

PRODUCT MONOGRAPH

Pr AURO-IRBESARTAN

Irbesartan tablets
75 mg, 150 mg & 300 mg

House Standard

Angiotensin II AT₁ Receptor Blocker

Auro Pharma Inc.

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CANADA

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April 29, 2013

Pr AURO-IRBESARTAN

(Irbesartan tablets 75 mg, 150 mg & 300 mg)

THERAPEUTIC CLASSIFICATION

Angiotensin II AT₁ Receptor Blocker

ACTION AND CLINICAL PHARMACOLOGY

AURO-IRBESARTAN (irbesartan) antagonizes angiotensin II by blocking AT₁ 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 AT₁ receptor found in many tissues. Irbesartan has no agonist activity at the AT₁ receptor. AT₂ 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 AT₂ 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 ¹⁴C-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 ¹⁴C-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 C_{MAX} values were about 20 - 50% greater than those of young subjects.

The mean AUC and C_{MAX} were not altered in patients with any degree of renal impairment, including patients on hemodialysis. However, a wide variance was seen in patients with severe renal impairment.

The pharmacokinetics of irbesartan following repeated oral administration were not significantly affected in patients with mild to moderate cirrhosis of the liver. No data is available in patients with severe liver disease.

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

Comparative Bioavailability Studies

A double blind, randomized, two treatment, two sequence, two period, cross-over, single-dose comparative oral bioavailability study of Auro-Irbesartan Tablets 300 mg (Test) of Aurobindo Pharma Ltd., India manufactured for Auro Pharma Inc. and Avapro® (Irbesartan) 300 mg tablets (Reference) of Sanofi-Aventis Canada Inc., Canada and distributed by Bristol-Myers Squibb Canada, Canada was conducted in 36 healthy, adult, male subjects under fasting conditions.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Irbesartan (1 x 300 mg) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test* (T)	Reference† (R)	% Ratio of Geometric Means	90% Confidence Interval
AUC_{0-t} (hr.ng/mL)	22221.0 23549.4 (37.1)	21363.7 22676.8 (34.8)	104.0	96.9-111.7
AUC_{0-∞} (hr. ng/mL)	22542.1 23921.1 (37.8)	21724.1 23071.5 (35.1)	103.8	96.6-111.5
C_{max} (ng/mL)	4340.8 4521.2 (28.9)	4589.5 4789.4 (30.4)	94.6	87.4-102.4
T_{max}§ (h)	1.5 (0.7-5.0)	1.5 (0.5-4.0)		
T_{1/2}§ (h)	8.4 (42.7)	8.8 (34.3)		

* AURO-IRBESARTAN (Irbesartan) tablets 300 mg by Auro Pharma Inc.

† AVAPRO® (Irbesartan Tablets 300 mg) by Sanofi-Aventis Canada Inc., Canada and distributed by Bristol-Myers Squibb Canada, Canada were purchased from Canada.

§ Expressed as the Median (Range) only.

§ Expressed as arithmetic mean (%CV) only.

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

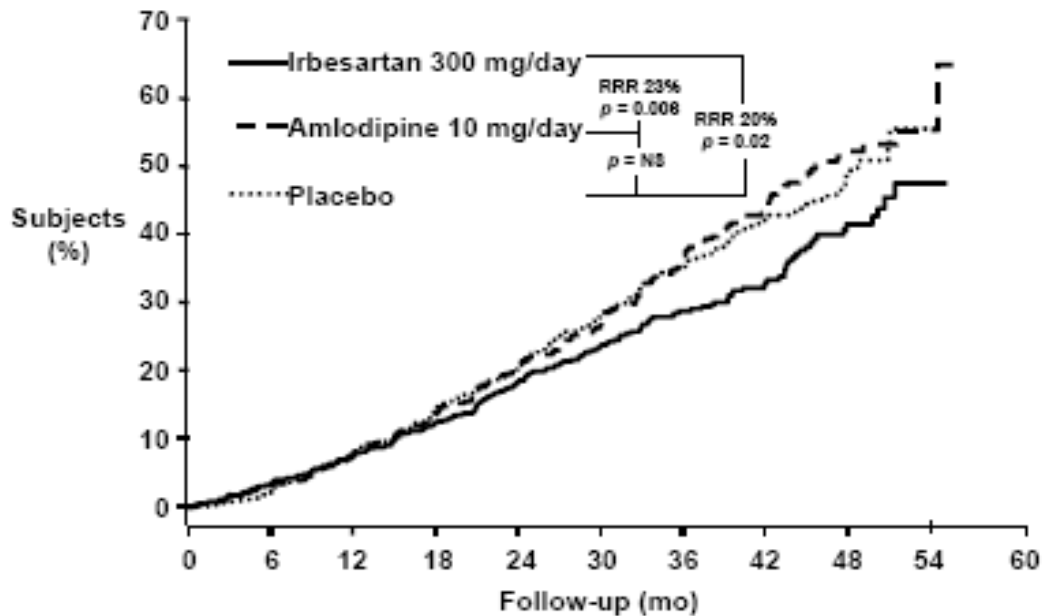


Table 1
Primary Composite Endpoint Comparison (IDNT)

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 amlodipine 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.

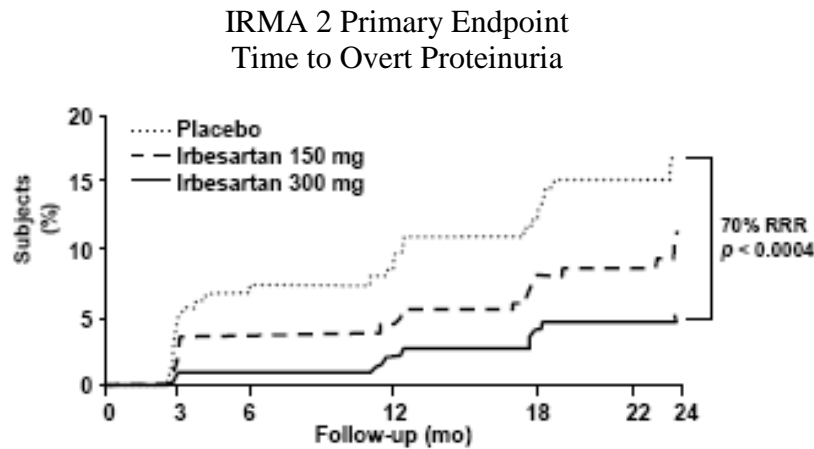
IRMA 2:

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 \leq 1.5 mg/dL in males and \leq 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.

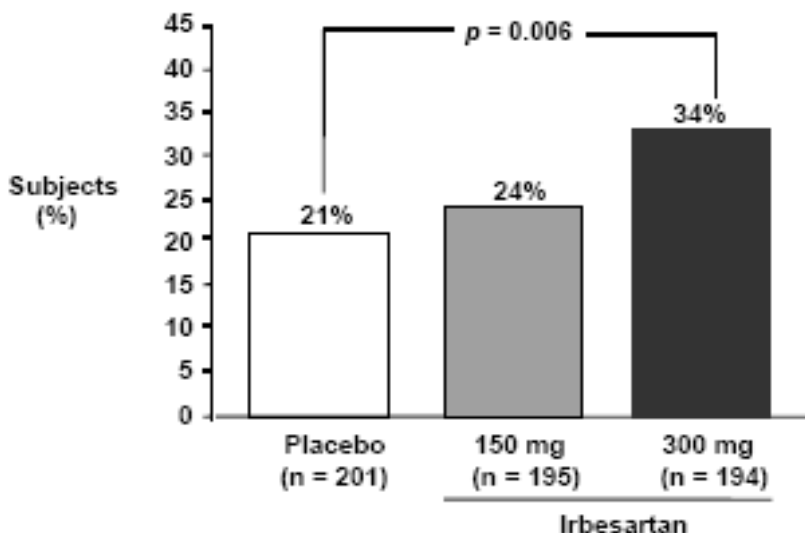


**Table 2
Time to occurrence of Overt Proteinuria
(Irbesartan 300 mg vs. Placebo Comparison) (IRMA 2)**

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.

INDICATIONS AND CLINICAL USE

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

AURO-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).

AURO-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

AURO-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 (AT₁) blockers (ARB) can cause injury or even death of the developing fetus. When pregnancy is detected, AURO-IRBESARTAN (irbesartan) should be discontinued as soon as possible (see WARNINGS, Special Populations).

Special Populations

Pregnant Women

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, AURO-IRBESARTAN (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, hyperkalemia).

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.

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 antagonists, including irbesartan, may be attenuated by NSAIDs including selective COX-2 inhibitors.

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 $\geq 1\%$ 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		
	2.8	2.7

Body System/Reaction	Irbesartan n = 1965 Incidence (%)	Placebo n = 641 Incidence (%)
Cough		
Urogenital System		
Urinary Tract Infection	1.1	1.4

The incidence of hypotension or orthostatic hypotension occurred 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 in post-marketing use, syncope, asthenia, myalgia, jaundice, elevated liver function tests and impaired renal function including 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 ≥ 900 mg/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 ≥ 3 X 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 ≥ 3 X 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/mm³) 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 overdose 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 overdose are expected to be hypotension and tachycardia; bradycardia might also occur from overdose.

No specific information is available on the treatment of overdose 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 overdose.

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 AURO-IRBESARTAN (irbesartan) may need to be adjusted.

AURO-IRBESARTAN may be administered with or without food.

Essential Hypertension

The recommended initial dose of AURO-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 AURO-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, AURO-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 AURO-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, AURO-IRBESARTAN should be administered with caution and the blood pressure monitored closely. The recommended starting dose of AURO-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

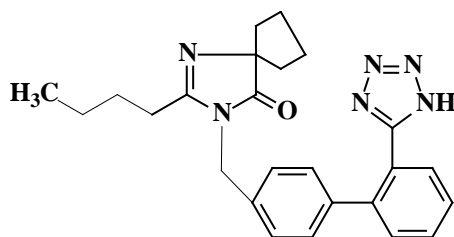
Trade Name: AURO-IRBESARTAN

Proper Name: Irbesartan

Chemical Name:

2-Butyl-3-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1,3-diazaspiro[4.4] non-1-en-4-one.
2-*n*-butyl-4-spirocyclopentane-1-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]-2-imidazolin-5-one.

Molecular Formula: C₂₅H₂₈N₆O



Structural Formula:

Molecular Weight: 428.53

Description:

White or almost white, crystalline powder. Two crystalline polymorphic forms of Irbesartan namely, form A and form B are known in chemical literature. Aurobindo prepares polymorph form A of Irbesartan. Irbesartan is slightly soluble in methylene chloride, Sparingly soluble in methanol and practically insoluble in water.

II. STORAGE

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

III. DOSAGE FORMS, COMPOSITION AND PACKAGING

Irbesartan Tablets are supplied as follows:

Dosage form	Tablets		
Strength	75 mg	150 mg	300 mg
Description	White to off-white, biconvex oval-shaped uncoated tablets debossed with 'H28' on one side and plain on the other side.	White to off-white, biconvex oval-shaped uncoated tablets debossed with 'H29' on one side and plain on the other side.	White to off-white, biconvex oval-shaped uncoated tablets debossed with 'H30' on one side and plain on the other side.
Composition	<p>Irbesartan 75 mg.</p> <p>Non-medicinal Ingredients: Microcrystalline Cellulose, Calcium Hydrogen Phosphate Dihydrate, Hypermellose, Polysorbate 80, Sodium Starch Glycolate (Type-A), Talc, Colloidal Anhydrous Silica, Sodium Stearyl Fumarate.</p>	<p>Irbesartan 150 mg.</p> <p>Non-medicinal Ingredients: Microcrystalline Cellulose, Calcium Hydrogen Phosphate Dihydrate, Hypermellose, Polysorbate 80, Sodium Starch Glycolate (Type-A), Talc, Colloidal Anhydrous Silica, Sodium Stearyl Fumarate.</p>	<p>Irbesartan 300 mg.</p> <p>Non-medicinal Ingredients: Microcrystalline Cellulose, Calcium Hydrogen Phosphate Dihydrate, Hypermellose, Polysorbate 80, Sodium Starch Glycolate (Type-A), Talc, Colloidal Anhydrous Silica, Sodium Stearyl Fumarate.</p>
Packaging	HDPE bottles of 30's, 90's, 100's and 500's.	HDPE bottles of 30's, 90's, 100's and 500's.	HDPE bottles of 30's, 90's, 100's and 500's.

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 2000mg/kg, about 25 - 50 fold the maximum human dose (300 mg) on a mg/m² 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	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • ≥ 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	<ul style="list-style-type: none"> • Irbesartan induced only a slight hyperplasia of the juxtaglomerular apparatus in 2/3 females receiving 5 mg/kg/day. C One high-dose animal presented a marked heart hypertrophy with marked ECG changes on D1 and D10 suggesting that it was a preexisting lesion.
Rat	M (20) - F (20) [main study] M (10) - F (10) [reversibility study for control and high dose groups] M (5) - F (5) [toxicokinetics study]	0, 10, 30, 90	po	26 weeks	<ul style="list-style-type: none"> • 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.
CHRONIC TOXICITY					

Species/ Strain	Sex (N/Dose)	Dose (mg/kg/day)	Route	Time	Effects
Rat	M (20) - F (20) [main study] M (10) - F (10) [reversibility study for control and high dose groups] M (5) - F (5) [toxicokinetics study]	0, 0, 250, 500, 1000	po	26 weeks	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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	<p>Irbesartan was well tolerated and most of the changes observed were considered to be due to the pharmacological activity of the drug:</p> <ul style="list-style-type: none"> 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).

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CONSUMER INFORMATION

Pr AURO-IRBESARTAN irbesartan

This leaflet is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about AURO-IRBESARTAN. Please read this leaflet carefully before you start to take your medicine, even if you have just refilled your prescription. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

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

What it does:

AURO-IRBESARTAN belongs to a class of drugs known as angiotensin II AT1 receptor blockers (ARB) which have been proven to be effective in lowering blood pressure.

AURO-IRBESARTAN lowers blood pressure by specifically blocking a natural substance called angiotensin II, which normally narrows your blood vessels. Treatment with AURO-IRBESARTAN allows the blood vessels to relax. Although your doctor will be able to tell you that the medicine is working by measuring your blood pressure, you will probably feel no different while you are taking AURO-IRBESARTAN.

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

This medicine does not cure high blood pressure, **but does help control it**. Therefore, it is important to continue taking AURO-IRBESARTAN regularly to keep your blood pressure down even if you feel fine.

When it should not be used:

Do not take AURO-IRBESARTAN if you:

- Are allergic to AURO-IRBESARTAN or to any non-medicinal ingredient in the formulation.

- Ever have experienced an allergic reaction and in particular with swelling of the face, lips, tongue, throat, or sudden difficulty AURO-IRBESARTAN (ARB). Be sure to tell your doctor that this has happened to you.
- **Are pregnant or thinking of becoming pregnant.**
- Are breastfeeding, you should discuss with your physician about taking AURO-IRBESARTAN.

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

AURO-IRBESARTAN 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:

Microcrystalline cellulose, calcium hydrogen phosphate dihydrate, hypermellose, polysorbate 80, sodium starch glycolate (Type-A), talc, colloidal anhydrous silica, sodium stearyl fumarate.

What dosage forms it comes in:

Oval tablets (white to off white); 75mg, 150 mg, and 300 mg

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions AURO-IRBESARTAN should not be used during pregnancy. If you discover that you are pregnant while taking AURO-IRBESARTAN, stop the medication and contact your physician as soon as possible.

BEFORE you use AURO-IRBESARTAN talk to your doctor or pharmacist if you:

- Have any of these health problems: liver disease, kidney disease or heart disease.
- Have narrowing of a heart valve.
- Have recently suffered from severe diarrhea or excessive vomiting.
- Are on a low-salt diet or use salt substitutes that contain potassium, potassium supplements, potassium-sparing diuretics (a specific kind of “water pills”), or any medicine that may increase your potassium level.
- Are on dialysis.
- Have ever experienced an allergic reaction to any drug to lower blood pressure. Be sure to tell your

IMPORTANT: PLEASE READ

doctor that this has happened to you. The doctor will decide if AURO-IRBESARTAN is right for you.

- To tell any other doctor, dentist or pharmacist with whom you consult that you are using AURO-IRBESARTAN.
- Dizziness or drowsiness may occasionally occur when taking AURO-IRBESARTAN. Therefore, before you perform tasks which may require special attention (driving a car or operating dangerous machinery), wait until you know how you respond to AURO-IRBESARTAN.
- If you are to undergo any surgery or receive anaesthetics, you should make sure your doctor knows that you are taking AURO-IRBESARTAN.

Effects on Pregnancy and Breastfeeding:

Taking AURO-IRBESARTAN during pregnancy can cause injury and even death to your baby. This medicine should not be used during pregnancy. If you become pregnant or are planning to become pregnant while taking AURO-IRBESARTAN, contact your doctor immediately. It is possible that AURO-IRBESARTAN passes into breast milk. Therefore, you should discuss with your doctor about taking AURO-IRBESARTAN while breast-feeding.

INTERACTIONS WITH THIS MEDICATION

Before taking AURO-IRBESARTAN, tell your doctor or pharmacist about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Drugs that may interact with AURO-IRBESARTAN include:

- Other medicines used to lower blood pressure, including diuretics (“water pills”).
- Any substance that may increase your potassium level, including salt substitutes that contain potassium, potassium supplements, potassium-sparing diuretics (a specific kind of “water pills”).
- Lithium-containing medicines to treat some types of depression.
- Nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin and ibuprofen. NSAIDs are used to reduce pain, fever, and swelling.
- 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 AURO-IRBESARTAN exactly as prescribed by your doctor. It may be easier to take your dose if you do it at the same time every day.

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

Usual dose:

High Blood Pressure (hypertension) including in patients with Type 2 Diabetes Mellitus: 150 mg once daily. Your doctor can increase the dosage to 300 mg once daily when required.

AURO-IRBESARTAN 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:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

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

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Along with its intended action, any medication, including AURO-IRBESARTAN, may cause side effects. Most patients do not have side effects from taking AURO-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

IMPORTANT: PLEASE READ

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	
Uncommon	Hypotension: Dizziness/ Fainting/ Light-headedness	√		
	Jaundice: yellowing of the skin or eyes, dark urine, abdominal pain, nausea, vomiting, loss of appetite		√	
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			√
Unknown	Hyperkalemia: increased levels of potassium in the blood, heart skips a beat, muscle weakness and generally feeling unwell		√	

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

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
 - Fax toll-free to 1-866-678-6789, or
 - Mail to: Canada Vigilance Program
Health Canada
Postal Locator 0701E
Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the Management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

HOW TO STORE IT

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

MORE INFORMATION

This document plus the full Product Monograph, prepared for health professionals can be found at: <http://www.auropharma.ca> or by contacting the sponsor, Auro Pharma Inc., at: 1-855-648-6681

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