PRODUCT MONOGRAPH

PrRIVA-IRBESARTAN

(Irbesartan tablets USP)

75 mg, 150 mg and 300 mg

Angiotensin II AT_1 Receptor Blocker

Laboratoire Riva Inc.
660 Boul.Industriel
Blainville, Québec
Canada, J7C 3V4

Date of Preparation:
June 6, 2014

Control No.: 174303

www.labriva.com

PRODUCT MONOGRAPH

[Pr]RIVA-IRBESARTAN

(Irbesartan tablets USP)

75 mg, 150 mg and 300 mg

THERAPEUTIC CLASSIFICATION

Angiotensin II AT_1 Receptor Blocker

ACTION AND CLINICAL PHARMACOLOGY

RIVA-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.

Pharmacokinetics

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

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 53-93 liters. Total plasma and renal clearances are in the range of 157 - 176 and 3.0 - 3.5 mL/minute, respectively.

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

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.

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.

In subjects over the age of 65 years, irbesartan elimination half-life was not significantly altered, but AUC and Cmax values were about 20 - 50% greater than those of young subjects.

The mean AUC and Cmax 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.

Pharmacodynamics

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.

CLINICAL TRIALS

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

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 - 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, a secondary endpoint, the effect of irbesartan on the risk of fatal or non-fatal cardiovascular events was assessed. Age of onset of Type II diabetes mellitus < 20 years, renovascular occlusive disease affecting both kidneys or a solitary kidney and unstable angina pectoris were among the most important exclusion criteria.

Patients were randomized to receive irbesartan 75 mg (n = 579), amlodipine 2.5 mg (n = 567), or matching placebo (n = 569) once-daily. Patients were then titrated to a maintenance dose of 300 mg irbesartan, 10 mg amlodipine, or placebo as tolerated. Additional antihypertensive agents for the three study arms (excluding ACE inhibitors, other angiotensin II receptor antagonists and calcium channel blockers) were added as needed to help achieve a blood pressure goal of 135/85 mmHg or less in all groups, or a 10 mmHg reduction in systolic pressure 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.

IDNT Primary Endpoint
Time to Doubling of Serum Creatinine, ESRD, or Death

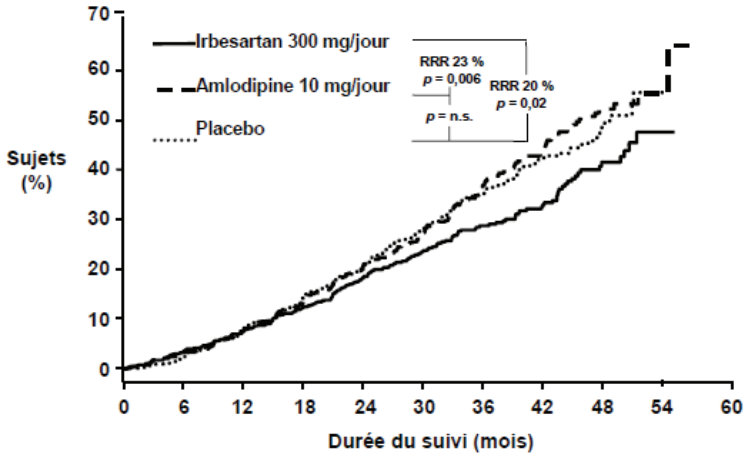


Table 1
Primary Composite Endpoint Comparison (IDNT)

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 (first 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 end stage renal disease were observed. However, a significant reduction was observed in doubling of serum creatinine. Irbesartan decreases 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 blood pressure 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 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 appears to be independent of systemic blood pressure 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 three treatment groups.

Safety data from this trial has been 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 (20-200 mcg/min; 30-300mg/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 study examined as a primary endpoint the long-term effects (2 years) of irbesartan on the progression to clinical (overt) proteinuria (urinary albumin excretion rate [AER] > 200 mcg/min [>300mg/day] and an increase in AER of at least 30% from baseline). In addition, after one and two years of treatment, the effect of irbesartan on the change in overnight AER and the change in 24-hour creatinine clearance was assessed. Age of onset of Type II diabetes mellitus < 20 years, renovascular occlusive disease affecting both kidneys or a solitary kidney and unstable angina pectoris were among the most important exclusion criteria.

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 three months and continued over the 2 year period.

IRMA 2 Primary Endpoint
Time to Overt Proteinuria

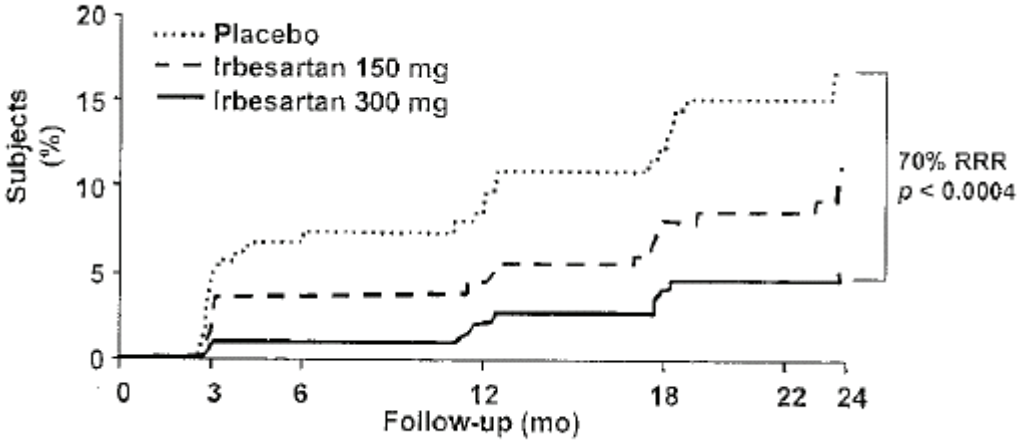
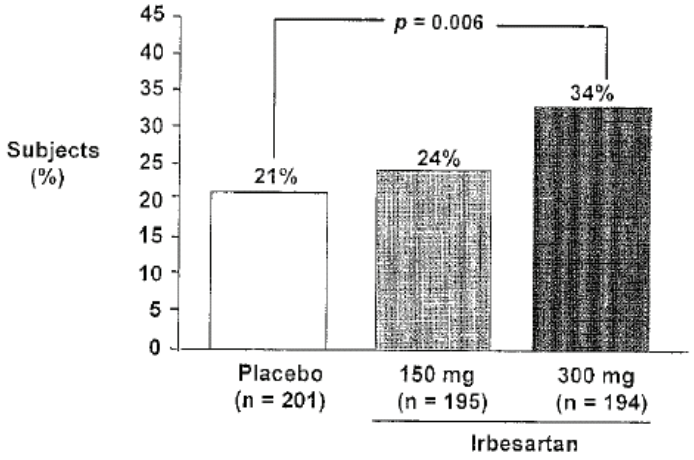


Table 2
Time to occurrence of Overt Proteinuria
(Irbesartan 300 mg vs. Placebo Comparison) (IRMA 2)

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).

IRMA 2
Normalization of Urinary Albumin Excretion Rate



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

Comparative Bioavailability Study

The objective of this study was to evaluate and compare the relative bioavailability and therefore the bioequivalence of two formulations of irbesartan tablets after a single oral dose administration under fasting conditions. The study was a single center, randomized, single dose, blinded, 2-way crossover study design performed in twenty-one healthy male subjects.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Irbesartan (1 x 300 mg tablet) From measured data **uncorrected for potency** Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test[*]	Reference[†]	% Ratio of Geometric Means[#]	Confidence Interval (90%)[#]
AUC_T (ng·h/mL)	19409.28 20847.82 (37.29)	19672.29 20813.02 (34.75)	98.66	88.56 – 109.92
AUC_I (ng·h/mL)	22490.59 23763.90 (31.74)	22269.26 23251.43 (30.07)	100.99	91.95 – 110.92
C_{max} (ng/mL)	3613.1 3693.8 (21.55)	3643.2 3832.9 (31.12)	99.17	91.29 – 107.74
T_{max}[§] (h)	1.25 (0.500 – 5.00)	1.25 (0.500 – 5.00)		
$T_{½}$[€] (h)	12.82 (41.09)	13.23 (49.74)		

[*]RIVA-IRBESARTAN 300 mg Tablets (Laboratoire Riva Inc.)
[†]AVAPRO® 300 mg Tablets (Sanofi- Synthelabo Canada Inc) were purchased in Canada
[§] Expressed as the median (range)
[€] Expressed as the arithmetic mean (CV %)
[#] based on least-squares mean estimates.

INDICATIONS AND CLINICAL USE

RIVA-IRBESARTAN (irbesartan) is indicated for the treatment of essential hypertension.

RIVA-IRBESARTAN is also indicated for the treatment of 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).

RIVA-IRBESARTAN may be used alone or concomitantly with thiazide diuretics.

The safety and efficacy of concurrent use with angiotensin converting enzyme inhibitors has not been established.

CONTRAINDICATIONS

RIVA-IRBESARTAN (irbesartan) is contraindicated in patients who are hypersensitive to any component of this product.

WARNINGS

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, RIVA-IRBESARTAN (irbesartan) should be discontinued as soon as possible (see WARNINGS AND PRECAUTIONS, Special Populations).

Special populations

Pregnancy

Drugs that act directly on the rennin-angiotensin system (RAAS) can cause fetal and neonatal morbidity and death when administered to pregnant women. When pregnancy is detected, irbesartan should be discontinued as soon as possible.

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

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

Infants with histories of *in utero* exposure to an ARBs should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion may be required as means of reversing hypotension and/or substituting for impaired renal function; however, limited experience with those procedures has not been associated with significant clinical benefit.

Irbesartan is not removed by hemodialysis.

Nursing Women

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.

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 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.

PRECAUTIONS

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.

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 irbesartan in IDNT had an early acute rise in serum creatinine attributable to renal artery disease. (See ACTION AND CLINICAL PHARMACOLOGY; Clinical Trials; Hypertension and Type 2 Diabetic Renal Disease.)

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.

Use in Children

Safety and effectiveness have not been established.

Use in the Elderly

Of the 4140 hypertensive patients receiving irbesartan in clinical studies, 793 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.

General

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

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 - 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.

Lithium Salts

As with other drugs which eliminate sodium, lithium clearance may be reduced. Therefore, serum lithium levels should be monitored carefully if lithium salts are to be administered.

Warfarin

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.

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.

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.

ADVERSE REACTIONS

Irbesartan has been evaluated for safety in more than 4100 patients with essential hypertension including approximately 1300 patients for over 6 months and 400 patients for 1 year or more.

In placebo-controlled clinical trials, therapy was discontinued due to a clinical adverse event 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.

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

Body System/Reaction	Irbesartan 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

The incidence of hypotension or orthostatic hypotension occured in 0.4% of irbesartan treated patients, unrelated to dosage, 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: 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 change, gout;

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

Musculoskeletal: muscle cramp, arthritis, myalgia, muscle 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 abnormality, conjunctivitis, taste disturbance.

Postmarketing Experience

Angioedema (involving swelling of the face, lips, and/or tongue) has been reported rarely in postmarketing use. The following adverse reactions, regardless of drug relationship, have been reported very rarely in post-marketing use, syncope, asthenia, myalgia, jaundice, elevated liver function tests and impaired renal function including isolated cases of renal failure in patients at risk (see PRECAUTIONS - Renal Impairment).

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

Clinical Studies in Hypertension and Type 2 Diabetic Renal Disease

In clinical studies in patients with hypertension and type 2 diabetic renal disease (see ACTION AND CLINICAL PHARMACOLOGY; Clinical Trials: Hypertension and Type 2 Diabetic Renal Disease), the adverse drug experiences were similar to those 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 1.0-3.0 mg/dL). In IDNT orthostatic symptoms occurred more frequently in the Irbesartan 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 (percents) of discontinuations due to orthostatic symptoms for Irbesartan 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.

Liver Function Tests: In placebo-controlled trials, elevations of AST and ALT ≥3X upper limit of normal occurred 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: For hypertension with type 2 diabetes and renal disease in clinical trials conducted in patients with diabetic renal disease, the laboratory test parameter profile was similar to that of hypertension, 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 and 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 - 3.0 mg/dl (IDNT), hyperkalemia ≥ 5.5 mEq/L occurred in 46.3% of the patients in the irbesartan group and 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.

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.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Few cases of overdosage with irbesartan have been reported, with no significant clinical sequelae. Reported overdoses ranged from 600 - 900 mg daily. Durations of overdosing ranged from 2 - 3 weeks up to 30 days and over. No complaints were associated with the overdoses and no clinical sequelae were observed. 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 expected to be hypotension and tachycardia; bradycardia might also occur from overdose.

No specific information is available on the treatment of overdosage with irbesartan. The patient should be closely monitored, and the treatment should be symptomatic and supportive. Suggested measures include induction of emesis and/or gastric lavage. Activated charcoal may be useful in the treatment of overdosage.

Irbesartan is not removed by hemodialysis.

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

DOSAGE AND ADMINISTRATION

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

RIVA-IRBESARTAN may be administered with or without food.

Essential Hypertension

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

No initial dosage adjustment is required in the elderly, or in patients with renal impairment (see ACTION AND CLINICAL PHARMACOLOGY- Pharmacokinetics and PRECAUTIONS - Use in the Elderly). However, due to the apparent greater sensitivity of hemodialysis patients, an initial dose of 75 mg is recommended in this group of patients.

No initial dosage adjustment is required in patients with mild-to-moderate hepatic impairment (see ACTION AND CLINICAL PHARMACOLOGY - Pharmacokinetics).

Concomitant Diuretic Therapy

In patients receiving diuretics, RIVA-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 RIVA-IRBESARTAN to reduce the likelihood of hypotension (see WARNINGS - Hypotension, and PRECAUTIONS - Drug Interactions). If this is not possible because of the patient's condition, RIVA-IRBESARTAN should be administered with caution and the blood pressure monitored closely. The recommended starting dose of RIVA-IRBESARTAN is 75 mg once daily in hypovolemic patients (see WARNING - Hypotension). Thereafter, the dosage should be adjusted according to the individual response of the patient.

PHARMACEUTICAL INFORMATION

I. DRUG SUBSTANCE

Trade Name: RIVA-IRBESARTAN

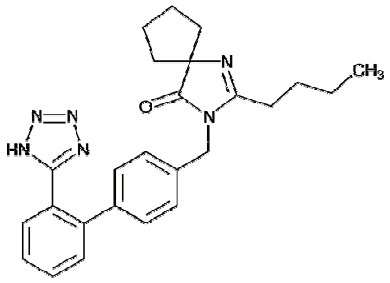
Proper Name: Irbesartan

Chemical Name:

- 1,3-Diazaspiro[4,4]non-1-en-4-one, 2-butyl-3-[[2'-(1H-tetra-zol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-
- 2-Butyl-3-[p-(o-1H-tetrazol-5-ylphenyl)benzyl]-1,3-diazaspiro[4,4]non-1-en-4-one.

Empirical Formula: $C_{25}\ H_{28}\ N_6O$

Structural Formula:



Molecular Weight: 428.5 g/mol

Description: 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.

II. COMPOSITION

In addition to the active ingredient, irbesartan, each tablet contains lactose monohydrate, colloidal silicon dioxide, copovidone, croscarmellose sodium and magnesium stearate.

III. STORAGE

RIVA-IRBESARTAN (irbesartan) Tablets can be stored at room temperature (15°C - 30°C).

AVAILABILITY OF DOSAGE FORMS

RIVA-IRBESARTAN (irbesartan) 75 mg are white to off-white, oval and biconvex tablets, debossed with “IS” on one side and “75” on the other side.

RIVA-IRBESARTAN (irbesartan) 150 mg are white to off-white, oval and biconvex tablets, debossed with “IS” on one side and “150” on the other side.

RIVA-IRBESARTAN (irbesartan) 300 mg are white to off-white, oval and biconvex tablets, debossed with “IS” on one side and “300” on the other side.

RIVA-IRBESARTAN is available in bottles of 100 tablets (75, 150 and 300 mg), and in bottles of 500 tablets (150 and 300 mg)

INFORMATION FOR THE PATIENT

Serious Warning and Precautions

RIVA-IRBESARTAN (irbesartan) should not be used during pregnancy. If you discover that you are pregnant while taking RIVA-IRBESARTAN, stop the medication and please contact your physician.

What is RIVA-IRBESARTAN?

RIVA-IRBESARTAN belongs to a class of drugs known as angiotensin II AT_1 receptor blockers which have been proven to be effective in lowering blood pressure.

RIVA-IRBESARTAN comes in the form of an oval shaped white tablet which contains irbesartan as the active ingredient. In addition, RIVA-IRBESARTAN tablets contain the following non-medicinal ingredients: lactose monohydrate, colloidal silicon dioxide, copovidone, croscarmellose sodium and magnesium stearate.

Why has my physician prescribed RIVA-IRBESARTAN?

Your physician has prescribed RIVA-IRBESARTAN because you have a condition known as hypertension or high blood pressure. Your physician may have also prescribed RIVA-IRBESARTAN if you have high blood pressure and type 2 diabetes mellitus to protect your kidney function.

What is blood pressure?

Blood pressure is the force of blood against the walls of your arteries (blood vessels that carry blood away from the heart). You need some blood pressure for the blood to circulate through your body. If the blood pressure gets too high, it is called high blood pressure or hypertension.

Your blood pressure changes during the day depending on activity, stress and excitement.

How is blood pressure measured?

Blood pressure is measured in millimeters of mercury (mm Hg) and is recorded as two numbers, for instance 120/80 (read as one hundred and twenty over eighty). The upper number is the systolic pressure and the lower number is the diastolic pressure.

The systolic pressure is the pressure in the arteries when the heart beats. The diastolic pressure is the pressure in the arteries when the heart relaxes between beats.

What is high blood pressure or hypertension?

You have high blood pressure or hypertension if your blood pressure is persistently higher than the

normal limits, even when calm or relaxed.

How do I know if I have high blood pressure?

There are usually no symptoms of high blood pressure. The only way of knowing that you have hypertension is to know your blood pressure. For that reason, you should have your blood pressure checked on a regular basis.

Why should high blood pressure be treated?

Left untreated, high blood pressure can damage vital organs like the heart and kidneys. You may feel fine and have no symptoms, but eventually hypertension can lead to strokes, heart attacks, heart failure, kidney failure or blindness.

What is kidney disease in patients with hypertension and type 2 diabetes mellitus?

When the kidneys deteriorate, they allow protein to pass in the urine. Early kidney disease is measured by detection of protein in the urine [microalbuminuria (MAU)] while more advanced stages are measured by increased levels of protein in urine (proteinuria). The presence of an abnormal protein level in the urine is a major risk factor for the progression of kidney disease (e.g. initiation of dialysis, kidney transplant) and heart disease.

How does RIVA-IRBESARTAN treat high blood pressure?

RIVA-IRBESARTAN lowers blood pressure by specifically blocking a natural substance called angiotensin II, which normally narrows your blood vessels. Treatment with RIVA-IRBESARTAN allows the blood vessels to relax. Although your physician 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 RIVA-IRBESARTAN.

If your blood pressure remains too high after an adequate trial period, your physician may decide to increase the dose of RIVA-IRBESARTAN. RIVA-IRBESARTAN reduces blood pressure further when the dose is increased. This may avoid the need for an additional medication to control your blood pressure.

If I have hypertension and Type 2 diabetes, how can RIVA-IRBESARTAN treat my condition?

In addition to controlling and lowering your blood pressure, recent studies have shown that RIVA-IRBESARTAN protects your kidneys by reducing protein in the urine. This in turn slows the progression of your kidney disease.

Who should not take RIVA-IRBESARTAN?

Do not take RIVA-IRBESARTAN if:

- **You are pregnant, breast-feeding or thinking of becoming pregnant**
  Taking RIVA-IRBESARTAN during pregnancy can cause injury and even death to your baby. This medicine should not be used during pregnancy. If you are planning to become pregnant while

taking RIVA-IRBESARTAN, contact immediately your doctor.

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

- If you are allergic to any of the ingredients.

RIVA-IRBESARTAN should not be given to children.

If any of the above apply to you, inform your doctor or pharmacist first and ask for their advice. **Other**

Important Information Before Taking RIVA-IRBESARTAN

There are certain conditions, which you may have, or have had, which require special care before or while taking RIVA-IRBESARTAN. Therefore, before taking this medicine, you should tell your doctor if you think any of the following applies to you:

a) You suffer from low blood pressure;
b) You are taking a "water pill";
c) You are vomiting or have severe diarrhea;
d) You are on a particular diet - low on salt;
e) You are on dialysis;
f) You have kidney problems.

If you are to undergo any surgery or receive anesthetics, you should make sure your doctor knows that you are taking RIVA-IRBESARTAN.

Can I take RIVA-IRBESARTAN with other medications?

Tell your doctor if you are taking other medications.

Do not take any other medications, including over-the-counter products, unless you have discussed the matter with your doctor. Certain medications tend to increase your blood pressure, for example, preparations for appetite control, asthma, colds, coughs, hay fever and sinus problems.

Can I drive or operate machinery while using RIVA-IRBESARTAN?

Almost all patients can, but you should not perform tasks, which may require special attention (for example, driving an automobile or operating dangerous machinery) until you know how you respond to your medicine.

How should I take RIVA-IRBESARTAN?

Take RIVA-IRBESARTAN every day exactly as your physician has instructed. It is important to continue taking RIVA-IRBESARTAN for as long as your physician prescribes it in order to maintain control of your blood pressure.

RIVA-IRBESARTAN may be taken with or without food.

What should I do if I miss a dose?

Try to take RIVA-IRBESARTAN daily as prescribed. If you miss a dose, do not take an extra dose. Just resume your normal schedule.

What should I do in case of an overdose?

Contact your physician immediately so that medical attention can be given promptly.

What undesirable effects may RIVA-IRBESARTAN have?

Along with its intended action, any medication, including RIVA-IRBESARTAN, may cause side effects. Most patients do not have side effects from taking RIVA-IRBESARTAN, but if you notice any of the following or any other unusual symptoms tell your pharmacist or your doctor right away:

- Dizziness
- Lightheadedness
- Rash
- Being tired
- Diarrhea
- 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 RIVA-IRBESARTAN 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.

Keep in mind that...

RIVA-IRBESARTAN has been prescribed to you for your current medical problem only. Do not give it to other people.

RIVA-IRBESARTAN should be stored at room temperature (15°C to 30 °C).

Keep this medication out of the reach of children.

TOXICOLOGY

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 - 50 fold the maximum human dose (300 mg) on a mg/m^2 basis, respectively.

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	• 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 was also noted. • One animal receiving 250 mg/kg/day presented the most severe heart lesions and marked electrocardiographic modifications on D1 and D29. • However, pre-existing lesions could not be excluded.
Monkey	M (3) F (3)	0 , 0.8 , 2 , 5	iv	2 weeks	• Irbesartan induced only a slight hyperplasia of the juxtaglomerular apparatus in 2/3 females receiving 5 mg/kg/day. • One high-dose animal presented a marked heart hypertrophy with marked ECG changes on D1 and D10 suggesting that it was a preexisting lesion.
Rat	M (20) - F (20) [main study] M (10) - F (10) [reversibility study for control and high dose groups] M (5) - F (5) [toxicokinetics study]	0 , 10, 30 , 90	po	26 weeks	• Slight reduction of the bodyweight gain in males at 90 mg/kg/day (-6 to - 8%). • Other changes can be considered to be of pharmacological origin for some of them and have no clear toxicological significance for all of them. • The no-observed adverse effect dose was considered to be 30 mg/kg/day

Species/ Strain	Sex (N/Dose)	Dose (mg/kg/day)	Route	Time	Effects
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 bodyweight 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 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 - 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).

SELECTED BIBLIOGRAPHY

1. Cazaubon C, Gougat J, Bousquet F, Guiraudou P, Gayraud R, Lacour C, et al. Pharmacological characterization of SR 47436, a new nonpeptide AT_1 subtype angiotensin II receptor antagonist.
   J Pharmacol Exp Ther 1993; 265:826-834

2. Hagmann M, Burnier M, Nussberger J, Leenhardt AF, Brouard R, Waeber B, et al. Natriuretic and hormonal effects of SR 47436 (BMS 186295), a new angiotensin II receptor antagonist in normotensive volunteers.
   Am J Hyperten 1994; 7 (4,Pt.2): 13A

3. Marino MR, Langenbacher KM, Raymond RH, Whigan D, and Ford NF Pharmacokinetics (pK) and antihypertensive effects of irbesartan (an AII receptor antagonist) in subjects with hypertension.
   J Hyperten 1996; 14(1): S348

4. Martinez F, Schmitt F, Savoiu C, Leenhardt AF, Brouard R, Peronnet P, et al. Effect of SR 47436 (BMS 186295) on renal hemodynamics and on glomerular permselectivity in healthy humans.
   J Am Soc Nephrol 1994; 5: 607

5. McIntyre M, McFadyen RJ, Meredith PA, Bruard R, and Reid JL Dose-ranging study of the angiotensin II receptor antagonist irbesartan (SR 47436 / BMS 186295) on blood pressure and neurohormonal effects in salt-deplete men. J Cardiovas Pharmacol 1996; 28: 101-106

6. Ribstein J, Sissmann J, Picard A, Bouroudian M, and Mimran A. Effects of the angiotensin II antagonist SR 47436 (BMS 186295) on the pressor response to exogenous angiotensin II and the renin-angiotensin system in sodium replete normal subjects.
   J Hypertens 1994; 12:131

7. Sissmann J, Bouroudian M, Armagnac C, Donazollo Y, Latreille M, and Panis R. Angiotensin II blockade in healthy volunteers: Tolerability and impact on renin angiotensin system components of single and repeated doses of a new angiotensin II receptor antagonist SR 47436 (BMS 186295).
   J Hypertens 1994; 12: S92

8. Binding of Irbesartan with Human Serum Proteins: a Re-evaluation (Horace Davi, Sept. 1998).

9. The Diabetes and Complications DCCT Research Group. Effect of intensive therapy on the development and progression of diabetic nephropathy in the diabetes control and

complications trials.
Kidney Int. 1995;47: 1703-1720.

10. Ravid M, Lang R, Rachman R, Lishner M. Lont-term renoprotective effect of angiotensinconverting enzyme inhibition in non-insulin-dependent diabetes mellitus.
Arch Intern Med. 196; 156: 286-289.

11. Maki DD, Ma JZ, Louis TA, Kasiske BL. Long term effects of antihypertensive agents on proteinuria and renal function.
Arch Intern Med. 1995;155: 1073-1080.

12. Cazaubon C, Gougat J, Bousquet F, et al. Pharmacological characterization of SR 47436 a new nonpeptide AT_1 subtype angiotensin II receptor antagonist.
J Pharmacol Exp Ther. 1993;265: 826-834.

13. Necciari J, Denolle T, Le Coz F, Donazollo Y, Pastor G, Sissmann J. Pharmacokinetics of SR 47436 BMS-186295, a new angiotensin II antagonist in man.
J Hypertens. 1994;12: 88.

14. Van Den Meiracker AH, Admiraal PJ, Janssen JA, et al. Hemodynamic and biochemical effects of the ATI receptor antagonist irbesartan in hypertension.
Hypertension. 1995;25: 22-29.

15. Parving HH et al. The Effects of Irbesartan on The Development of Diabetic Nephropathy in Patients with Type 2 Diabetes Mellitus (IRMA 2)
N Engl J Med 2001; 345(12):870-878

16. Lewis EJ et al. Renoprotective Effect of the Angiotensin-Receptor Antagonist Irbesartan in Patients with Nephropathy Due to Type 2 Diabetes. The Irbesartan Diabetic Nephropathy Trial (IDNT).
N Engl J Med 2001; 345 (12): 851-860

17. Ribstein J, Picard a, Armagnac C, Sissmann J and Mimran A.
Inhibition of the Acute Effects of Angiotensin Ii by the Receptor Antagonist Irbesartan in Normotensive Men.
J Cardiovas Pharmacol 2001; 37:449-460

18. Product Monograph for AVAPRO®, Date of revision: December 29, 2008, Control No.: 125069, sanofi-aventis Canada Inc, Laval (QC), Canada.