PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]APO-IRBESARTAN

Irbesartan Tablets

Tablets, 75 mg, 150 mg and 300 mg, Oral

USP

Angiotensin II AT_1 Receptor Blocker

APOTEX INC.
150 Signet Drive
Toronto, Ontario
M9L 1T9

Date of Initial Authorization:
MAY 24, 2012

Date of Revision:
DEC 13, 2023

Submission Control Number: 279112

RECENT MAJOR LABEL CHANGES

None at the time of the most recent authorization

TABLE OF CONTENTS

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

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

APO-IRBSESARTAN (irbesartan) is indicated for the treatment of:

- essential hypertension. APO-IRBESARTAN may be used alone or concomitantly with thiazide diuretics.
- hypertensive patients with type 2 diabetes mellitus and renal disease to reduce the rate of progression of nephropathy as measured by the reduction of microalbuminuria, and the occurrence of doubling of serum creatinine (see CLINICAL TRIALS).

1.1 Pediatrics

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

2 CONTRAINDICATIONS

APO-IRBESARTAN (irbesartan) 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 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- 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 WARNINGS AND PRECAUTIONS, Cardiovascular and Renal, and DRUG INTERACTIONS)
- Combination with Angiotensin-Converting Enzyme Inhibitors (ACEIs) in patients with diabetic nephropathy (see WARNINGS AND PRECAUTIONS, Cardiovascular and Renal, and DRUG INTERACTIONS).
- Pregnant women (see WARNINGS AND PRECAUTIONS, Special Populations).
- Nursing women (see WARNINGS AND PRECAUTIONS, Special Populations).

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

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

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Initiation of therapy requires consideration of recent antihypertensive drug treatment, the extent of blood pressure (BP) elevation, salt restriction, and other pertinent clinical factors. The dosage of other antihypertensive agents used with APO-IRBESARTAN (irbesartan) may need to be adjusted.

4.2 Recommended Dose and Dosage Adjustment

Essential Hypertension

The recommended initial dose of APO-IRBESARTAN is 150 mg once daily. In patients whose BP is not adequately controlled, the daily dose may be increased to 300 mg.

Essential Hypertension with Type 2 Diabetic Renal Disease

The recommended initial dose of APO-IRBESARTAN is 150 mg once daily. In patients whose BP is not adequately controlled, the daily dose may be increased to 300 mg once daily, the preferred maintenance dose.

Geriatric

No initial dosage adjustment is required in the elderly (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Population and Conditions and WARNINGS AND PRECAUTIONS).

Renal Insufficiency

No initial dosage adjustment is required in patients with renal impairment (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Population and Conditions).
However, due to the apparent greater sensitivity of hemodialysis patients, an initial dose of 75 mg is recommended in this group of patients.

Hepatic Insufficiency

No initial dosage adjustment is required in patients with mild-to-moderate hepatic impairment (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Population and Conditions).

Concomitant Diuretic Therapy

In patients receiving diuretics, APO-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 to 3 days prior to the administration of APO-IRBESARTAN to reduce the likelihood of hypotension (see WARNINGS AND PRECAUTIONS, Cardiovascular, and DRUG INTERACTIONS). If this is not possible because of the patient's condition, APO-IRBESARTAN should be administered with caution and the blood pressure monitored closely. The recommended starting dose of APO-IRBESARTAN is 75 mg once daily

in hypovolemic patients (see WARNING AND PRECAUTIONS, Cardiovascular). Thereafter, the dosage should be adjusted according to the individual response of the patient.

4.4 Administration

APO-IRBESARTAN may be administered with or without food.

4.5 Missed Dose

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

5 OVERDOSAGE

Few cases of overdosage with irbesartan have been reported, with no complaints and no significant clinical sequelae. Reported overdoses ranged from 600 to 900 mg daily. Durations of overdosing ranged from 2 to 3 weeks up to 30 days and over. Experience in adults exposed to doses of up to 900 mg/day for 8 weeks revealed no toxicity.

The most likely manifestations of overdosage are hypotension and tachycardia; bradycardia might also occur.

No specific information is available on the treatment of overdosage with irbesartan tablets. The patient should be closely monitored, and the treatment should be supportive and relieve symptoms.

Suggested measures include induction of emesis and/or gastric lavage. Activated charcoal may be useful in the treatment of overdosage.

APO-IRBESARTAN tablets is not removed by hemodialysis.

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, 75 mg, 150 mg, and 300 mg	Anhydrous dibasic calcium phosphate, crospovidone, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, and titanium dioxide.

APO-IRBESARTAN tablets 75 mg tablets are white coloured, oval shaped, biconvex film coated tablets, engraved “APO” on one side and “IRB 75” on the other side.

APO-IRBESARTAN tablets 150 mg tablets are white coloured, oval shaped, biconvex film coated tablets, engraved “APO” on one side and “IRB 150” on the other side.

APO-IRBESARTAN tablets 300 mg tablets are white coloured, oval shaped, biconvex film coated tablets, engraved “APO” on one side and “IRB 300” on the other side.

APO-IRBESARTAN tablets 75 mg, 150 mg and 300 mg are available in bottles of 100 and 500 tablets.

7 WARNINGS AND PRECAUTIONS

Cardiovascular

Hypotension - Volume Depleted Patients

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 BP, 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 BP could result in myocardial infarction or cerebrovascular accident.

Dual Blockade of the Renin-Angiotensin System (RAS)

There is evidence that co-administration of angiotensin receptor antagonists (ARBs), such as APO-IRBESARTAN, 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 APO-IRBESARTAN in combination with aliskiren-containing drugs is contraindicated in these patients (see CONTRAINDICATIONS).

The use of APO-IRBESARTAN in combination with of ACE inhibitors is contraindicated in

patients with diabetic nephropathy (see CONTRAINDICATIONS).

Further, co-administration of ARBs, including APO-IRBESARTAN, 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.

Lithium

Increases in serum lithium concentrations and lithium toxicity (including fatal outcome) have been reported with concomitant use of irbesartan and lithium (see DRUG INTERACTIONS). Therefore, this combination is not recommended. Serum lithium levels should be monitored carefully in patients receiving irbesartan and lithium if the combination is necessary.

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.

Driving and Operating Machinery

The effect of irbesartan on the ability to drive and use of 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

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

Renal

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 APO-IRBESARTAN, or of ACE inhibitors, with aliskiren-containing drugs is contraindicated in patients with moderate to severe renal impairment (GFR < 60

mL/min/1.73m^2) (see CONTRAINDICATIONS and DRUG INTERACTIONS).

The use of ARBs including APO-IRBESARTAN in combination with an ACEI is contraindicated in patients with diabetic nephropathy due to risk of hyperkalemia, hypotension and renal impairment (see CONTRAINDICATIONS and DRUG INTERACTIONS).

Use of APO-IRBESARTAN should include appropriate assessment of renal function.

In hypertensive type 2 diabetic patients with proteinuria (≥900 mg/day), a population which has a high risk of renal artery stenosis, no patient treated with APO-IRBESARTAN in IDNT had an early acute rise in serum creatinine attributable to renal artery disease (see CLINICAL PHARMACOLOGY).

Skin

The use of APO-IRBESARTAN 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-aldosterone system (RAAS) can cause fetal and neonatal morbidity and death when administered to pregnant women. When pregnancy is detected, APO-IRBESARTAN (irbesartan) should be discontinued as soon as possible.

The use of ARBs 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 ARBs, 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, hyperkalemia).

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 BP 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.

7.1.2 Breast-feeding

It is not known whether irbesartan is excreted in human milk, but significant levels have been found in the milk of lactating rats. Because many drugs are excreted in human milk, and because of their potential for affecting the nursing infant adversely, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

7.1.3 Pediatrics

Pediatrics (< 18 years of age): The safety and efficacy of irbesartan tablets have not been established in children < 18 years of age. Therefore, APO-IRBESARTAN is not indicated in this patient population.

7.1.4 Geriatrics

Geriatrics (> 65 years of age): Of the 4140 hypertensive patients receiving irbesartan in clinical studies, 793 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

8.2 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.

Irbesartan was evaluated for safety in > 4100 patients with essential hypertension including approximately 1300 patients treated for > 6 months and 400 patients for ≥ 1 year.

In placebo-controlled clinical trials, therapy was discontinued due to a clinical adverse event (AE) in 3.3 % of patients treated with irbesartan, versus 4.5 % of patients given placebo.

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

AEs occurring in ≥1% of the 2606 hypertensive patients in placebo-controlled clinical trials include the following (see Table 1):

Table 1 - Adverse events occurring in ≥1% of the 2606 hypertensive patients in placebo-controlled clinical trials

Body System/Reaction	Irbesartan tablets n = 1965 Incidence (%)	Placebo n = 641 Incidence (%)
General		
Abdominal Pain	1.4	2.0
Chest pain	1.8	1.7
Edema	1.5	2.3
Fatigue	4.3	3.7
Cardiovascular		
Tachycardia	1.2	0.9
Dermatologic		
Rash	1.3	2
Gastrointestinal		
Diarrhea	3.1	2.2
Dyspepsia/Heartburn	1.7	1.1
Nausea/Vomiting	2.1	2.8
Musculoskeletal / Connective Tissue		
Musculoskeletal pain	6.6	6.6
Nervous System		
Anxiety/Nervousness	1.1	0.9
Headache	12.3	16.7
Dizziness	4.9	5.0
Respiratory		
Cough	2.8	2.7
Urogenital System		
Urinary Tract Infection	1.1	1.4

AEs of hypotension or orthostatic hypotension, unrelated to dosage, occurred in 0.4% of irbesartan treated patients and in 0.2% of patients receiving placebo.

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

Body as a whole: fever;

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

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

Endocrine: gout, libido change, sexual dysfunction;

Gastrointestinal: constipation, distension abdomen, flatulence, gastroenteritis, hepatitis;

Hematologic: anemia, lymphocytopenia, thrombocytopenia;

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

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

Renal/Genitourinary: abnormal urination;

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

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

Clinical Studies in Hypertension and Type 2 Diabetic Renal Disease

In clinical studies in patients with hypertension and type 2 diabetic renal disease, the adverse drug experiences were similar to those seen in clinical trials of hypertensive patients with the exception of orthostatic symptoms (dizziness, orthostatic dizziness, and orthostatic hypotension) observed in IDNT (The Irbesartan Diabetic Nephropathy Trial) (proteinuria ≥900mg/day, and serum creatinine from 1.0 to 3.0 mg/dL). In IDNT, orthostatic symptoms occurred more frequently in the irbesartan tablets group (dizziness 10.2%, orthostatic dizziness 5.4%, orthostatic hypotension 5.4%) than in the placebo group (dizziness 6.0%, orthostatic dizziness 2.7%, orthostatic hypotension 3.2%). The rates of discontinuations due to orthostatic symptoms for irbesartan tablets versus placebo were: dizziness 0.3% vs 0.5%; orthostatic dizziness 0.2% vs 0.0%; and orthostatic hypotension, 0.0% vs 0.0%.

Laboratory Test Findings

In controlled clinical trials of hypertension, clinically important differences in laboratory tests were rarely associated with irbesartan.

Creatine Phosphokinase: Significant increases in plasma creatine phosphokinase (CPK) were commonly observed (1.6%) in irbesartan treated subjects.

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.

Hyperkalemia: The laboratory test parameter profile was similar in clinical trials conducted in patients with hypertension, type 2 diabetes and renal disease compared to that of patients with hypertension only, with the exception of hyperkalemia. In a placebo-controlled trial in 590 patients with hypertension, type 2 diabetes, microalbuminuria, and normal renal function (IRMA 2), hyperkalemia ≥ 5.5 mEq/L occurred in 29.4% of the patients

in the irbesartan 300 mg group compared to 22% of the patients in the placebo group. Discontinuation for hyperkalemia occurred in 0.5% of the patients in the irbesartan group.

In another placebo-controlled trial in 1715 patients with hypertension, type 2 diabetes, proteinuria ≥ 900 mg/day, and serum creatinine ranging from 1.0 to 3.0 mg/dl (IDNT), hyperkalemia ≥ 5.5 mEq/L occurred in 46.3% of the patients in the irbesartan group compared to 26.3% of the patients in the placebo group. Discontinuation for hyperkalemia occurred in 2.1% and 0.4% of the patients in the irbesartan and placebo groups, respectively.

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

Neutropenia: Neutropenia (<1000 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

Ear/Nose/Throat: tinnitus.

Endocrine and Metabolism: hypoglycemia (see WARNINGS AND PRECAUTIONS).

General: asthenia, syncope.

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

Hepatic/Biliary/Pancreatic: elevated liver function tests, jaundice.

Immune: anaphylactic shock, angioedema (involving swelling of the face, lips, and/or tongue) has been reported rarely in postmarketing use. Photosensitivity.

Musculoskeletal: muscle pain, muscle weakness, myositis and rhabdomyolysis have been reported in patients receiving ARBs. Myalgia.

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

Skin: psoriasis (and psoriasis exacerbation).

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 2 - Established or Potential Drug-Drug Interactions

Proper/Common name	Source of Evidence	Effect	Clinical comment
Agents increasing Serum Potassium	RCS	Based on experience with the use of other drugs that affect the renin- angiotensin system, concomitant use of irbesartan with potassium- sparing diuretics, potassium supplements, salt substitutes containing potassium or other potassium-raising medicinal products may lead to increases in serum potassium, sometimes severe. Such co-administration requires close monitoring of serum potassium.	
Antidiabetic agents (e.g. insulin and oral antihyperglycemic agent) (e.g. repaglinide)	CT	Irbesartan reduces blood glucose level due to potential effects on glucose metabolism. 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 patient should be monitored for hypoglycemia when co- administration of irbesartan with oral antidiabetic agents or insulin is required. Dose adjustment of oral antidiabetic treatment or insulin may be required. Dose adjustment of repaglinide may be required when repaglinide is co-administrated with irbesartan (see WARNINGS AND

Proper/Common name	Source of Evidence	Effect	Clinical comment
		the two drugs), increased the C_{max} and AUC of repaglinide (substrate of OATP1B1) by 1.8-fold and 1.3-fold, respectively.	PRECAUTIONS).
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.	
Diuretics	T	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 APO-IRBESARTAN.	The possibility of symptomatic hypotension with the use of APO-IRBESARTAN can be minimized by discontinuing the diuretic prior to initiation of treatment and/or lowering the initial dose of APO-IRBESARTAN (see WARNINGS AND PRECAUTIONS, Cardiovascular, and DOSAGE AND ADMINISTRATION). No drug interaction of clinical significance has been identified with thiazide diuretics.
Dual Blockade of the Renin-Angiotensin-System (RAS) with ARBs, ACE inhibitors or aliskiren-containing drugs	CT	Dual Blockade of the Renin-Angiotensin-System with ARBs and 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	See CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS, Cardiovascular.

Proper/Common name	Source of Evidence	Effect	Clinical comment
		hypotension, renal failure, and hyperkalemia. The use of APO-IRBESARTAN in combination with an ACE inhibitor 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 hyperkalemia, severe hypotension and renal failure.	
Lithium	CT	As with other drugs which eliminate sodium, lithium clearance may be reduced. Increases in serum lithium concentrations and lithium toxicity (including fatal outcome) have been reported with concomitant use of irbesartan and lithium.	Serum lithium levels should be monitored carefully in patients receiving irbesartan and lithium (see WARNINGS AND PRECAUTIONS).
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, coadministration of NSAIDs, including selective COX-2 inhibitors, with ARBs, including irbesartan, may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible. The antihypertensive effect of ARBs, including irbesartan, may be attenuated by NSAIDs including selective COX-2 inhibitors.	Monitor renal function periodically in patients receiving irbesartan and NSAID therapy.
Simvastatin	CT	When irbesartan was	

Proper/Common name	Source of Evidence	Effect	Clinical comment
		administered in a small single-dose study with 12 young, healthy males aged 19-39, 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.	
Warfarin	CT	When irbesartan was administered as 300 mg once daily under steady- state conditions, no pharmacodynamic effect on PT (prothrombin time) was demonstrated in subjects stabilized on warfarin.	

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

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

APO-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 kinase 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.

10.2 Pharmacodynamics

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.

Hypertensive patients: Angiotensin II receptor inhibition following chronic administration of irbesartan causes a 1.5 to 2 fold rise in angiotensin II plasma concentration and a 2 to 3 fold increase in plasma renin levels. Aldosterone plasma concentrations generally decline following irbesartan administration; however, at recommended dose, serum potassium levels are not significantly affected.

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

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

There was no rebound effect after withdrawal of irbesartan.

Race: Black hypertensive patients had a smaller BP response to irbesartan monotherapy than Caucasians.

10.3 Pharmacokinetics

Absorption:

Irbesartan is an orally active agent. The oral absorption of irbesartan is rapid and complete with an average absolute bioavailability of 60% to 80%. Irbesartan exhibits linear pharmacokinetics over the therapeutic dose range with an average terminal elimination half-life of 11 to 15 hours. Following oral administration, peak plasma concentrations are attained at 1.5 to 2 hours after dosing. Steady-state concentrations are achieved within 3 days.

Distribution:

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

The average volume of distribution of irbesartan is 53 to 93 L. Total plasma and renal clearances are in the range of 157 to 176 mL/min and 3.0 to 3.5 mL/minute, respectively.

Metabolism:

Irbesartan is metabolized via glucuronide conjugation, and oxidation primarily by the

cytochrome P-450 isoenzyme CYP 2C9. Metabolism of irbesartan by CYP 3A4 is negligible. In addition, irbesartan is not metabolized by the following isoenzymes: CYP 1A1, 1A2, 2A6, 2B6, 2D6, 2E1.

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.

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.

Special Populations and Conditions

- **Geriatrics**
  In subjects > 65 years of age, irbesartan elimination half-life was not significantly altered, but AUC and C_{max} values were about 20 to 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 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.

11 STORAGE, STABILITY AND DISPOSAL

APO-IRBESARTAN tablets can be stored at room temperature (15°C - 30°C).

PART II: SCIENTIFIC INFORMATION

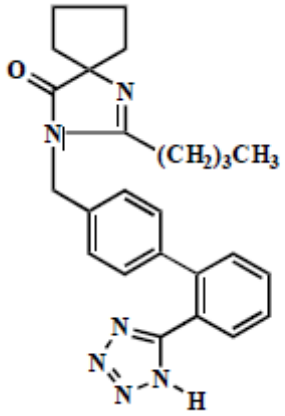
13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: irbesartan

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.

Molecular formula and molecular mass: C_{25} H_{28} N_6O, 428.5 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.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Two trials were done to investigate the effects of irbesartan in patients with hypertension and type 2 diabetic nephropathy, the IDNT and IRMA 2 trials.

IDNT:

The Irbesartan Diabetic Nephropathy Trial (IDNT) was a multicenter, randomized, controlled, double-blind, morbidity and mortality trial comparing irbesartan, amlodipine and placebo. In 1715 hypertensive patients with type 2 diabetes (proteinuria ≥900 mg/day and serum creatinine 1.0 to 3.0 mg/dL) the long-term effects (mean 2.6 years) of irbesartan on the progression of renal disease and all-cause mortality were examined. In addition, as a secondary endpoint, the effect of irbesartan on the risk of fatal or non-fatal cardiovascular

events was assessed. The most important exclusion criteria were: onset of type II diabetes mellitus at < 20 years of age, renovascular occlusive disease affecting both kidneys or a solitary kidney, and unstable angina pectoris.

Patients were randomized to receive once daily irbesartan 75 mg (n = 579), amlodipine 2.5 mg (n = 567), or matching placebo (n = 569). Patients were then titrated to a maintenance dose of 300 mg irbesartan, 10 mg amlodipine, or placebo as tolerated. Additional antihypertensive agents for the 3 study arms [excluding ACE inhibitors, other angiotensin II receptor blockers (ARBs) and calcium channel blockers (CCBs)] were added as needed to help achieve a BP goal of ≤ 135/85 mmHg in all groups, or a 10 mmHg reduction in systolic blood pressure (SBD) if baseline was > 160 mmHg. Of the total of 579 patients randomized to irbesartan, 442 completed the double blind phase. All analyses were conducted on the intent to treat (ITT) patient population.

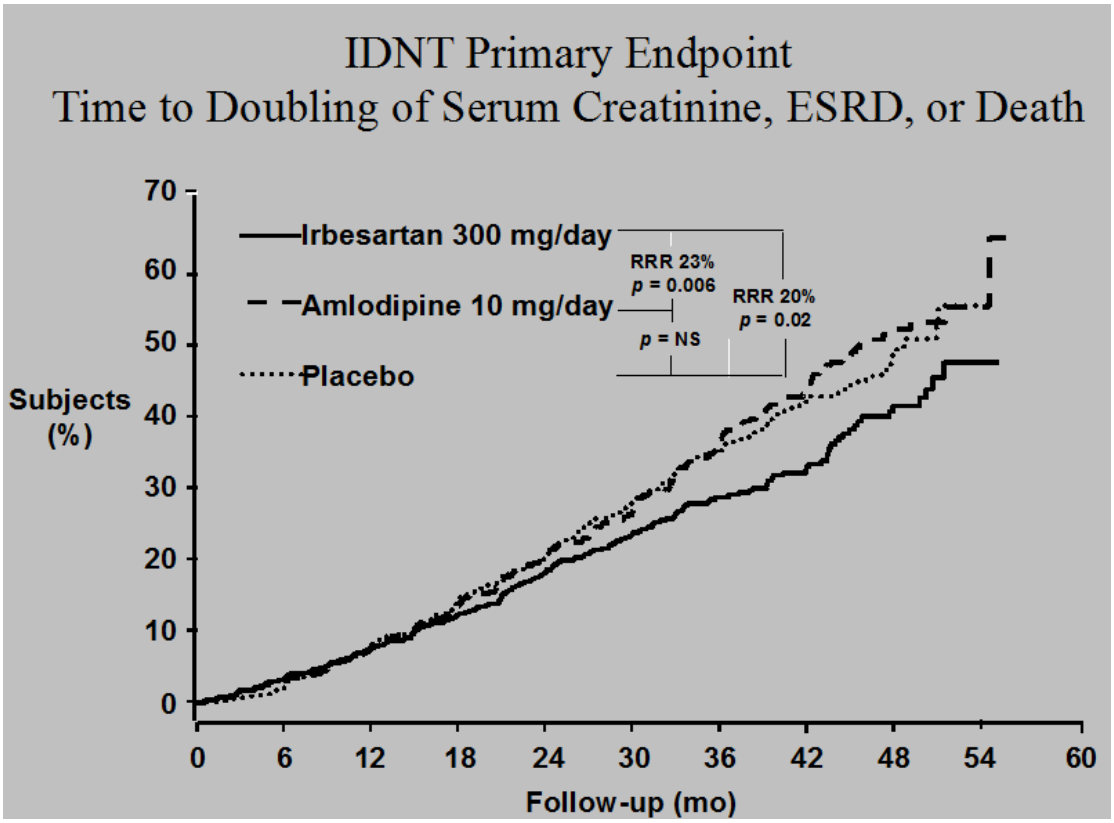


Table 3 - Primary Composite Endpoint Comparison (IDNT)

Event	Number (%) of Subjects			Relative Risk		
	Placebo N=569	Irbesartan N=579	Amlodipine N=567	Estimate (% Reduction)	95% Confidence Interval	p
Irbesartan vs. Placebo						
Primary Composite Endpoint*	222 (39.0)	189 (32.6)	-	0.80 (20)	0.66-0.97	0.023
Irbesartan vs. Amlodipine						
Primary Composite Endpoint*	-	189 (32.6)	233 (41.1)	0.77 (23)	0.63-0.93	0.006

* First occurrence of any of the following: doubling of serum creatinine, end-stage renal disease (ESRD) or all-cause mortality

Irbesartan demonstrated a 20% relative risk reduction (absolute risk reduction 6.4%) in the composite primary endpoint (1st occurrence of any of the following: doubling of serum creatinine, end-stage renal disease (ESRD) or all-cause mortality) compared to placebo (p=0.023), and a 23% relative risk reduction (absolute risk reduction 8.5%) compared to amlodipine (p=0.006). When the individual components of the primary composite endpoint were analysed, no effect in all-cause mortality and no significant effect on time to ESRD were observed. However, a significant reduction in doubling of serum creatinine was observed.

Irbesartan decreased the progression of renal disease in patients with chronic renal insufficiency and overt proteinuria. Irbesartan also produced significant reduction in the rate of urine excretion of protein and albumin relative to placebo or amlodipine ($p<0.001$ for both comparisons). Similar BP was achieved in the irbesartan 300 mg and amlodipine 10 mg groups.

Treatment with irbesartan reduced the occurrence of sustained doubling of serum creatinine as a separate endpoint (33%) with an absolute risk reduction of 6.8%.

The risk of developing a doubling of serum creatinine or ESRD was reduced by 26% relative to placebo with an absolute risk reduction of 6.2% and by 34% relative to amlopidine with an absolute risk reduction of 10.0% (pooled risk reduction 30%, p=0.0005). This renal protective effect of irbesartan appeared to be independent of systemic BP reduction.

There was no significant difference in the assessment of fatal or non-fatal cardiovascular events (cardiovascular death, non-fatal myocardial infarction, hospitalization for heart failure, permanent neurologic deficit attributed to stroke, or above-the-ankle amputation) among the 3 treatment groups.

Safety data from this trial are reported in the ADVERSE REACTIONS section.

IRMA 2:

The study of the Effects of Irbesartan on MicroAlbuminuria in Hypertensive Patients with Type 2 Diabetes Mellitus (IRMA 2) was a multicenter, randomized, placebo-controlled, double-blind morbidity study, conducted in 590 hypertensive patients with type 2 diabetes, microalbuminuria (20 to 200 mcg/min; 30 to 300 mg/day) and normal renal function (serum creatinine ≤ 1.5 mg/dL in males and ≤ 1.1 mg/dL in females). Screening of urine for albumin has revealed that patients with microalbuminuria have a 10 to 20 fold higher risk of developing diabetic nephropathy than patients with normoalbuminuria. Of the 590 patients, 201 received placebo, 195 received irbesartan 150 mg and 194 patients received irbesartan 300 mg.

The primary endpoint was the long-term effects (2 years) of irbesartan on the progression to clinical (overt) proteinuria (urinary albumin excretion rate [AER] > 200 mcg/min [>300 mg/day] and an increase in AER of ≥ 30% from baseline). In addition, after 1 and 2 years of treatment, the effect of irbesartan on the change in overnight AER and the change in 24-hour creatinine clearance was assessed. The most important exclusion criteria were: onset of type II diabetes mellitus at < 20 years of age, renovascular occlusive disease affecting both kidneys or a solitary kidney, and unstable angina pectoris.

Irbesartan 300 mg demonstrated a 70% relative risk reduction (absolute risk reduction 9.8%) in the development of clinical (overt) proteinuria compared to placebo (p=0.0004). Relative risk reduction in the development of proteinuria with 150 mg irbesartan was not statistically significant. The slowing of progression to clinical (overt) proteinuria was evident as early as 3 months and continued over the 2 year period.

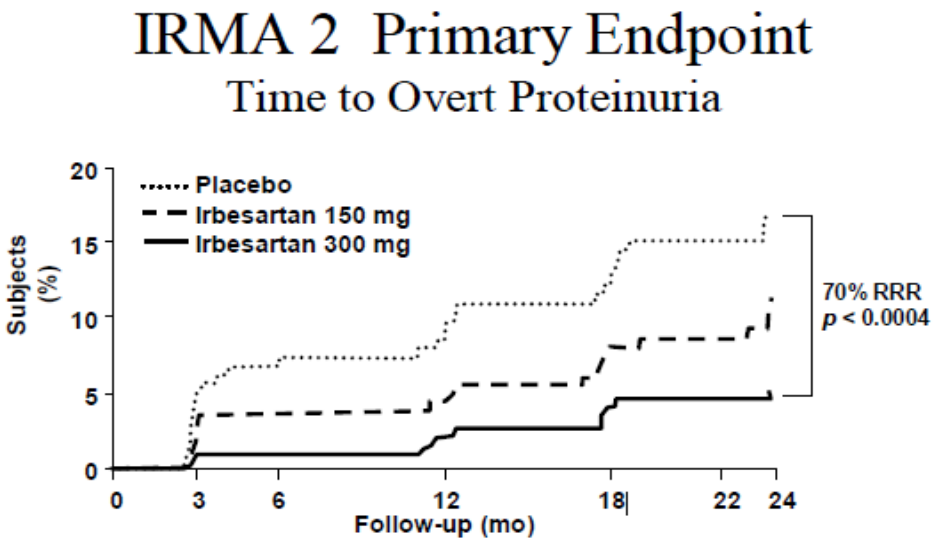
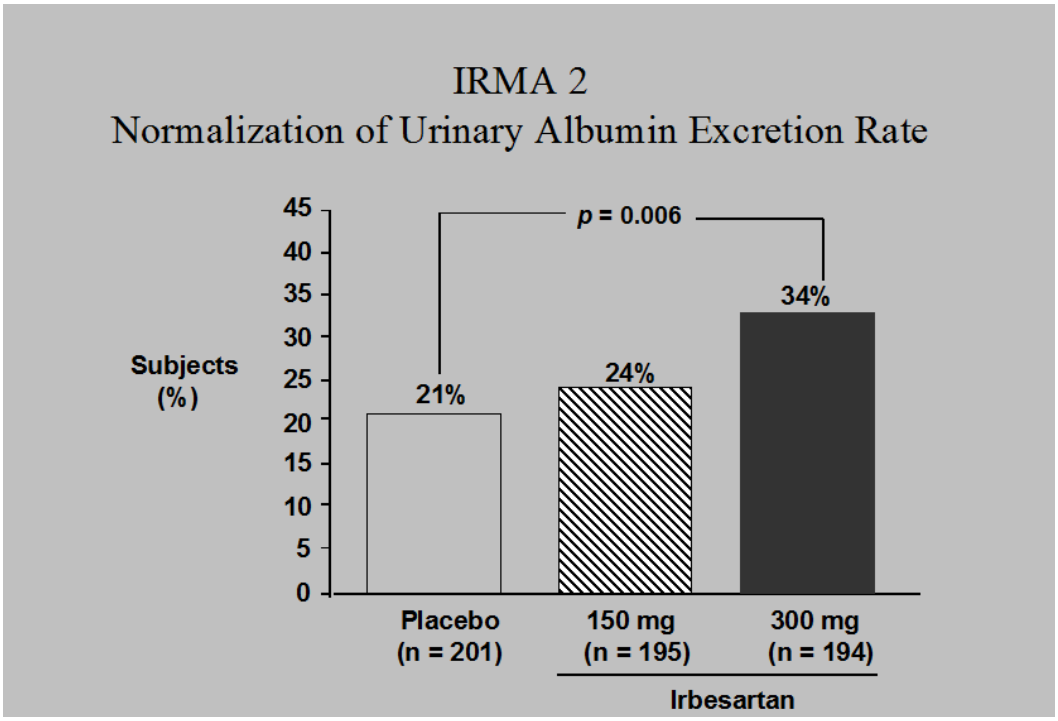


Table 4 - Time to occurrence of Overt Proteinuria (Irbesartan 300 mg vs. Placebo Comparison) (IRMA 2)

Event	Number (%) of Subjects		Relative Risk		
	Placebo N=201	Irbesartan N=195	Estimate (% Reduction)	95% Confidence Interval	p
Primary Endpoint	30 (14.9)	10 (5.2)	0.295 (70)	0.144 - 0.606	0.0004

Regression to normoalbuminuria (<20 mcg/min; <30 mg/day) was more frequent in the irbesartan 300 mg group (34%) than in the placebo group (21%). Irbesartan 300 mg reduced the level of urinary albumin excretion at 24 months by 43% (p=0.0001).



Safety data from this trial has been reported in the ADVERSE REACTIONS section

14.2 Comparative Bioavailability Studies

A double blinded, single dose, standard randomized 2-way crossover comparative bioavailability study, conducted under fasting conditions was performed on healthy adult male subjects. The results obtained from 18 volunteers who completed the study are summarized in the following tables. The rate and extent of absorption of irbesartan were measured and compared following a single oral dose (1x 300 mg tablet) of APO-IRBESARTAN (irbesartan) 300 mg tablets and AVAPRO® (irbesartan) 300 mg tablets.

Summary Table of the Comparative Bioavailability Data Irbesartan (1 x 300 mg dose) From Measured Data/Fasting Conditions Geometric Mean Arithmetic Mean (CV%)				
Parameter	Test*	Reference†	Ratio of Geometric Means (%)	90% Confidence Interval (%)
AUC_T (pg*h/mL)	16041.3 16314.9 (20)	16798.9 17222.1 (24)	95.5	90.6 -100.7
AUC_I (pg*h/mL)	16304.4 16567.5 (19)	17058.0 17476.3 (24)	95.6	90.6 -100.8
C_{max} (pg/mL)	3103.4 3205.7 (25)	3119.4 3200.5 (23)	99.5	91.4 – 108.3
T_{max}# (h)	1.88 (50)	1.68 (47)		
$T_{1/2}$# (h)	9.07 (31)	9.35 (31)		
* APO-IRBESARTAN (irbesartan) 300 mg tablets (Apotex Inc.). † AVAPRO® (irbesartan) 300 mg tablets (sanofi-aventis Canada Inc.) were purchased in Canada. Expressed as arithmetic mean (CV%) only.				

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

Table 5 - Acute Toxicity

Species	Sex (N)	Route	LD_{50} (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 to 50 fold the maximum human dose (300 mg) on a mg/m^2 basis, respectively.

Table 6 - Subacute and Chronic Toxicity

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	C 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^G urinary concentrations and excretions (≥ 30 mg/kg).
Rat	M (10) F (10)	0, 0.8, 2, 5	iv	16 days	C Very slight increase in Na^+ and Cl^G plasma levels (≥ 0.8 mg/kg/day in males) C 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	C 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	C ≥ 250 mg/kg/day: changes in the kidney (hyperplasia of the juxtaglomerular apparatus), heart (myocardial fibrosis) and erythrocytes parameters (slight anemia). C At 500 mg/kg/day: increased platelet count, fibrogen and neutrophil levels and at 1000 mg/kg/day, health deterioration was also noted. C 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.

Species/ Strain	Sex (N/Dose)	Dose (mg/kg/day)	Route	Time	Effects
Monkey	M (3) F (3)	0, 0.8, 2, 5	iv	2 weeks	C Irbesartan induced only a slight hyperplasia of the juxtaglomerular apparatus in 2/3 females receiving 5 mg/kg/day. C 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 and high dose groups]	0, 10, 30, 90	po	26 weeks	C Slight reduction of the bodyweight gain in males at 90 mg/kg/day (- 6 to - 8%). C Other changes can be considered to be of pharmacological origin for some of them and have no clear toxicological significance for all of them. C The no-observed adverse effect dose was considered to be 30 mg/kg/day.
	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, 0, 250, 500, 1000	po	26 weeks	C Slight reduction of bodyweight gain without any dose-relationship-reversible. C 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. C Hyperplasia/hypertrophy of the juxtaglomerular apparatus in males (≥ 250 mg/kg/day) and in females (≥ 500 mg/kg/day), partially reversible.

Species/ Strain	Sex (N/Dose)	Dose (mg/kg/day)	Route	Time	Effects
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	C Dose-related hyperplasia of juxtaglomerular apparatus in all treated animals partially reversible at the end of treatment. C 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: C 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. C Dose-related hyperplasia / hypertrophy of the juxtaglomerular apparatus in all treated animals with degenerative kidney changes at 500 mg/kg/day. C Slight decrease in bodyweight gain and erythrocyte parameters at doses ≥ 100 mg/kg/day.

Subacute and Chronic Toxicity (Cont'd)

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 increased 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.

Reproduction and Teratology

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.

Carcinogenicity and Mutagenicity

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 to 24.9 times (rats) and 3.8 to 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 abberations (*in vitro* - human lymphocyte assay; *in vivo* - mouse micronucleus study).

17 SUPPORTING PRODUCT MONOGRAPHS

1. AVAPRO® (Irbesartan tablets, 75 mg, 150 mg and 300 mg), submission control 265391, Product Monograph, sanofi-aventis Canada Inc. (NOV 22, 2022).

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]APO-IRBESARTAN

Irbesartan Tablets

Read this carefully before you start taking **APO-IRBESARTAN** 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 **APO-IRBESARTAN**.

Serious Warnings and Precautions

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

What is APO-IRBESARTAN used for?

- APO-IRBESARTAN is used in adults to lower high blood pressure. It can be used alone or together with a thiazide diuretic (a "water pill").
- If you have high blood pressure, type 2 diabetes and kidney disease, APO-IRBESARTAN may help to protect kidney function.

How does APO-IRBESARTAN work?

APO-IRBESARTAN is an angiotensin receptor blocker (ARB). It lowers blood pressure. This medicine does not cure your disease. It helps to control it. Therefore, it is important to continue taking APO-IRBESARTAN regularly even if you feel fine.

What are the ingredients in APO-IRBESARTAN?

Medicinal ingredients: Irbesartan.

Non-medicinal ingredients: Anhydrous dibasic calcium phosphate, crospovidone, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, and titanium dioxide.

APO-IRBESARTAN comes in the following dosage forms:

Tablets 75 mg, 150 mg and 300 mg.

Do not use APO-IRBESARTAN if you:

- are allergic to irbesartan or to any non-medicinal ingredient in the formulation.
- have experienced an allergic reaction (angioedema) with swelling of the hands, feet, or ankles, face, lips, tongue, throat, or sudden difficulty breathing or swallowing, to any ARB. Be sure to tell your healthcare professional that this has happened to you.
- 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 APO-IRBESARTAN during pregnancy can cause injury and even death to your baby.
- are breastfeeding. It is possible that APO-IRBESARTAN passes into breast milk.

APO-IRBESARTAN 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 APO-IRBESARTAN. 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.
- 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. APO-IRBESARTAN may cause low blood sugar levels.
- 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 APO-IRBESARTAN is not recommended.
- are taking an angiotensin converting enzyme (ACE) inhibitor. The combination with APO-IRBESARTAN is not recommended.
- are taking a medicine that contains lithium. The combination with APO-IRBESARTAN is not recommended.

Other warnings you should know about:

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

Allergic Reactions: Allergic reactions (swelling of areas of tissue under the skin, sometimes affecting the face and throat, hives and severe allergic reactions) have been reported. Stop taking APO-IRBESARTAN 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 APO-IRBESARTAN. 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 APO-IRBESARTAN:

- Agents increasing serum potassium, such as a salt substitute that contains potassium, potassium supplements, or a potassium-sparing diuretic (a specific kind of "water pill").
- Lithium used to treat bipolar disease.
- Nonsteroidal anti-inflammatory drugs (NSAIDs), used to reduce pain and swelling. Examples include ibuprofen, naproxen, and celecoxib.
- Blood pressure-lowering drugs, including diuretics ("water pills"), aliskiren-containing products (e.g. RASILEZ®), or angiotensin converting enzyme (ACE) inhibitors.
- Certain medications tend to increase your blood pressure, for example, preparations for appetite control, asthma, colds, coughs, hay fever and sinus problems.
- Medicines used to lower blood sugar levels, including insulin and oral medicines, such as repaglinide.

How to take APO-IRBESARTAN:

- Take APO-IRBESARTAN every day exactly as prescribed.
- It is recommended to take your dose at about the same time every day.
- APO-IRBESARTAN may be taken with or without food.

Usual adult dose:

Recommended Initial Dose: 150 mg once a day.

Your healthcare professional can increase the dosage to 300 mg once daily if required.

Overdose:

If you think you, or a person you are caring for, have taken too much APO-IRBESARTAN, 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 APO-IRBESARTAN?

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

Side effects may include:

- dizziness
- drowsiness, insomnia, being tired
- rash
- diarrhea, vomiting
- headache
- back or leg pain, muscle cramps
- lightheadedness
- ringing in the ears

APO-IRBESARTAN 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			
Increased levels of potassium in the blood: irregular heartbeats, muscle weakness, generally feeling unwell		X	
Increased levels of creatine phosphokinase: blood tests may show raised levels of an enzyme that measures breakdown of muscle (creatine phosphokinase)			X
UNCOMMON			

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**	
Low blood pressure: dizziness, fainting, light-headedness. May occur when you go from lying or sitting to standing up.	X		
Edema: swelling of hands, ankles, or feet		X	
Tachycardia: fast heart beat		X	
Liver problems: yellowing of the skin or eyes, dark urine, abdominal pain, nausea, vomiting, loss of appetite		X	
Kidney problems: change in frequency of urination, nausea, vomiting, swelling of extremities, fatigue		X	
RARE			
Rhabdomyolysis: muscle pain that you cannot explain, muscle tenderness or weakness, dark brown urine		X	
Allergic reaction and angioedema: rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			X
VERY RARE			
Decreased platelets: bruising, bleeding, fatigue and weakness, small purple or red dots under the skin		X	
UNKNOWN			
Skin problems: psoriasis, increased skin sensitivity to sunlight		X	
Low blood sugar: sweating, weakness, hunger, dizziness, trembling, headache			X

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**	
Anemia (decreased number of red blood cells): fatigue, loss of energy, looking pale, weakness, shortness of breath		X	

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

Reporting Side Effects

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

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

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

Storage:

Store APO-IRBESARTAN tablets at room temperature (15°C to 30°C).

Keep out of reach and sight of children.

If you want more information about APO-IRBESARTAN:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website (http://www.apotex.ca/products) or by calling 1-800-667-4708.

This leaflet was prepared by Apotex Inc., Toronto, Ontario, M9L 1T9.

Last Revised: DEC 13, 2023

RASILEZ® is a trademark of Novartis AG, Switzerland