PRODUCT MONOGRAPH

# [Pr] Q-IRBESARTAN

Irbesartan Tablets

75 mg, 150 mg and 300 mg

USP

Angiotensin II $AT_1$ Receptor Blocker

QD Pharmaceuticals ULC
85 Advance Road
Etobicoke, ON
M8Z 2S6

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## THERAPEUTIC CLASSIFICATION

Angiotensin II $AT_1$ Receptor Blocker

## ACTION AND CLINICAL PHARMACOLOGY

**Mechanism of Action**
Q-IRBESARTAN (irbesartan) antagonizes angiotensin II by blocking $AT_1$ receptors.

Angiotensin II is the primary vasoactive hormone in the renin-angiotensin system. Its effects include vasoconstriction and the stimulation of aldosterone secretion by the adrenal cortex.

Irbesartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking in a non competitive manner the binding of angiotensin II to the $AT_1$ receptor found in many tissues. Irbesartan has no agonist activity at the $AT_1$ receptor. $AT_2$ receptors have been found in many tissues, but to date they have not been associated with cardiovascular homeostasis. Irbesartan has essentially no affinity for the $AT_2$ receptors.

Irbesartan does not inhibit angiotensin converting enzyme, also known as kininase II, the enzyme that converts angiotensin I to angiotensin II and degrades bradykinin, nor does it affect renin or other hormone receptors or ion channels involved in cardiovascular regulation of blood pressure and sodium homeostasis.

**Pharmacokinetics**

***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 $\alpha_1$-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 ɵ ≤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 blood pressure response to irbesartan monotherapy than Caucasians.

## CLINICAL TRIALS

### Pivotal Comparative Bioavailability Study

A blinded, randomized, single-dose, two-way crossover comparative bioavailability study was conducted in 28 normal, healthy adult male subjects. The rate and extent of irbesartan absorption was measured and compared following a single oral dose of 300 mg as Q-IRBESARTAN or Avapro® (sanofi-aventis Canada Ltd.) under fasting conditions. The results of the comparison between the two products are provided in the table below.

**Irbesartan**
**(300 mg dose; 1 x 300 mg)**
**From measured data**
**Geometric Mean[+]**
**Arithmetic Mean (CV %)**

| Parameter | Test[*] | Reference[†] | % Ratio of Geometric Means[+] | 90% Confidence Interval[+] |
|---|---|---|---|---|
| $AUC_T$ (µg·h/mL) | 18.72<br>19.82 (31) | 19.79<br>20.97 (32) | 94.6 | 89.9 – 99.5 |
| $AUC_I$ (µg·h/mL) | 19.79<br>20.96 (31) | 20.75<br>22.40 (31) | 95.4 | 90.8 – 100.1 |
| $C_{max}$ (µg/mL) | 3.63<br>3.75 (26) | 3.35<br>3.48 (28) | 108.4 | 102.0 – 115.4 |
| $T_{max}$[§] (h) | 1.75 (38) | 1.78 (37) | | |
| $T_{½}$[§] (h) | 9.58 (35) | 9.42 (38) | | |

[*] Q-IRBESARTAN 300 mg tablets

† Avapro® (sanofi-aventis Canada Inc.) 300 mg tablets purchased in Canada.
§ Expressed as the arithmetic mean (CV%)
+ Based on least square estimates.

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

**IDNT:**

The Irbesartan Diabetic Nephropathy Trial (IDNT) was a multicenter, randomized, controlled, double-blind, morbidity and mortality trial comparing irbesartan, amlodipine and placebo. In 1715 hypertensive patients with type 2 diabetes (proteinuria ≥900 mg/day and serum creatinine 1.0 - 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 < 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 antagonists 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 (SBP) 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

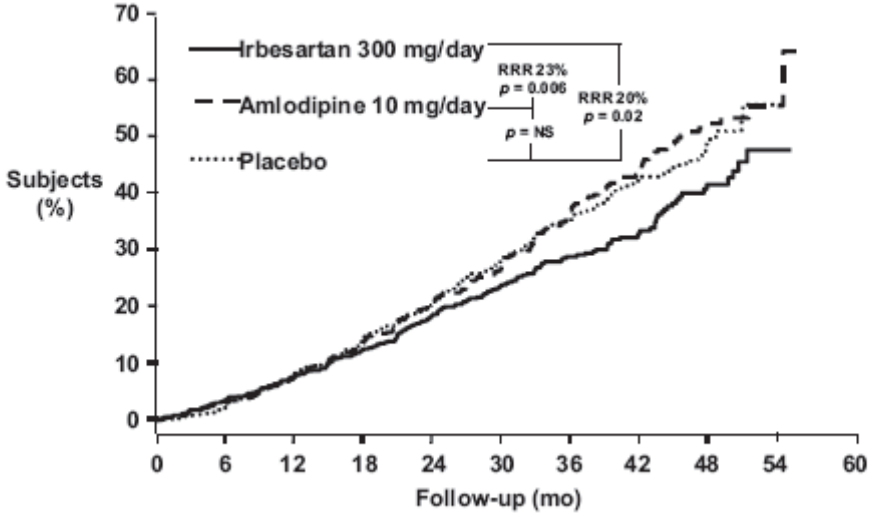



**Table 1**
**Primary Composite Endpoint Comparison (IDNT)**

| 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 (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 end stage renal disease 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 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 by 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 appeared 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 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; 30-300 mg/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 - 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 the long-term effects (2 years) of irbesartan on the progression to clinical (overt) proteinuria (urinary albumin excretion rate [AER] > 200 mcg/min [>300 mg/day] and an increase in AER of $\geq$ 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

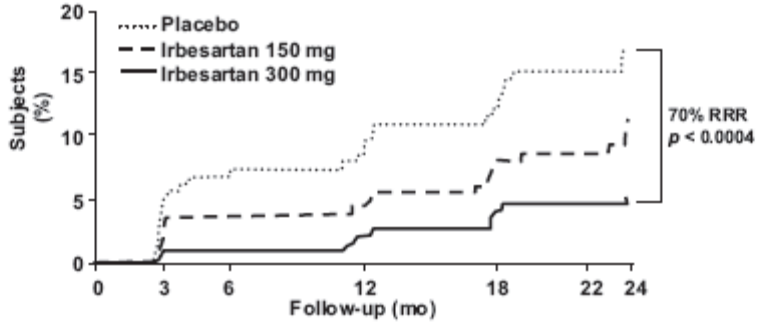
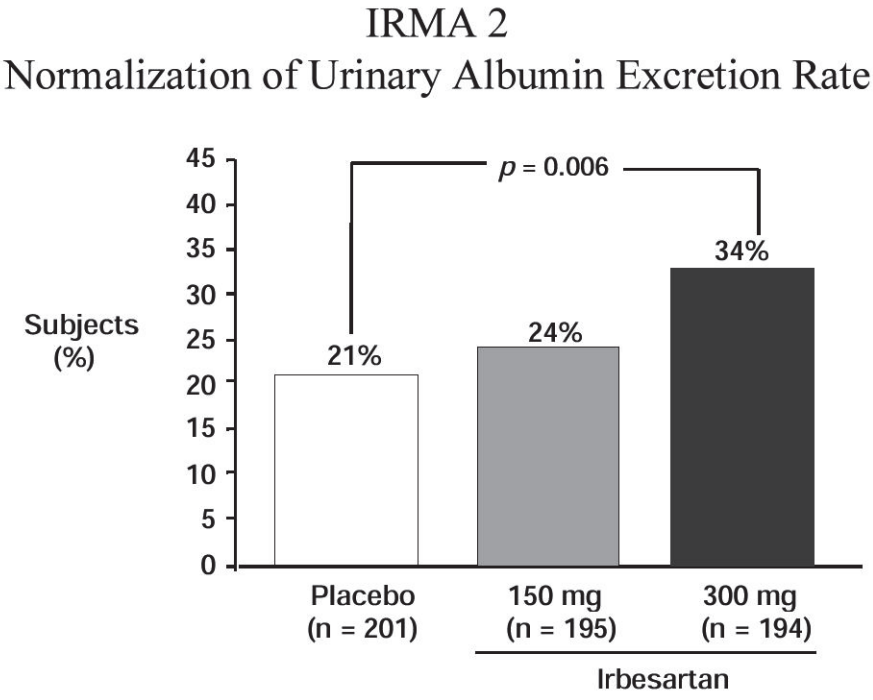


**Table 2**
**Time to occurrence of Overt Proteinuria**
**(Irbesartan 300 mg vs. Placebo Comparison) (IRMA 2)**

| 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

Q-IRBESARTAN (irbesartan) is indicated for the treatment of:

- essential hypertension. Q-IRBESARTAN may be used alone or concomitantly with thiazide diuretics.

- hypertensive patients with type 2 diabetes mellitus and renal disease to reduce the rate of progression of nephropathy as measured by the reduction of microalbuminuria, and the occurrence of doubling of serum creatinine. (See Clinical Trials).

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

## CONTRAINDICATIONS

Q-IRBESARTAN (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/1.73m2) (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 Q-IRBESARTAN tablets)
- Pregnant women (see WARNINGS, Special Populations, Pregnant Women)
- Nursing women (see WARNINGS, Special Populations, Nursing Women).

## WARNINGS

Serious Warnings and Precautions

When used in pregnancy, angiotensin receptor ($AT_1$) blockers (ARB) can cause injury or even death of the developing fetus. When pregnancy is detected, Q-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, Q-IRBESARTAN (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 ARB 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

**Dual Blockade of the Renin-Angiotensin System (RAS):**

There is evidence that co-administration of angiotensin receptor antagonists (ARBs), such as Q-IRBESARTAN, or of angiotensin converting enzyme (ACE) inhibitors with aliskiren increases the risk of hypotension, syncope, stroke, hyperkalemia and deterioration of renal function, including renal failure, in patients with diabetes mellitus (type 1 or type 2) and/or moderate to severe renal impairment (GFR < 60 ml/min/1.73m$^2$). Therefore, the use of Q-IRBESARTAN in combination with aliskiren-containing drugs is contraindicated in these patients (see CONTRAINDICATIONS).

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

Further, co-administration of ARBs, including Q-IRBESARTAN, with other agents blocking the RAS, such as ACE inhibitors or aliskiren-containing drugs, is generally not recommended in other patients, since such treatment has been associated with an increased incidence of severe hypotension, renal failure, and hyperkalemia.

**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.

The use of ARBs including Q-IRBESARTAN or 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 Q-IRBESARTAN in combination with an ACEI is contraindicated in patients with diabetic nephropathy due to risk of hyperkalemia, hypotension and renal impairment. (See CONTRAINDICATIONS and DRUG INTERACTIONS, Dual Blockade of the Renin-Angiotensin-System (RAS) with ARBs, ACE inhibitors, or aliskiren-containing drugs).

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.

Pediatrics (<18 years of age)

The safety and efficacy of Q-IRBESARTAN have not been established in children < 18 years of age. Therefore, Q-IRBESARTAN 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.

**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

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.

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 Q-IRBESARTAN. The possibility of symptomatic hypotension with the use of Q-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 Q-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 blockers (ARBs), 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 - 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, ACE inhibitors or aliskiren-containing drugs is contraindicated in patients with diabetes and/or 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. See CONTRAINDICATIONS and PRECAUTIONS, Dual Blockade of the Renin-Angiotensin-System (RAS).

The use of Q-IRBESARTAN in combination with an ACE inhibitor is contraindicated in patients with diabetic nephropathy and is generally not recommended in other patients since such treatment has been associated with an increased incidence of hyperkalemia, severe hypotension and renal failure.

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

## ADVERSE REACTIONS

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

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

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

Adverse events 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 | 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 |

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

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

Body as a whole: fever;

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

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

Endocrine: gout, libido change, sexual dysfunction;

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

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 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 of discontinuations due to orthostatic symptoms for irbesartan versus placebo were: dizziness 0.3% vs 0.5%; orthostatic dizziness 0.2% vs 0.0%; and orthostatic hypotension, 0.0% vs 0.0%.

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

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

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 irbesartan alone versus 0.9% on placebo.

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

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

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

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

## SYMPTOMS AND TREATMENT OF OVERDOSAGE

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

Few cases of overdosage with 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 irbesartan. 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.

Irbesartan is not removed by hemodialysis.

## 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 Q-IRBESARTAN (irbesartan) may need to be adjusted.

Q-IRBESARTAN may be administered with or without food.

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

**Essential Hypertension with Type 2 Diabetic Renal Disease**
The recommended initial dose of Q-IRBESARTAN is 150 mg once daily. In patients whose BP is not adequately controlled, the daily dose may be increased to 300 mg once daily, the preferred maintenance dose.

***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, Q-IRBESARTAN therapy should be initiated with caution, since these patients may be volume-depleted and thus more likely to experience hypotension following initiation of additional antihypertensive therapy. Whenever possible, all diuretics should be discontinued 2 to 3 days prior to the administration of Q-IRBESARTAN 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, Q-IRBESARTAN should be administered with caution and the blood pressure monitored closely. The recommended starting dose of Q-IRBESARTAN 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**

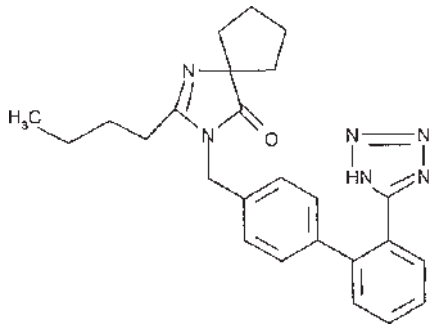
Trade Name: Q-IRBESARTAN

Proper Name: irbesartan

Chemical Names: i) 2-butyl-3-[[2[1]-( 1*H*-tetrazol-5-yl)[1,1[1]-biphenyl]-4-yl]methyl] -1,3 – diazaspiro[4,4]non-1-en-4-one.
ii) 2-buty1-31p-(o-1H-tetrazol-5-ylphenyl)benzy1]-1,3-diazaspiro [4,4]non-1- en-4-one
iii) 2-n-buty1-4-spirocyclopentane-1-[(2[1]-(tetrazole-5-yl)biphenyl-4-yl)methyl]-2-imidazolin-5-one

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

Structural Formula:




Molecular Weight: 428.53 g/mol

Description: Irbesartan is a white to off-white crystalline powder. It is a nonpolar compound with a partition coefficient (octanol/water) of 10.1 at a pH of 7.4. Irbesartan is slightly soluble in alcohol and methylene chloride and practically insoluble in water.

II. **COMPOSITION**

In addition to the active ingredient, irbesartan, each tablet contains colloidal anhydrous silica, croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone, hydroxypropyl methylcellulose, polyethylene glycol, polysorbate and titanium dioxide.

III. **STORAGE**

Q-IRBESARTAN should be stored between 15°C and 30°C.

## AVAILABILITY OF DOSAGE FORMS

Q-IRBESARTAN (irbesartan) 75 mg tablets are white, oblong, biconvex film-coated tablets, engraved “IS 75” on one side and "M" on the other side.

Q-IRBESARTAN (irbesartan) 150 mg tablets are white, oblong, biconvex film-coated tablets, engraved “IS 150” on one side and "M" on the other side.

Q-IRBESARTAN (irbesartan) 300 mg tablets are white, oblong, biconvex film-coated tablets, engraved “IS 300” on one side and "M" on the other side.

Q-IRBESARTAN 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)<br>F (5) | PO | > 2000 |
| Rat | M (5)<br>F (5) | PO | > 2000 |
| Mouse | M (5)<br>F (5) | IV | > 50 |
| Rat | M (5)<br>F (5) | IV | > 50 |
| Mouse | M (5)<br>F (5) | IP | 200 - 2000 |
| Rat | M (5)<br>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.

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## Subacute and Chronic Toxicity

| Species/ Strain | Sex (N/Dose) | Dose (mg/kg/day) | Route | Time | Effects |
|---|---|---|---|---|---|
| **SUBACUTE TOXICITY** | | | | | |
| Rat | M (10)<br>F (10) | 0, 30, 70, 150 | po | 4 weeks | • Irbesartan only induced slight decrease in hemoglobin levels (at 150 mg/kg) and slight increase in glucose (≥ 30 mg/kg), urea (≥ 70 mg/kg), creatinine and $K^+$ levels (at 150 mg/kg), and slight decrease in $Na^+$ and $Cl^-$ urinary concentrations and excretions (≥ 30 mg/kg). |
| Rat | M (10)<br>F (10) | 0, 0.8, 2, 5 | iv | 16 days | • Very slight increase in $Na^+$ and $Cl^-$ plasma levels (≥ 0.8 mg/kg/day in males)<br>• 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)<br>F (3) | 0, 10, 30, 90 | po | 4 weeks | • Dose-related hyperplasia of the juxtaglomerular apparatus (from 30 mg/kg/day upwards). |
| Monkey | M (3)<br>F (3) | 0, 250, 500, 1000 | po | 4 weeks | • ≥ 250 mg/kg/day: changes in the kidney (hyperplasia of the juxtaglomerular apparatus), heart (myocardial fibrosis) and erythrocytes parameters (slight anemia).<br>• At 500 mg/kg/day: increased platelet count, fibrogen and neutrophil levels and at 1000 mg/kg/day, health deterioration was also noted.<br>• 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)<br>F (3) | 0, 0.8, 2, 5 | iv | 2 weeks | • Irbesartan induced only a slight hyperplasia of the juxtaglomerular apparatus in 2/3 females receiving 5 mg/kg/day.<br>• 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]<br>M (10) - F (10) [reversibility study for control and high dose groups]<br>M (5) - F (5) [toxicokinetics study] | 0, 10, 30, 90 | po | 26 weeks | • Slight reduction of the bodyweight gain in males at 90 mg/kg/day (- 6 to - 8%).<br>• Other changes can be considered to be of pharmacological origin for some of them and have no clear toxicological significance for all of them.<br>• The no-observed adverse effect dose was considered to be 30 mg/kg/day. |
| **CHRONIC TOXICITY** | | | | | |
| Rat | M (20) - F (20) [main study]<br>M (10) - F (10) | 0, 0, 250, 500, 1000 | po | 26 weeks | • Slight reduction of bodyweight gain without any dose-relationship-reversible.<br>• Changes in hematology and blood biochemistry parameters demonstrating an effect on red blood cells and on the renal function, likely associated with the |

| Species/ Strain | Sex (N/Dose) | Dose (mg/kg/day) | Route | Time | Effects |
|---|---|---|---|---|---|
| | [reversibility study for control and high dose groups]<br>M (5) - F (5)<br>[toxicokinetics study] | | | | pharmacological activity of irbesartan and reversible.<br>• 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]<br>M (3) - F (3) [reversibility study for control and high dose groups)] | 0, 10, 30, 90 | po | 6 months | • Dose-related hyperplasia of juxtaglomerular apparatus in all treated animals partially reversible at the end of treatment.<br>• 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)<br>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:<br>• 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.<br>• Dose-related hyperplasia / hypertrophy of the juxtaglomerular apparatus in all treated animals with degenerative kidney changes at 500 mg/kg/day.<br>• 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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# PART III: CONSUMER INFORMATION

**Pr Q-IRBESARTAN**
Irbesartan Tablets
75 mg, 150 mg and 300 mg
USP

This leaflet is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Q-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:**

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

**What it does:**
Q-IRBESARTAN 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 Q-IRBESARTAN regularly even if you feel fine.

**When it should not be used:**
Do not take Q-IRBESARTAN if you:

- Are allergic to irbesartan or to any non-medicinal ingredient in the formulation.
- Have experienced an allergic reaction (angioedema) with swelling of the hands, feet or ankles, face, lips, tongue, throat, or sudden difficulty breathing or swallowing, to any ARB.. Be sure to tell your 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 Q-IRBESARTAN during pregnancy can cause injury and even death to your baby.
- Are breastfeeding. It is possible that Q-IRBESARTAN 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 Q-IRBESARTAN.

Q-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:**
Colloidal anhydrous silica, croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone, hydroxypropyl methylcellulose, polyethylene glycol, polysorbate, and titanium dioxide.

**What dosage forms it comes in:**
Q-IRBESARTAN (irbesartan) 75 mg tablets are white, oblong, biconvex film-coated tablets, engraved "IS 75" on one side and "M" on the other side.

Q-IRBESARTAN (irbesartan) 150 mg tablets are white, oblong, biconvex film-coated tablets, engraved "IS 150" on one side and "M" on the other side.

Q-IRBESARTAN (irbesartan) 300 mg tablets are white, oblong, biconvex film-coated tablets, engraved "IS 300" on one side and "M" on the other side.

Q-IRBESARTAN 75, 150 and 300 mg tablets are available in bottles of 90 tablets.

## WARNINGS AND PRECAUTIONS

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

BEFORE you use Q-IRBESARTAN 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.
- 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 Q-IRBESARTAN is not recommended.
- Are taking an angiotensin converting enzyme (ACE) inhibitor. The combination with Q-IRBESARTAN 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 Q-IRBESARTAN. 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 Q-IRBESARTAN.

## 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 Q-IRBESARTAN:

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

## PROPER USE OF THIS MEDICATION

Take Q-IRBESARTAN 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.

**Q-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:**

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

**If any of these affects you severely, tell your doctor, nurse or pharmacist.**
Q-IRBESARTAN 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 emergency medical attention** |
| | | **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 Q-IRBESARTAN, contact your doctor or pharmacist.*

## HOW TO STORE IT

Q-IRBESARTAN should be stored between 15°C and 30°C.

**Keep this medication out of the reach and sight of children.**

**Reporting Side Effects**

You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

**3 ways to report:**

- Online at MedEffect (http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php);
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 0701E
    Ottawa, ON
    K1A 0K9

Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect (http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php).

*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.*

## MORE INFORMATION

This document can be found at:
www.qdpharmaceuticals.ca.

The full Product Monograph prepared for health professionals can be obtained by contacting the sponsor, QD Pharmaceuticals ULC at: 1-800-661-3429.

This leaflet was prepared by QD Pharmaceuticals ULC
Etobicoke, Ontario M8Z 2S6

Revised on: June 3, 2015