PRODUCT MONOGRAPH

PrAVA-IRBESARTAN/HCTZ

(irbesartan/hydrochlorothiazide)

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

Manufacturer's Standard

Angiotensin II AT_1 Receptor Blocker / Diuretic

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[Pr] AVA-IRBESARTAN/HCTZ

(irbesartan/hydrochlorothiazide)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form/Strength	Clinically Relevant Non Medicinal Ingredients
Oral	Tablets/ 150/12.5 mg 300/12.5 mg 300/25 mg	Pregelatinized starch *For a complete listing, see Dosage Forms, Composition and Packaging section*

INDICATIONS AND CLINICAL USE

AVA-IRBESARTAN/HCTZ (irbesartan/hydrochlorothiazide) is indicated for the treatment of essential hypertension in patients for whom combination therapy is appropriate (see DOSAGE AND ADMINISTRATION).

AVA-IRBESARTAN/HCTZis also indicated 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).

AVA-IRBESARTAN/HCTZis 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 over 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

AVA-IRBESARTAN/HCTZ(irbesartan/hydrochlorothiazide) is contraindicated in patients who are hypersensitive to any component of this product.

Because of the hydrochlorothiazide component, this product is contraindicated in patients with anuria, and in patients who are hypersensitive to other sulfonamide-derived drugs.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

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

General

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

Carcinogenesis and Mutagenesis

See **TOXICOLOGY** for discussion of animal data**.**

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.

Endocrine and Metabolism

Thiazides, including hydrochlorothiazide, can cause fluid or electrolyte imbalance (hypokalemia, hyponatremia and hypochloremic alkalosis).

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 PB1 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.

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 disease the diuretic should be discontinued.

Renal Impairment

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function have been seen in susceptible individuals. In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, such as patients with bilateral renal artery stenosis, unilateral renal artery stenosis to a solitary kidney, or severe congestive heart

failure, treatment with agents that inhibit this system has been associated with oliguria, progressive azotemia, and rarely, acute renal failure and/or death. In susceptible patients, concomitant diuretic use may further increase risk.

Use of irbesartan should include appropriate assessment of renal function.

Thiazides should be used with caution.

Because of the hydrochlorothiazide component, AVA-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 can cause fetal and neonatal morbidity and death when administered to pregnant women. When pregnancy is detected, AVA-IRBESARTAN/HCTZshould be discontinued as soon as possible.

The use of ARB is not recommended during pregnancy. Epidemiological evidence regarding the risk of teratogenicity following exposure to angiotensin converting enzyme inhibitors (another class of therapeutic products interfering with the RAAS) during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Given the current evidence available on the risk with ARB, similar risks may exist for this class of drugs. Patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with angiotensin II antagonists should be stopped immediately, and, if appropriate, alternative therapy should be started.

The use of ARBs during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification, retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia).

Infants with histories of *in utero* exposure to ARBs should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion may be required as 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 milk of lactating rats. Thiazides appear in human milk. Because many drugs are excreted in human milk and because of their potential for affecting the nursing infant adversely, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatrics
Safety and effectiveness have not been established.

Geriatrics
Of the 2650 hypertensive patients receiving irbesartan/hydrochlorothiazide in clinical studies, 618 patients were 65 years of age and over. 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 has been evaluated for safety in 2746 patients with essential hypertension including 968 patients for 1 year or more.

The most commonly reported adverse events (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 adverse events most frequently resulting in clinical intervention (discontinuation of irbesartan/hydrochlorothiazide) were due to dizziness (0.7%) and headache (0.7%). The adverse event 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 adverse event in 3.6 percent of patients treated with irbesartan/hydrochlorothiazide, versus 6.8 percent of patients given placebo.

Adverse events 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				
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

	Irbesartan/ HCTZ n = 898 (%)	Irbesartan n = 400 (%)	HCTZ n = 380 (%)	Placebo n = 236 (%)
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 adverse events 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)
Diarrhaea	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 adverse events 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 adverse events 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 less than 1% of patients receiving irbesartan, regardless of drug relationship:

Body as a Whole: fever;

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

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

Endocrine: sexual dysfunction, libido disorder, gout;

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

Musculoskeletal: muscle cramp, arthritis, myalgia, muscular weakness;

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

Renal/Genitourinary: abnormal urination;

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

Special Senses: visual disturbance, hearing impaired, conjunctivitis, taste disturbance.

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 AST and ALT ≥3X upper limit of normal occured in 0.1% and 0.2%, respectively, of irbesartan treated patients compared to 0.3% and 0.3%, respectively, of patients receiving placebo. The cumulative incidence of AST

and/or ALT elevations ≥ 3X upper limit of normal was 0.4% in patients treated with irbesartan for a mean duration of over 1 year.

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 blood urea nitrogen (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, thrombocytopenia, lymphocytopenia, and increased CPK.

Post-Market Adverse Drug Reactions
Angioedema (involving swelling of the face, lips, and/or tongue) has been reported rarely in post marketing use. The following adverse reactions, regardless of drug relationship, were reported very rarely in post-marketing use: syncope, asthenia, jaundice, myalgia, elevated liver function tests, and impaired renal function including occasional cases of renal failure in patients at risk (see WARNINGS AND PRECAUTIONS – Renal - Renal Impairment).

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

DRUG INTERACTIONS

Drug-Drug Interactions

Diuretics
Patients on diuretics, and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with irbesartan. The possibility of symptomatic hypotension with the use of irbesartan can be minimized by discontinuing the diuretic prior to initiation of treatment and/or lowering the initial dose of irbesartan (see WARNINGS AND PRECAUTIONS – Cardiovascular - Hypotension, and DOSAGE AND ADMINISTRATION). No drug interaction of clinical significance has been identified with thiazide diuretics.

Agents increasing Serum Potassium
Since irbesartan decreases the production of aldosterone, potassium-sparing diuretics or potassium supplements should be given only for documented hypokalemia and with frequent monitoring of serum potassium. Potassium-containing salt substitutes should also be used with caution. Concomitant thiazide diuretic use may attenuate any effect that irbesartan may have on serum potassium.

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

Lithium generally should not be given with diuretics. Diuretic agents reduce the renal clearance of lithium and increase risk of lithium toxicity.

Warfarin
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.

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

Simvastatin
When irbesartan was administered in a small single-dose study with 12 young, healthy males aged 19 to 39, the single-dose pharmacokinetics of simvastatin were not affected by the concomitant administration of 300 mg irbesartan. Simvastatin values were highly variable whether simvastatin was administered alone or in combination with irbesartan.

Nifedipine
The pharmacokinetics of irbesartan were not affected by coadministration of nifedipine.

Alcohol, Barbiturates, or Narcotics
Diuretic potentiation of orthostatic hypotension may occur.

Antidiabetic Drugs (oral agents and insulin)
In the presence of diuretics, dosage adjustment of the antidiabetic drug may be required.

Other Antihypertensive Drugs
Diuretic additive effect or potentiation may occur.

Cholestyramine and Colestipol Resins
Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. AVA-IRBESARTAN/HCTZshould be taken at least one hour before or four hours after these medications.

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

Pressor Amines (e.g., Norepinephrine)
In the presence of diuretics, possible decreased response to pressor amines may be seen but not sufficient to preclude their use.

Skeletal Muscle Relaxants, Nondepolarizing (e.g., Tubocurarine)
In the presence of diuretics, possible increased responsiveness to the muscle relaxant may occur.

Non-steroidal Anti-inflammatory Drugs
In some patients, the administration of a non-steroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics. Therefore, when AVA-IRBESARTAN/HCTZand non-steroidal anti- inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

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 AVA-IRBESARTAN/HCTZ(irbesartan/hydrochlorothiazide) should be determined by the titration of the individual components.
- Use of AVA-IRBESARTAN/HCTZwith 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).

<u>Recommended Dose and Dosage Adjustment</u>

Once the patient has been stabilized on the individual components as described below, either one tablet of AVA-IRBESARTAN/HCTZ150/12.5 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.

AVA-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 AVA-IRBESARTAN/HCTZ for initial treatment of severe hypertension is one tablet of AVA-IRBESARTAN/HCTZ 150/12.5 mg once daily (see INDICATIONS AND CLINICAL USE and CLINICAL TRIALS: Severe Hypertension). The dosage may be increased after two to four weeks of therapy to a maximum of one 300/25 mg tablet once daily. AVA-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 two to three 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 monitered 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 – 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 AVA-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 AVA-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 AVA-IRBESARTAN/HCTZ is not recommended.

Missed Dose
Patients should be instructed to take AVA-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 Immediately.

No specific information is available on the treatment of overdosage with AVA-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, 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. 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 angiotensin converting enzyme, 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 angiotensin II AT_1 receptor blocker 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 up to 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 causes 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 decline following irbesartan administration, however serum potassium levels are not significantly affected at recommended doses.

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

The blood pressure lowering effect of irbesartan is 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 is no rebound effect after withdrawal of irbesartan.

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

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

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

Pharmacokinetics

Table 3: Pharmacokinetic Parameters for Irbersartan

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 4: 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

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 to 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 over the age of 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

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

DOSAGE FORMS, COMPOSITION AND PACKAGING

AVA-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".

AVA-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".

AVA-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.

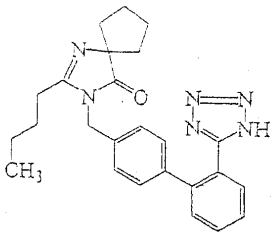
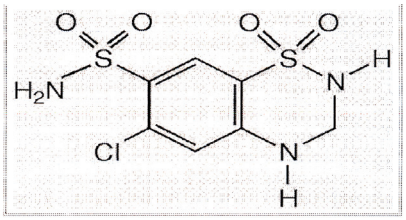
AVA-IRBESARTAN/HCTZ 150/12.5, 300/12.5 and 300/25 mg tablets are available in bottles of 100 tablets.

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 AVA-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)		

* AVA-IRBESARTAN/HCTZ 300 mg/25 mg Tablets (Avanstra Inc.., 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)		

* AVA-IRBESARTAN/HCTZ 300 mg/25 mg Tablets (Avanstra Inc., 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 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.

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 two separate occasions off all antihypertensive therapy) was studied in a seven-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 one week to irbesartan 300 mg/HCTZ 25 mg or to irbesartan 300 mg, respectively. The primary endpoint was a comparison at five weeks of the proportion of patients who achieved trough 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 seated systolic blood pressure (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 5 - 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 6.

After five 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 the 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 6 - 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

Pharmacodynamics

Irbesartan

In healthy subjects, single oral doses of irbesartan up to 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 causes 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 decline following irbesartan administration, however serum potassium levels are not significantly affected at recommended doses.

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

The blood pressure lowering effect of irbesartan is 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 is no rebound effect after withdrawal of irbesartan.

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

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 over one year.

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

Pharmacokinetics

Irbesartan

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

In vitro studies of irbesartan indicate that the oxidation of irbesartan is primarily by cytochrome P-450 isoenzyme CYP 2C9. Metabolism of irbesartan by CYP 3A4 is negligible. Irbesartan is 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.

The mean AUC and C_{MAX} 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.

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.

Hydrochlorothiazide

Hydrochlorothiazide is not metabolized but is eliminated rapidly by the kidney. The plasma half-life has been observed to vary between 5.6 and 14.8 hours when the plasma levels can be followed for at least 24 hours. At least 61 percent of the oral dose is eliminated unchanged within 24 hours. Hydrochlorothiazide crosses the placental but not the blood-brain barrier and is excreted in breast milk.

TOXICOLOGY

Acute Toxicity

Irbesartan

Table 7: 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 8: 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 9: 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 10: 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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11. **AVALIDE®** Product Monograph by Sanofi-aventis Canada Inc. (product Distributed by Bristol-Myers Squibb Canada). Date of Revision: December 29, 2008.

PART III: CONSUMER INFORMATION

[Pr]AVA-IRBESARTAN/HCTZ

(irbesartan/hydrochlorothiazide) tablets

This leaflet is Part III of a three-part "Product Monogaph" published when AVA-IRBESARTAN/HCTZ was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about AVA-IRBESARTAN/HCTZ. Please read this leaflet carefully before you start to take your medicine, even if you have just refilled your prescription. Contact your doctor or pharmacist if you have any questions about the drug. Remember that your doctor has prescribed this medicine only for you. Never give it to anyone else.

ABOUT THIS MEDICATION

What the medication is used for:
AVA-IRBESARTAN/HCTZ is used to treat hypertension (high blood pressure).

What it does:
The irbesartan ingredient of AVA-IRBESARTAN/HCTZ lowers blood pressure by specifically blocking a naturally occurring substance called angiotensin II, which normally narrows your blood vessels. The irbesartan ingredient of AVA-IRBESARTAN/HCTZ allows the blood vessels to relax. The hydrochlorothiazide ingredient of AVA-IRBESARTAN/HCTZ works by making your kidneys pass more water and salt. Together irbesartan and hydrochlorothiazide lower high blood pressure. Although your doctor will be able to tell you that the medicine is working by measuring your blood pressure, you will probably feel no different while you are taking AVA-IRBESARTAN/HCTZ.

If your blood pressure remains too high after an adequate trial period, your doctor may decide to increase the dose of either irbesartan or hydrochlorothiazide.

When it should not be used:
Do not take AVA-IRBESARTAN/HCTZ:

- If you are allergic to any of its ingredients or to sulfonamide. (See **What the nonmedicinal ingredients are**)
- If you have difficulty in producing urine.
- If you are not sure whether you should start taking AVA-IRBESARTAN/HCTZ, contact your doctor or your pharmacist.
- Pregnancy and Breast-feeding: It is not recommended that you use AVA-IRBESARTAN/HCTZ while you are pregnant or breast-feeding. If you are pregnant or planning to become pregnant while taking AVA-IRBESARTAN/HCTZ, talk to your doctor as soon as possible.

Children: AVA-IRBESARTAN/HCTZ should not be given to children.

What the medicinal ingredient is:
Each tablet of AVA-IRBESARTAN/HCTZ contains irbesartan and hydrochlorothiazide.

What the nonmedicinal ingredients are:
AVA-IRBESARTAN/HCTZ tablets contain the following nonmedicinal ingredients: 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:
AVA-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
AVA-IRBESARTAN/HCTZ should not to be used during pregnancy. If you discover that you are pregnant while taking AVA-IRBESARTAN/HCTZ stop the medication and please contact your physician.

BEFORE you use AVA-IRBESARTAN/HCTZ talk to your doctor or pharmacist about any medical problems you have or have had, and about any allergies. Tell your doctor if you have recently suffered from excess vomiting or diarrhea.
- It is particularly important to tell your doctor if you have liver or kidney disease, gout, diabetes, lupus erythematosus, or if you are being treated with other diuretics (water pills). In these cases, your doctor may need to adjust the dose of your medications.
-Before surgery and general anesthesia (even at the dentist's office), tell the doctor or dentist that you are taking AVA-IRBESARTAN/HCTZ, as there may be a sudden fall in blood pressure associated with general anesthesia.

- You are pregnant, breast-feeding or thinking of becoming pregnant?
Taking AVA-IRBESARTAN/HCTZ during pregnancy can cause injury and even death to your baby. This medication should not be used during pregnancy. If you are planning to become pregnant while taking AVA-IRBESARTAN/HCTZ, contact immediately your doctor.

It is possible that AVA-IRBESARTAN/HCTZ passes into breast milk. You should discuss with your doctor about taking AVA-IRBESARTAN/HCTZ while breast-feeding.

Wait until you know how you respond to your medication before performing tasks that require special attention (for example, driving an automobile or operating dangerous machinery).

INTERACTIONS WITH THIS MEDICATION

You should have informed your doctor of any medicines you are taking. These include medicines obtained without prescription.

The diuretic agent, hydrochlorothiazide, contained in AVA-IRBESARTAN/HCTZ may interact with other medicines.

Preparations containing lithium should not be taken with AVA-IRBESARTAN/HCTZ without close supervision by your doctor. Special precautionary measures (e.g., blood tests) may be appropriate if you take potassium supplements, potassium-containing salt substitutes or potassium sparing medicines, other diuretics (water pills), warfarin, digoxin, antidiabetic drugs, alcohol, barbiturates, narcotics, pressor amines, skeletal muscle relaxants, cholestyramine and colestipol resins.

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.

It is important for your doctor to know if you are taking other medicines to reduce your blood pressure, or if you are taking steroids, or anti-inflammatory medicines used in arthritis.

PROPER USE OF THIS MEDICATION

Usual dose:
Take AVA-IRBESARTAN/HCTZ every day exactly as your doctor has instructed.
It is important to continue taking AVA-IRBESARTAN/HCTZ for as long as your doctor prescribes it in order to maintain control of your blood pressure.
AVA-IRBESARTAN/HCTZ may be taken with or without food, however it should be taken consistently with respect to food intake.

Overdose:
For management of a suspected drug overdose, or in case of an actual overdose, contact your Regional Poison Centre or your doctor immediately, so that medical attention may be given promptly.

Missed Dose:
Try to take AVA-IRBESARTAN/HCTZ daily as prescribed. However, if you miss a dose, do not take an extra dose. Just resume your normal schedule.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Along with its intended action, any medication, including AVA-IRBESARTAN/HCTZ, may cause

side effects. In most patients, irbesartan/hydrochlorothiazide is well tolerated. Side effects may include:

- Headache
- Dizziness
- Fatigue
- Muscle pain

Side effects such as myalgia (muscle pain), myasthenia (muscle weakness), myositis (muscle inflammation) and rhabdomyolysis (a muscle-wasting disease), in rare cases leading to kidney failure, have been reported with the use of angiotensin II receptor blockers, the class of drugs to which a component of AVA-IRBESARTAN/HCTZ belongs. You should contact your physician promptly if you experience muscle pain that you cannot explain, muscle tenderness or weakness, generalised weakness, or when you notice dark/brown urine. Your physician or pharmacist has a more complete list. Tell your physician or pharmacist promptly about these or any other unusual symptoms.

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	
Uncommon	low blood pressure associated with dizziness/light headedness (hypotension)			
	fainting (syncope)			
	Muscle pain you cannot explain			
	Muscle tenderness or weakness			
	Generalized weakness			
	Dark/brown urine			

This is not a complete list of side effects. If you have any unexpected effects while taking AVA-IRBESARTAN/HCTZ, contact your doctor or pharmacist.

HOW TO STORE IT

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

Keep this medication out of the reach 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 0701C
    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 obtained by contacting, Avanstra Inc.:
1-855-709-3678 or medinfo@avanstra.com

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