PRODUCT MONOGRAPH

^{Pr}AVAPRO®

(irbesartan tablets, USP)

75, 150 and 300 mg

Angiotensin II AT_1 Receptor Blocker

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THERAPEUTIC CLASSIFICATION

Angiotensin II AT_1 Receptor Blocker

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

AVAPRO (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.

Pharmacokinetics

Absorption: 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.

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 53-93 L. Total plasma and renal clearances are in the range of 157 - 176 mL/min and 3.0 - 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.

Excretion: Irbesartan and its metabolites are excreted by both biliary and renal routes. Following either oral or intravenous administration of ^{14}C-labeled irbesartan, about 20% of radioactivity is recovered in the urine and the remainder in the feces. Less than 2% of the dose is excreted in urine as unchanged irbesartan.

Special populations and condition

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

Renal impairment: 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.

Hepatic 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

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 1.5-2 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, 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 1-2 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. 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.

CLINICAL TRIALS

Two trials were done to investigate the effects of AVAPRO 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 - 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.

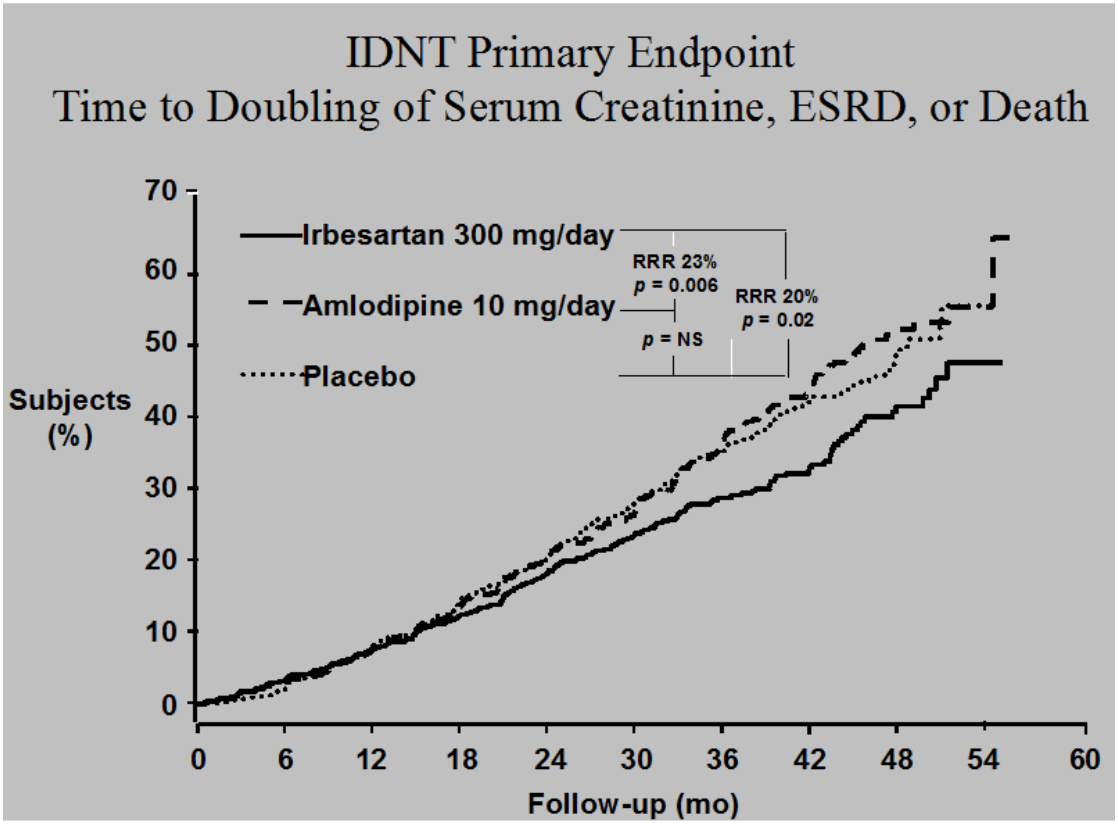


Table 1
Primary Composite Endpoint Comparison (IDNT)

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 (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 (20-200 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 - 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 [>300mg/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.

IRMA 2 Primary Endpoint

Time to Overt Proteinuria

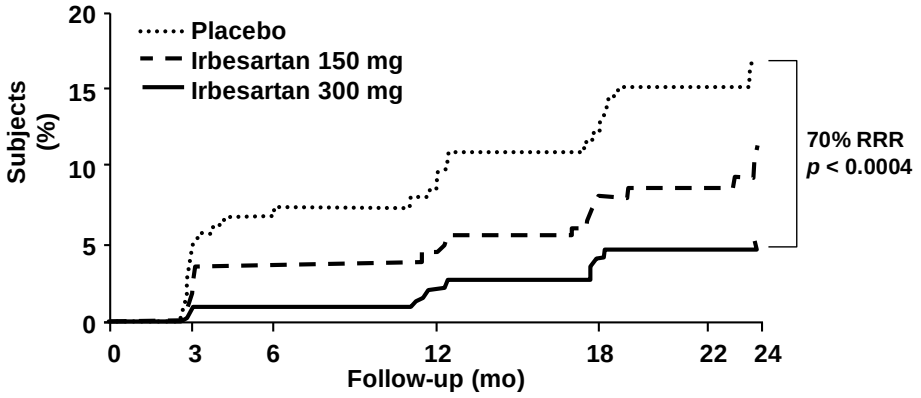
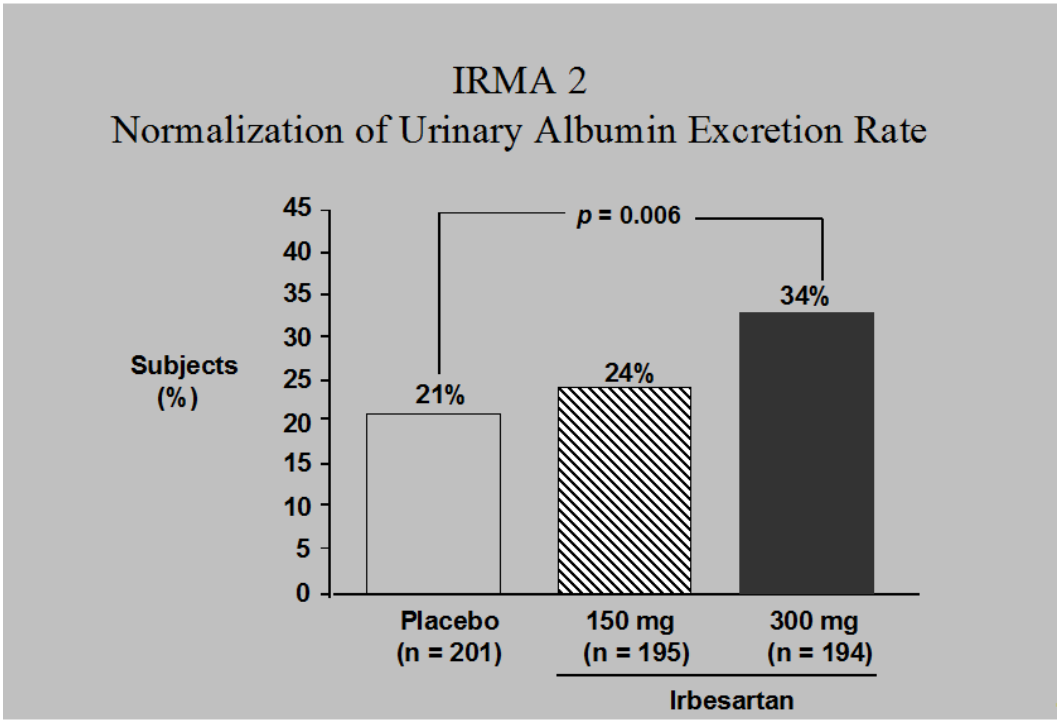


Table 2
Time to occurrence of Overt Proteinuria
(Irbesartan 300 mg vs. Placebo Comparison) (IRMA 2)

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).



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

INDICATIONS AND CLINICAL USE

AVAPRO (irbesartan) is indicated for the treatment of:

- essential hypertension. AVAPRO 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).

CONTRAINDICATIONS

AVAPRO (irbesartan) is contraindicated in:

- Patients who are hypersensitive to this drug or to any ingredient in the formulation. For a complete listing, see the AVAILABILITY OF THE DOSAGE FORMS section of the Product monograph.
- 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 PRECAUTIONS, Dual Blockade of the Renin-Angiotensin System (RAS) and Renal Impairment, and DRUG INTERACTIONS, Dual Blockade of the Renin-Angiotensin-System (RAS) with ARBs, ACE inhibitors or aliskiren-containing drugs)

- Combination with Angiotensin-Converting Enzyme Inhibitors (ACEIs) in patients with diabetic nephropathy (see PRECAUTIONS, Dual Blockade of the Renin-Angiotensin System (RAS) and Renal Impairment, and DRUG INTERACTIONS, Dual Blockade of the Renin-Angiotensin-System (RAS) with ARBs, ACE inhibitors or aliskiren-containing drugs)
- Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption (due to the lactose component of AVAPRO tablets)
- Pregnant women (see WARNINGS, Special Populations, Pregnant Women).
- Nursing women (see WARNINGS, Special Populations, Nursing Women).

WARNINGS AND PRECAUTIONS

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, AVAPRO (irbesartan) should be discontinued as soon as possible (see WARNINGS, Special Populations).

General

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

Cardiovascular

Hypotension - 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 AVAPRO, 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 AVAPRO in combination with aliskiren-containing drugs is contraindicated in these patients (see CONTRAINDICATIONS).

The use of AVAPRO in combination with of ACE inhibitors is contraindicated in patients with diabetic nephropathy (see CONTRAINDICATIONS).

Further, co-administration of ARBs, including AVAPRO, 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.

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 AVAPRO, 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, Dual Blockade of the Renin-Angiotensin-System (RAS) with ARBs, ACE inhibitors, or aliskiren-containing drugs).

The use of ARBs including AVAPRO 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, Dual Blockade of the Renin-Angiotensin-System (RAS) with ARBs, ACE inhibitors, or aliskiren-containing drugs).

Use of AVAPRO 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 AVAPRO 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.

Special Populations

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

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

Nursing Women
It is not known whether AVAPRO (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.

Pediatrics (<18 years of age)

The safety and efficacy of AVAPRO have not been established in children < 18 years of age. Therefore, AVAPRO is not indicated in this patient population.

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.

DRUG INTERACTIONS

Overview

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

Drug-Drug Interaction

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 AVAPRO. The possibility of symptomatic hypotension with the use of AVAPRO can be minimized by discontinuing the diuretic prior to initiation of treatment and/or lowering the initial dose of AVAPRO (see WARNINGS - Hypotension, and DOSAGE AND ADMINISTRATION). No drug interaction of clinical significance has been identified with thiazide diuretics.

Agents increasing Serum Potassium

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.

NSAIDs

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 angiotensin II receptor antagonists, including irbesartan, may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible. Monitor renal function periodically in patients receiving irbesartan and NSAID therapy. The antihypertensive effect of angiotensin II receptor blockers (ARBs), including irbesartan, may be attenuated by NSAIDs including selective COX-2 inhibitors.

Lithium

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).

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 - 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.

Dual Blockade of the Renin-Angiotensin-System (RAS) with ARBs, ACE inhibitors or aliskiren-containing drugs

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 hypotension, renal failure, and hyperkalemia.

The use of AVAPRO 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.

[See CONTRAINDICATIONS and PRECAUTIONS, Dual Blockade of the Renin-Angiotensin-System (RAS)].

ADVERSE REACTIONS

AVAPRO (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 AVAPRO 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 3):

Table 3: Adverse events occurring in ≥1% of the 2606 hypertensive patients in placebo-controlled clinical trials

Body System/Reaction	AVAPRO 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 AVAPRO-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;

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 (see ACTION AND CLINICAL PHARMACOLOGY; Clinical Trials: 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 1.0-3.0 mg/dL). In IDNT, orthostatic symptoms occurred more frequently in the AVAPRO 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 AVAPRO 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 AVAPRO.

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 AVAPRO treated patients compared to 0.3% and 0.3%, respectively, of patients receiving placebo. In patients treated with AVAPRO for a mean duration of over 1 year, the cumulative incidence of AST and/or ALT elevations ≥ 3X ULN was 0.4%.

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 - 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.

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 AVAPRO alone versus 0.9% on placebo.

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

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

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

Postmarketing Experience

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

The following adverse reactions have been reported in post-marketing use: asthenia, elevated liver function tests and impaired renal function including cases of renal failure in patients at risk (see PRECAUTIONS - Renal Impairment), jaundice, myalgia, syncope, tinnitus.

Cases of muscle pain, muscle weakness, myositis and rhabdomyolysis have been reported in patients receiving ARBs.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Few cases of overdosage with AVAPRO (irbesartan) have been reported, with no complaints and 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. 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 AVAPRO. 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.

AVAPRO 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 (BP) elevation, salt restriction, and other pertinent clinical factors. The dosage of other antihypertensive agents used with AVAPRO (irbesartan) may need to be adjusted.

AVAPRO may be administered with or without food.

Essential Hypertension
The recommended initial dose of AVAPRO 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 AVAPRO 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.

Elderly patients: No initial dosage adjustment is required in the elderly (see ACTION AND CLINICAL PHARMACOLOGY- Pharmacokinetics , Special Population and Conditions, Geriatrics (> 65 years of age) and PRECAUTIONS - Geriatrics (> 65 years of age)).

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

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

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

PHARMACEUTICAL INFORMATION

I. DRUG SUBSTANCE

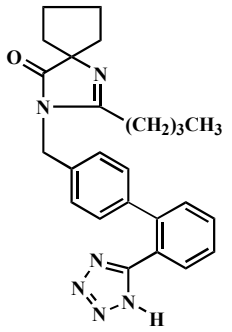
Trade Name: AVAPRO

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.

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

Structural Formula:



Molecular Weight: 428.5

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

Regular Mass Tablets:
Medicinal ingredient: irbesartan,
Nonmedicinal ingredients: croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, pregelatinized starch, poloxamer 188, silicon dioxide.

Reduced Mass Tablets:
Medicinal ingredient: irbesartan
Nonmedicinal ingredients: carnauba wax, croscarmellose sodium, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol 3000, silicon dioxide, titanium dioxide.

III. STORAGE

AVAPRO (irbesartan) Tablets can be stored at room temperature (15 - 30^{o}C).

AVAILABILITY OF DOSAGE FORMS

Regular Mass Tablets:
AVAPRO (irbesartan) 75 mg tablets: white to off-white biconvex, oval tablets, with a heart shape debossed on one side and the digits 2771 on the other.

AVAPRO (irbesartan) 150 mg tablets: white to off-white biconvex, oval tablets, with a heart shape debossed on one side and the digits 2772 on the other.

AVAPRO (irbesartan) 300 mg tablets: white to off-white biconvex, oval tablets, with a heart shape debossed on one side and the digits 2773 on the other.

AVAPRO 75, 150 and 300 mg tablets are available in bottles of 90 tablets.

Reduced Mass Tablets:
AVAPRO (irbesartan) 75 mg tablets: white biconvex, film coated oval tablets, with a heart shape debossed on one side and the digits 2871 on the other.

AVAPRO (irbesartan) 150 mg tablets: white biconvex, film coated oval tablets, with a heart shape debossed on one side and the digits 2872 on the other.

AVAPRO (irbesartan) 300 mg tablets: white biconvex, film coated oval tablets, with a heart shape debossed on one side and the digits 2873 on the other.

AVAPRO 75, 150 and 300 mg tablets are available in bottles of 90 tablets.

TOXICOLOGY

Acute Toxicity

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

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

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	X 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	X Very slight increase in Na^+ and Cl^- plasma levels (≥ 0.8 mg/kg/day in males) X 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	X 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	X ≥ 250 mg/kg/day: changes in the kidney (hyperplasia of the juxtaglomerular apparatus), heart (myocardial fibrosis) and erythrocytes parameters (slight anemia). X At 500 mg/kg/day: increased platelet count, fibrogen and neutrophil levels and at 1000 mg/kg/day, health deterioration was also noted. X 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	X Irbesartan induced only a slight hyperplasia of the juxtaglomerular apparatus in 2/3 females receiving 5 mg/kg/day. X 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	X Slight reduction of the bodyweight gain in males at 90 mg/kg/day (- 6 to - 8%). X Other changes can be considered to be of pharmacological origin for some of them and have no clear toxicological significance for all of them. X 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	X Slight reduction of bodyweight gain without any dose-relationship-reversible. X 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. X 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	X Dose-related hyperplasia of juxtaglomerular apparatus in all treated animals partially reversible at the end of treatment. X 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: X 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. X Dose-related hyperplasia / hypertrophy of the juxtaglomerular apparatus in all treated animals with degenerative kidney changes at 500 mg/kg/day. X 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 abberations (*in vitro* - human lymphocyte assay; *in vivo* - mouse micronucleus study).

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CONSUMER INFORMATION

[Pr]AVAPRO®

(irbesartan tablets, USP)

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

ABOUT THIS MEDICATION

What the medication is used for:

- AVAPRO lowers high blood pressure
- If you have high blood pressure, type 2 diabetes and kidney disease, **AVAPRO** may help to protect kidney function

What it does:
AVAPRO is an angiotensin receptor blocker (ARB). You can recognize an ARB because its medicinal ingredient ends in "-SARTAN".

This medicine does not cure your disease. It helps to control it. Therefore, it is important to continue taking **AVAPRO** regularly even if you feel fine.

When it should not be used:
Do not take AVAPRO 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 doctor, nurse, or pharmacist 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 AVAPRO during pregnancy can cause injury and even death to your baby.
- Are breastfeeding. It is possible that AVAPRO passes into breast milk.
- Have one of the following rare hereditary diseases:
    - Galactose intolerance
    - Lapp lactase deficiency
    - Glucose-galactose malabsorption

Because lactose is a non-medicinal ingredient in **AVAPRO**.

AVAPRO is not recommended for use in children and adolescents (under the age of 18 years).

What the medicinal ingredient is:
Irbesartan.

What the nonmedicinal ingredients are:
Tablets with numbers 2771, 2772 and 2773: Croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, poloxamer 188, pregelatinized starch, and silicon dioxide.

Tablets with numbers 2871, 2872 and 2873: Carnauba wax, croscarmellose sodium, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol 3000, silicon dioxide and titanium dioxide

What dosage forms it comes in:
Tablets with numbers 2771, 2772 and 2773: Oval tablets (white to off white); 75 mg, 150 mg, and 300 mg.

Tablets with numbers 2871, 2872 and 2873: Film coated oval tablets (white); 75 mg, 150 mg and 300 mg.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions - Pregnancy

AVAPRO should not be used during pregnancy. If you discover that you are pregnant while taking AVAPRO, stop the medication and contact your physician as soon as possible.

BEFORE you use AVAPRO talk to your doctor, nurse or pharmacist 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 diabetes, liver or kidney disease.
- 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 AVAPRO is not recommended.
- Are taking an angiotensin converting enzyme (ACE) inhibitor. The combination with AVAPRO is not recommended.
- Are taking a medicine that contains lithium. The combination with AVAPRO is not recommended.
- Are less than 18 years old.

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

Please remember:
- If you are to undergo any surgery or receive anaesthetics, you should make sure your doctor knows that you are taking AVAPRO.

INTERACTIONS WITH THIS MEDICATION

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

The following may interact with AVAPRO:
- 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.

PROPER USE OF THIS MEDICATION

Take AVAPRO exactly as prescribed. It is recommended to take your dose at about the same time every day.

Do not stop taking your medication without having first informed your doctor.

Usual Adult Dose:
High Blood Pressure (hypertension) including in patients with Type 2 Diabetes Mellitus:

Recommended Initial Dose: 150 mg once a day.

Your doctor can increase the dosage to 300 mg once daily when required.

AVAPRO may be taken with or without food.

Remember that your doctor has prescribed this medicine only for you. Never give it to anyone else.

Overdose:

If you think you have taken too much AVAPRO contact your doctor, nurse, pharmacist, 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 one at the usual time. Do not double dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Side effects may include:
- dizziness
- drowsiness, insomnia, being tired
- rash
- diarrhea, vomiting
- headache
- back or leg pain, muscle cramps
- Lightheadedness
- Ringing in the ears

If any of these affects you severely, tell your doctor, nurse or pharmacist.

AVAPRO can cause abnormal blood test results. Your doctor will decide when to perform blood tests and will interpret the results.

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

Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and seek immediate medical help
	Only if severe	In all cases	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		**Talk with your doctor or pharmacist**		**Stop taking drug and seek immediate medical help**
		Only if severe	**In all cases**	
Common	**Increased levels of potassium in the blood:** irregular heartbeats**,** muscle weakness and generally feeling unwell		√	
Uncommon	**Low blood pressure**: Dizziness/ Fainting/ Light-headedness	√		
	Jaundice (Liver disorder): yellowing of the skin or eyes, dark urine, abdominal pain, nausea, vomiting, loss of appetite		√	
	Kidney Disorder: change in frequency of urination, nausea, vomiting, swelling of extremities, fatigue		√	
Rare	**Rhabdomyolysis:** muscle pain that you cannot explain, muscle tenderness or weakness, dark brown urine		√	
	Allergic Reaction: rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			√
Very Rare	**Decreased Platelets:** bruising, bleeding, fatigue and weakness		√	

This is not a complete list of side effects. If you have any unexpected effects while taking AVAPRO, contact your doctor or pharmacist.

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.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.

HOW TO STORE IT

Store AVAPRO tablets at room temperature (15 to 30°C).

Keep out of reach and sight of children.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at: www.sanofi.ca or by contacting the sponsor, sanofi-aventis Canada Inc., at: 1-800-265-7927.

This leaflet was prepared by sanofi-aventis Canada Inc.

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