugar control. Depletion of serum potassium augments glucose intolerance. May induce hypoglycemia. Irbesartan has the potential to inhibit OATP1B1. In a clinical study, co-administration of irbesartan and repaglinide, 300 mg irbesartan once daily for 4 days, then followed by a single dose of 2 mg repaglinide, 1 hour after irbesartan (with consideration of the T_{max} difference between the two drugs), increased the C_{max} and AUC of repaglinide (substrate of OATP1B1) by 1.8-fold and 1.3-fold, respectively.	Monitor glycemic control, supplement potassium if necessary, to maintain appropriate serum potassium levels, Dose adjustment of antidiabetic treatment such as repaglinide may be required (see 7 WARNINGS AND PRECAUTIONS).
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, beta-blockers, 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

Proper / Common Name	Source of Evidence	Effect	Clinical Comment
			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 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. 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.	
Digoxin	CT	When irbesartan was administered as 150 mg once daily under steady-state conditions, no effect was seen on the pharmacokinetics of digoxin at steady-state.	Concomitant administration of hydrochlorothiazide and digoxin requires caution. Monitor electrolytes and digoxin levels closely.

Proper / Common Name	Source of Evidence	Effect	Clinical Comment
		Thiazide-induced electrolyte disturbances, i.e., hypokalemia, hypomagnesemia, increase the risk of digoxin toxicity, which may lead to fatal arrhythmic events.	Supplement potassium or adjust doses of digoxin or thiazide, as required.
Dual Blockade of the Renin-Angiotensin-System (RAS) with ARBs, ACE inhibitors or aliskiren-containing drugs	CT	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, renal failure and hyperkalemia.	See 2 CONTRAINDICATIONS; and 7 WARNINGS AND PRECAUTIONS, Dual Blockade of the Renin-Angiotensin System (RAS) .
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.

Proper / Common Name	Source of Evidence	Effect	Clinical Comment
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 anti-inflammatory drugs (NSAID) (including selective COX-2 inhibitors)	CT	In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, co-administration 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	Monitor renal function periodically in patients receiving irbesartan and NSAID therapy.

Proper / Common Name	Source of Evidence	Effect	Clinical Comment
		including selective COX-2 inhibitors. In some patients, the administration of a NSAID can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics.	When pms-IRBESARTAN-HCTZ 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

9.5 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, T_{max} 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.

9.6 Drug-Herb Interactions

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

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

pms-IRBESARTAN-HCTZ (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 co-administration 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.

10.2 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.

10.3 Pharmacokinetics

Table 4: Pharmacokinetic Parameters for Irbesartan

Irbesartan	**T_{max} (h)**	**$t_{½}$ (h)**	**Clearance (mL/minute)**	**Volume of Distribution (L)**
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)**	**$t_{½}$ (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

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.

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.

Elimination
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.

<u>Hydrochlorothiazide</u>

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.

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.

Elimination

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 old, irbesartan elimination half-life was not significantly altered, but AUC and C_{max} values were about 20% – 50% greater than those of young subjects.

- **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.

- **Renal Insufficiency**
  The mean AUC and Cmax 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.

11 STORAGE, STABILITY AND DISPOSAL

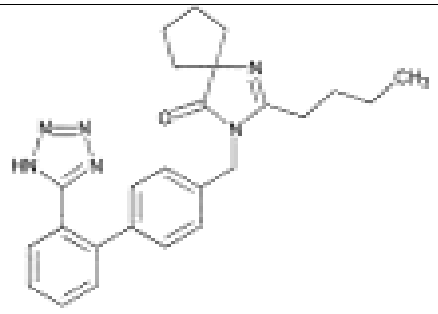
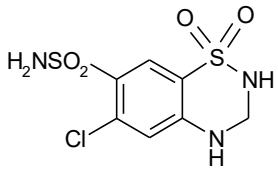
Store between 15°C and 30°C.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: Irbesartan/Hydrochlorothiazide

	Irbesartan	**Hydrochlorothiazide**
Chemical Name	2-butyl-3-[(2[1]-(1*H*-tetrazol-5-yl) biphenyl-4-yl)methyl]-1,3-diazaspiro [4,4] non-1-en-4-one.	6-chloro-3,4-dihydro-2*H*-1,2,4-benzo-thiadiazine-7-sulfonamide 1,1-dioxide
Molecular Formula	$C_{25}H_{28}N_6O$	$C_7H_8ClN_3O_4S_2$
Molecular Mass	428.53 g/mol	297.72 g/mol
Structural Formula		
Physicochemical Properties	Irbesartan is a white to off-white crystalline powder. It is a nonpolar compound with a partition coefficient (octanol/water) of 10.1 at a 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. Hydrochlorothiazide is slightly soluble in water and freely soluble in sodium hydroxide solution.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

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 1,914 patients randomized to fixed doses of irbesartan (37.5 to 300 mg) and concomitant hydrochlorothiazide (6.25 to 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.

<u>Severe Hypertension</u>
The efficacy of irbesartan/hydrochlorothiazide as initial therapy for severe hypertension (defined as a mean seated diastolic blood pressure (SeDBP) $\geq$ 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 1 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%

14.2 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

14.3 Comparative Bioavailability Studies

A single-dose, crossover comparative bioavailability study was conducted in healthy male volunteers (n = 26) under fasting conditions comparing pms-IRBESARTAN-HCTZ (irbesartan/hydrochlorothiazide) 300 mg/25 mg tablets (Pharmascience Inc.) to AVALIDE® (irbesartan/hydrochlorothiazide) 300 mg/25 mg tablets (Sanofi-Aventis Canada Inc.). A summary of the pharmacokinetic data is presented in the following tables.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Irbesartan (1 x 300mg/25mg 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)	20,144.5 20,953.4 (29.5)	19,543.1 20,593.4 (32.9)	103.08	98.67 – 107.68
AUC_I (ng·h/mL)	21,817.2 22,573.6 (29.7)	21,792.4 22,726.2 (32.3)	100.11	95.13 – 105.36
C_{max} (ng/mL)	3,845.6 3,989.4 (30.4)	3,425.4 3,528.2 (29.2)	112.27	106.98 – 117.81
T_{max}§ (h)	1.25 (0.500 – 5.00)	1.25 (0.500 – 5.00)		
$T_{½}$€ (h)	10.34 (27.4)	13.39 (39.2)		

*pms-IRBESARTAN-HCTZ, Pharmascience Inc., Montréal, Canada

†AVALIDE® Tablets (Sanofi-Aventis Canada Inc.) were purchased in Canada

§ Expressed as the median (range)

€ Expressed as the arithmetic mean (CV %)

+ Based on least squares estimates

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Hydrochlorothiazide (1 x 300mg/25mg 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)	889.01 917.76 (24.5)	873.99 903.72 (25.3)	101.72	97.24 – 106.40
AUC_I (ng·h/mL)	1,000.38 1,029.70 (24.1)	978.90 1,006.75 (23.5)	102.19	98.07– 106.49
C_{max} (ng/mL)	146.83 157.00 (38.7)	145.52 153.24 (35.5)	100.90	92.17 – 110.45
T_{max}[§] (h)	1.75 (1.00–3.00)	1.75 (1.00–3.00)		
$T_{½}$[€] (h)	10.28 (15.7)	10.20 (17.3)		

[*]pms-IRBESARTAN-HCTZ, Pharmascience Inc., Montréal, Canada
[†]AVALIDE® Tablets (Sanofi-Aventis Canada Inc.) were purchased in Canada
[§] Expressed as the median (range)
[€] Expressed as the arithmetic mean (CV %)
[+] Based on least squares estimates

16 NON-CLINICAL TOXICOLOGY

Acute Toxicity

Irbesartan

Table 8: Acute Toxicity for Irbesartan

Species	Sex (N)	Route	LD50 (mg/kg)
Mouse	M (5) F (5)	PO	> 2,000
Rat	M (5) F (5)	PO	> 2,000
Mouse	M (5) F (5)	IV	> 50
Rat	M (5) F (5)	IV	> 50
Mouse	M (5) F (5)	IP	200 – 2,000

Species	Sex (N)	Route	LD50 (mg/kg)
Rat	M (5) F (5)	IP	200 – 2,000

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 2,000 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 2,000 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	> 2,000	> 4,000	> 2,000/4,000
Rat	M (5)	PO	> 3,000	> 500	> 3,000/500

No mortality occurred following administration of the irbesartan/hydrochlorothiazide combination up to and including the highest dose of irbesartan/hydrochlorothiazide (2,000/4,000 mg/kg in mice or 3,000/500 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, 1,000	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 1,000 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.
Rat	M (20) – F (20) [main study] M (10) – F (10) [reversibility study for control	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.

Species/ Strain	Sex (N/Dose)	Dose (mg/kg/ day)	Route	Time	Effects
SUBACUTE TOXICITY					
	and high dose groups] M (5) – F (5) [toxicokinetics study]				
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, 250, 500, 1,000	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.

Species/ Strain	Sex (N/Dose)	Dose (mg/kg/ day)	Route	Time	Effects
SUBACUTE TOXICITY					
					• Slight decrease in body weight gain and erythrocyte parameters at doses ≥ 100 mg/kg/day.

After repeated oral administrations at dose levels up to 1,000 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

Species/ Strain	Sex (N/Dose)	Dose (mg/kg/day)	Route	Time	Effects
					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 $\geq$ 50 mg/kg/day and subcutaneous edema at doses $\geq$ 180 mg/kg/day. Slight decreases in body weight gain were noted (prior to weaning) in offspring of females receiving irbesartan at doses $\geq$ 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 150/150 mg/day/kg did not show any teratogenic potential. There was decreased fetal 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 500/1,000 mg/kg/day (males/females, respectively) in rats and 1,000 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).

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 pheochromocytoma 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 although there is no relevant mutagenic potential *in vivo*, 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.

17 SUPPORTING PRODUCT MONOGRAPHS

[Pr]AVALIDE® tablets, 150/12.5 mg and 300/12.5 mg, submission control number 265405, Product Monograph, sanofi-aventis Canada Inc., Jamuary 30, 2023.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr] pms-IRBESARTAN-HCTZ
Irbesartan and Hydrochlorothiazide Tablets

Read this carefully before you start taking **pms-IRBESARTAN-HCTZ** 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 **pms-IRBESARTAN-HCTZ**.

Serious Warnings and Precautions
pms-IRBESARTAN-HCTZ should not be used during pregnancy. Taking pms-IRBESARTAN-HCTZ during pregnancy can cause injury or even death to your baby. If you discover that you are pregnant while taking pms-IRBESARTAN-HCTZ, stop the medication and contact your healthcare professional as soon as possible.

What is pms-IRBESARTAN-HCTZ used for?
pms-IRBESARTAN-HCTZ is used in adults to lower high blood pressure.

How does pms-IRBESARTAN-HCTZ work?
pms-IRBESARTAN-HCTZ is a combination of 2 drugs, irbesartan and hydrochlorothiazide:
- Irbesartan is an angiotensin receptor blocker (ARB). It lowers blood pressure.
- Hydrochlorothiazide is a diuretic or “water pill” that increases urination. This also helps to lower blood pressure.

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

What are the ingredients in pms-IRBESARTAN-HCTZ?
Medicinal ingredients: Irbesartan and hydrochlorothiazide
Non-medicinal ingredients: Colloidal Silicon Dioxide, Copovidone, Croscarmellose Sodium, Lactose Monohydrate, Magnesium Stearate.

The coating of the tablets contains: Hypromellose, Iron Oxide Black, Iron Oxide Red, Iron Oxide Yellow, Polyethylene Glycol, Titanium Dioxide.

pms-IRBESARTAN-HCTZ comes in the following dosage forms:
Tablets, in three strengths:
Irbesartan / hydrochlorothiazide: 150 mg / 12.5 mg
Irbesartan / hydrochlorothiazide: 300 mg / 12.5 mg
Irbesartan / hydrochlorothiazide: 300 mg / 25 mg

Do not use pms-IRBESARTAN-HCTZ if you:

- are allergic to irbesartan or hydrochlorothiazide or to any non-medicinal ingredients 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 healthcare professional 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 pms-IRBESARTAN-HCTZ during pregnancy can cause injury and even death to your baby.
- are breast-feeding. pms-IRBESARTAN-HCTZ passes into breast milk.
- have one of the following rare hereditary diseases:
  - Galactose intolerance
  - Lapp lactase deficiency
  - Glucose-galactose malabsorption

  because lactose is a non-medicinal ingredient in pms-IRBESARTAN-HCTZ.

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

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

- have experienced an allergic reaction to any drug used to lower blood pressure, including angiotensin converting enzyme (ACE) inhibitors.
- are allergic to penicillin.
- have narrowing of an artery or a heart valve.
- have had a heart attack or stroke.
- have heart failure.
- have liver or kidney disease.
- have diabetes. pms-IRBESARTAN-HCTZ may cause low blood sugar levels.
- have gout, or lupus erythematosus.
- have psoriasis or a history of psoriasis.
- 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 pms-IRBESARTAN-HCTZ is not recommended.
- are taking an angiotensin converting enzyme (ACE) inhibitors. The combination with pms-IRBESARTAN-HCTZ is not recommended.
- are taking a medicine that contains lithium. The combination with pms-IRBESARTAN-HCTZ is not recommended.
- have had skin cancer or have a family history of skin cancer.
  have a greater chance of developing skin cancer because you have light-coloured skin, get sunburned easily, or are taking drugs to 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 or certain diuretics (i.e., "water pills"). If you develop any severe shortness of breath or difficulty breathing after taking pms-IRBESARTAN-HCTZ, stop the medication and seek medical attention immediately.

Other warnings you should know about:

Risk of skin cancer:

- pms-IRBESARTAN-HCTZ contains hydrochlorothiazide. Treatment with hydrochlorothiazide may increase the risk of developing non-melanoma skin cancer. The risk is higher if you have been taking AVALIDE for many years (more than 3) or at a high dose.
- While taking pms-IRBESARTAN-HCTZ:
  - Make sure to regularly check your skin for any new lesions. Check areas that are most exposed to the sun, such as the face, ears, hands, shoulders, upper chest and back.
  - You may become sensitive to the sun.
  - Limit your exposure to the sun and to indoor tanning. Always use sunscreen (SPF-30 or higher) and wear protective clothing when going outside.

Talk to your healthcare professional immediately if you become more sensitive to the sun or UV light or if you develop an unexpected skin lesion (such as a lump, bump, sore, or patch) during treatment.

Sudden Eye Disorders:

- pms-IRBESARTAN-HCTZ contains hydrochlorothiazide. Treatment with hydrochlorothiazide may increase the risk of developing sudden eye problems.
- **Myopia:** sudden nearsightedness or blurred vision.
- **Glaucoma:** an increased pressure in your eyes, eye pain. Untreated, it may lead to permanent vision loss.
- **Choroidal effusion:** abnormal buildup of liquid in your eye that may result in vision changes.

If your vision changes, stop taking AVALIDE and seek immediate medical help. These eye disorders are related and can develop within hours to weeks of starting pms-IRBESARTAN-HCTZ. If you have had a penicillin or sulfonamide allergy, you can be at higher risk of developing this. Talk to your healthcare professional immediately if you develop any eye problems while taking pms-IRBESARTAN-HCTZ.

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

Allergic Reactions: Allergic (swelling of areas of tissue under the skin, sometimes affecting the face and throat, hives and severe allergic reactions) have been reported. Stop taking pms-IRBESARTAN-HCTZ and get immediate medical help if you experience any symptoms of an allergic reaction.

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

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

The following may interact with pms-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, such as repaglinide.
- Beta-blockers (medications for heart disease).
- 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 agents, 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.

How to take pms-IRBESARTAN-HCTZ:

- Take pms-IRBESARTAN-HCTZ every day exactly as prescribed.
- It is recommended to take your dose at about the same time every day.
- pms-IRBESARTAN-HCTZ can be taken with or without food, but it should be taken the same way each day.
- If pms-IRBESARTAN-HCTZ causes upset stomach, take it with food or milk.

Usual dose:
1 tablet once daily.

Overdose

If you think you, or a person you are caring for, have taken too much pms-IRBESARTAN-HCTZ, 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, carry on with the next dose at the usual time. Do not double the dose.

What are possible side effects from using pms-IRBESARTAN-HCTZ?
These are not all the possible side effects you may feel when taking pms-IRBESARTAN-HCTZ. If you experience any side effects not listed here, contact your healthcare professional.
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
- rash, red patches on the skin
- drowsiness, insomnia
- reduced libido
- lightheadedness

- ringing in the ears.

pms-IRBESARTAN-HCTZ can cause abnormal blood test results. Your healthcare professional will decide when to perform blood tests and will interpret the results.

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			
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: fast heartbeat		✓	
Decreased or increased levels of potassium in the blood: irregular heartbeats, muscle weakness, generally feeling unwell		✓	
Increased levels of creatine phosphokinase: blood tests may show raised levels of an enzyme that measures breakdown of muscle (creatine phosphokinase)			✓
Non-melanoma skin cancer: lump or discoloured patch on the skin that stays after a few weeks and slowly changes. Cancerous lumps are red/pink and firm and sometimes turn into ulcers. Cancerous patches are usually flat and scaly.		✓	
UNCOMMON			
Allergic reaction and angiodema: rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			✓
Kidney problems: change in frequency of urination, nausea, vomiting, swelling of extremities, fatigue		✓	
Liver problems: yellowing of the skin or eyes, dark urine, abdominal pain, nausea, vomiting, loss of appetite		✓	
High 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, weakness, small purple or red dots under the skin		✓	

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**	
VERY RARE			
Acute respiratory distress (inflammation of lung tissue or excess fluid in the lungs)**:** severe shortness of breath or difficulty breathing, fever, weakness, and confusion.			✓
Serious skin reactions (Steven-Johnson Syndrome, Toxic Epidermal Necrolysis): any combination of itchy skin rash, redness, blistering and peeling of the skin and/or of the lips, eyes, mouth, nasal passages or genitals, accompanied by fever, chills, headache, cough, body aches or joint pain, yellowing of the skin or eyes, dark urine			✓
UNKNOWN FREQUENCY			
Eye disorders: – **Myopia:** sudden near sightedness or blurred vision – **Glaucoma:** increased pressure in your eyes, eye pain – **Choroidal effusion:** blind spots, eye pain, blurred vision			✓
Anemia (decreased number of red blood cells)**:** fatigue, loss of energy, looking pale, weakness, shortness of breath.		✓	
Inflammation of the pancreas: abdominal pain that lasts and gets worse when you lie down, nausea, vomiting		✓	
Skin problems: psoriasis, increased skin sensitivity to sunlight		✓	
Low blood pressure: sweating, weakness, hunger, dizziness, trembling, headache			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to 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 between 15°C and 30°C.

Keep out of reach and sight of children.

If you want more information about pms-IRBESARTAN-HCTZ:

- 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), or by contacting the sponsor Pharmascience Inc. at: 1-888-550-6060.

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