PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrAVALIDE®

Irbesartan and hydrochlorothiazide Tablets

Read this carefully before you start taking **AVALIDE** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **AVALIDE**.

Serious Warnings and Precautions

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

What is AVALIDE used for?

- AVALIDE is used in adults to lower high blood pressure.

How does AVALIDE work?

AVALIDE is a combination of 2 drugs, irbesartan and hydrochlorothiazide:

- Irbesartan is an angiotensin receptor blocker (ARB). It lowers blood pressure.
- Hydrochlorothiazide is a diuretic or "water pill" that increases urination. This also helps to lower blood pressure.

This medicine does not cure high blood pressure. It helps to control it. Therefore, it is important to continue taking AVALIDE regularly even if you feel fine.

What are the ingredients in AVALIDE?

Medicinal ingredients: Irbesartan and hydrochlorothiazide

Non-medicinal ingredients: Carnauba wax, croscarmellose sodium, ferric oxide red, ferric oxide yellow, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, silicon dioxide, titanium dioxide

AVALIDE comes in the following dosage forms:

Tablets, in two strengths:

irbesartan/hydrochlorothiazide: 150 mg /12.5 mg
irbesartan/hydrochlorothiazide: 300 mg /12.5 mg

Do not use AVALIDE if you:

- are allergic to irbesartan or hydrochlorothiazide or to any non-medicinal ingredients in the formulation.

highest dose and adrenal pheocytochroma in one rat study but not in another. Current evidence is inadequate to draw a clear conclusion for a carcinogenic effect of hydrochlorothiazide in animals.

The mutagenic potential was assessed in a series of *in vitro* and *in vivo* test systems. While some positive results were obtained *in vitro*, all *in vivo* studies provided negative results. Hydrochlorothiazide enhanced the UVA-induced formation of pyrimidine dimers *in vitro* and in the skin of mice following oral treatment. It is therefore concluded that although there is no relevant mutagenic potential *in vivo*, hydrochlorothiazide could enhance the genotoxic effects of UVA light. This mechanism of photosensitization could be associated with a higher risk for non-melanoma skin cancer.

Reproduction and Teratology

Irbesartan

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.

Irbesartan/hydrochlorothiazide

In a Segment II teratology study carried out in rats, a dose of the combination irbesartan/hydrochlorothiazide up to 150/150mg/day/kg did not show any teratogenic potential. There was decreased foetal body weight in the litters of dams given 150/150 mg/kg/day.

Carcinogenicity and Mutagenicity

Irbesartan

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).

Irbesartan/hydrochlorothiazide

No carcinogenicity studies have been conducted with the irbesartan/hydrochlorothiazide combination.

Irbesartan/hydrochlorothiazide was not mutagenic in standard *in vitro* tests (Ames microbial test and Chinese hamster mammalian-cell forward gene-mutation assay).

Irbesartan/hydrochlorothiazide was negative in tests for induction of chromosomal aberrations (*in vitro* - human lymphocyte assay; *in vivo* - mouse micronucleus study).

Hydrochlorothiazide

According to the experimental data available, hydrochlorothiazide revealed inconsistent evidence of carcinogenic activity in rats and mice, with conflicting evidence of hepatic adenoma in male mice at the

Species / Strain	Sex (N/Dose)	Dose (mg/kg/day)	Route	Time	Effects
Monkey	M (20) F (20)	0*/0**, 10/10, 90/90 0/90, 90/0	PO	6 months	• Exposure to HCTZ was approximately 60% greater when administered in combination with irbesartan than when administered alone. • Body weights of males in the high dose combination group (90/90) were mildly decreased. • Mean hemoglobin, hematocrit and erythrocyte values were mildly to moderately decreased at the high dose combination (90/90). • Moderate increases in BUN; mild to moderate increases in creatinine values; mean sodium, potassium, and chloride values were mildly to moderately decreased. • Mild to moderate juxtaglomerular apparatus, hypertrophy/hyperplasia [all treated with irbesartan either alone or in combination]

* Irbesartan

** Hydrochlorothiazide

Subacute and Chronic Toxicity (Cont'd)

Irbesartan/hydrochlorothiazide

Table 12 : Subacute and Chronic Toxicity Irbesartan/hydrochlorothiazide

Species / Strain	Sex (N/Dose)	Dose (mg/kg/day)	Route	Time	Effects
Rat	M (20) F (20)	0*/0**, 10/10, 90/90 90/0, 0/90	PO	6 months	• Exposure to HCTZ was greater when administered in combination with irbesartan, than when given alone. • Body weight gains in the high dose group (90/90 mg/kg) were slightly decreased in females and moderately decreased in males. • Hemoglobin, hematocrit, and erythrocyte counts were slightly decreased in females given the high dose combination (90/90). • In the high dose combination, serum urea nitrogen and alkaline phosphatase (males) were slightly elevated; serum potassium and calcium (Week 12) were slightly decreased in males; serum cholesterol and triglycerides were slightly to moderately decreased. • In the low dose combination, serum cholesterol, triglycerides and potassium were slightly decreased. • Slight increases in urine pH; urine protein concentrations markedly lower in high dose combination group. • Decreased heart weights in males and females at 10/10, 99/90 and 90/0. • Decreased liver weights in males. • Juxtaglomerular-cell hypertrophy/hyperplasia. • Increased urine output. • Increased kidney weights in females. • At necropsy, discoloration of the glandular stomach correlated with focal coagulative necrosis or ulceration of the mucosa were noted in all treated groups with an incidence slightly greater in rats given the high-dose combination.

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 increase 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.

Species / Strain	Sex (N/Dose)	Dose (mg/kg/day)	Route	Time	Effects
Monkey	M (5) F (5)	0, 20, 100, 500	PO	52 weeks	• Irbesartan was well tolerated and most of the changes observed were considered to be due to the pharmacological activity of the drug: • Dose-related decrease in blood pressure at doses ≥ 20 mg/kg/day associated with necrosis of the tip of the tail likely due to a decrease in blood flow at 500 mg/kg/day. • Dose-related hyperplasia / hypertrophy of the juxtaglomerular apparatus in all treated animals with degenerative kidney changes at 500 mg/kg/day. • Slight decrease in body weight gain and erythrocyte parameters at doses ≥ 100 mg/kg/day.

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, 250, 500, 1000	PO	26 weeks	• Slight reduction of body weight gain without any dose-relationship reversible. • Changes in hematology and blood biochemistry parameters demonstrating an effect on red blood cells and on the renal function, likely associated with the pharmacological activity of irbesartan and reversible. • Hyperplasia/hypertrophy of the juxtaglomerular apparatus in males (≥250 mg/kg/day) and in females (≥ 500 mg/kg/day) partially reversible.
Monkey	M (5) - F (5) [main study] M (3) - F (3) [reversibility study for control and high dose groups)]	0, 10, 30, 90	PO	6 months	• Dose-related hyperplasia of juxtaglomerular apparatus in all treated animals partially reversible at the end of treatment. • Slight dose-related decrease in weight gain from the 30 mg/kg/day dose level upwards and slight anemia from 10 mg/kg/day upwards, both reversible on cessation of treatment.

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, 10, 30, 90	PO	26 weeks	• Slight reduction of the body weight 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					

Subacute and Chronic Toxicity

Irbesartan

Table 11 : Subacute and Chronic Toxicity Irbesartan

Species / Strain	Sex (N/Dose)	Dose (mg/kg/day)	Route	Time	Effects
SUBACUTE TOXICITY					
Rat	M (10) F (10)	0, 30, 70, 150	PO	4 weeks	• Irbesartan only induced slight decrease in hemoglobin levels (at 150 mg/kg) and slight increase in glucose (≥30 mg/kg), urea (≥ 70 mg/kg), creatinine and K+ levels (at 150 mg/kg), and slight decrease in Na+ and Cl^- urinary concentrations and excretions (≥30 mg/kg).
Rat	M (10) F (10)	0, 0.8, 2, 5	IV	16 days	• Very slight increase in Na+ and Cl^- plasma levels (≥0.8 mg/kg/day in males) • Very slight increase in K+ plasma levels, in ASAT and slight decrease in kidney relative weight at 5 mg/kg/day in males.
Monkey	M (3) F (3)	0, 10, 30, 90	PO	4 weeks	• Dose-related hyperplasia of the juxtaglomerular apparatus (from 30 mg/kg/day upwards).
Monkey	M (3) F (3)	0, 250, 500, 1000	PO	4 weeks	• ≥250 mg/kg/day: changes in the kidney (hyperplasia of the juxtaglomerular apparatus), heart (myocardial fibrosis) and erythrocytes parameters (slight anemia). • At 500 mg/kg/day: increased platelet count, fibrogen and neutrophil levels and at 1000 mg/kg/day, health deterioration were also noted. • One animal receiving 250 mg/kg/day presented the most severe heart lesions and marked electrocardiographic modifications on D1 and D29 However, pre-existing lesions could not be excluded.
Monkey	M (3) F (3)	0, 0.8, 2, 5	IV	2 weeks	• Irbesartan induced only a slight hyperplasia of the juxtaglomerular apparatus in 2/3 females receiving 5 mg/kg/day. • One high-dose animal presented a marked heart hypertrophy with marked ECG changes on D1 and D10 suggesting that it was a preexisting lesion.

Irbesartan - hydrochlorothiazide

Table 10 : Acute Toxicity for Irbesartan – hydrochlorothiazide

Species	Sex (N)	Route	LD50 (mg/kg)		
			Irbesartan	HCTZ	Irbesartan/ HCTZ
Mouse	M (5) F (5)	PO	> 2000	> 4000	> 2000/4000
Rat	M (5)	PO	> 3000	> 500	> 3000/500

No mortality occurred following administration of the irbesartan/hydrochlorothiazide combination up to and including the highest dose of irbesartan:hydrochlorothiazide (2000/4000 mg/kg in mice or 3000/500 mg/kg in rats) No treatment-related clinical signs and body weight changes were observed. At necropsy, performed at the end of the 14-day observation period, pathologic examinations did not reveal any treatment-induced changes.

▪ Proportion of subjects whose BP was controlled (simultaneous SeDBP <90 mmHg and SeSBP <140 mmHg)	34.6%	19.2%	< 0.0001
▪ Mean changes from baseline in trough			
SeDBP	-24.0	-19.3	< 0.0001
SeSBP	-30.8	-21.1	< 0.0001

16 NON-CLINICAL TOXICOLOGY

Acute Toxicity

Irbesartan

Table 9 : Acute Toxicity for Irbesartan

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

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

Table 7 : Summary of patient demographics for clinical trial with AVALIDE in subjects with severe hypertension

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age in years (Range)	Gender
CV131176	Multicenter, randomized, double-blind, active controlled , 7-week, parallel group study	Oral administration of irbesartan /HCTZ 150/12.5 mg or irbesartan 150 mg increased at 1 week to irbesartan /HCTZ 300/25 mg or to irbesartan 300 mg.	697 Irbesartan: 229 Irbesartan/HCTZ: 468	52.5 (23.0 - 83.0)	Male 57.5% Female 42.5%

14.2 Study Results

The study results are summarized in table 7.

After 5 weeks of therapy, the mean SeDBP was 4.7 mmHg lower (p≤0.0001) and the mean SeSBP was 9.7 mmHg lower (p<0.0001) in the group treated with AVALIDE than in the group treated with irbesartan. Mean reductions from baseline for SeDBP and SeSBP at trough were 24.0 mmHg and 30.8 mmHg for AVALIDE-treated patients and 19.3 mmHg and 21.1 mmHg for irbesartan-treated patients, respectively. A greater proportion of patients on AVALIDE achieved a diastolic blood pressure <90 mmHg (47.2% for AVALIDE, 33.2% for irbesartan; p=0.0005) and a greater proportion of the patients on AVALIDE achieved simultaneous control of SeSBP <140 mmHg and SeDBP <90 mmHg (34.6% versus 19.2%; p<0.0001). Similar results were seen when the patients were grouped according to gender, race or age (<65 years, ≥65 years). The proportions of subjects with controlled SeDBP, as well as with simultaneous SeDBP/SeSBP control, at each week of the double-blind period were consistently larger and statistically significantly greater for AVALIDE-treated patients than for irbesartan-treated patients.

Table 8 : Results at week 5 of study with AVALIDE in subjects with severe hypertension

Endpoints	irbesartan /HCTZ 150/12.5 mg force titrated to 300/25 mg	Irbesartan 150 mg force titrated to 300 mg	p value
Primary Endpoint: Proportion of subjects in each treatment group whose SeDBP was controlled (SeDBP < 90 mmHg).	47.2%	33.2%	0.0005
Other Endpoints:			

hydrochlorothiazide (6.25 - 25 mg). One factorial study compared all combinations of irbesartan (37.5, 100 and 300 mg or placebo) and hydrochlorothiazide (6.25, 12.5, and 25 mg or placebo). The irbesartan-hydrochlorothiazide combinations of 75/12.5 mg and 150/12.5 mg were compared to their individual components and placebo in a separate study. A third study investigated the ambulatory blood pressure responses to irbesartan-hydrochlorothiazide (75/12.5 mg and 150/12.5 mg) and placebo after 8 weeks of dosing. Another trial investigated the effects of the addition of irbesartan (75 mg) in patients not controlled on hydrochlorothiazide (25 mg) alone.

In controlled trials, the addition of irbesartan 150–300 mg to hydrochlorothiazide doses of 6.25, 12.5 or 25 mg produced further dose-related reductions in blood pressure of 8–10/3–6 mmHg, comparable to those achieved with the same monotherapy dose of irbesartan. The addition of hydrochlorothiazide to irbesartan produced further dose related reductions in blood pressure at trough (24 hours post-dose) of 5–6/2–3 mmHg (12.5 mg) and 7–11/4–5 mmHg (25 mg), also comparable to effects achieved with hydrochlorothiazide alone. Once-daily dosing with 150 mg irbesartan and 12.5 mg hydrochlorothiazide, 300 mg irbesartan and 12.5 mg hydrochlorothiazide, or 300 mg irbesartan and 25 mg hydrochlorothiazide produced mean placebo-adjusted blood pressure reductions at trough (24 hours post-dosing) of about 13–15/7–9, 14/9–12, and 19–21/11–12 mmHg, respectively. Peak effects occurred at 3–6 hours, with the trough-to peak ratios >65%.

In another study, irbesartan (75–150 mg) or placebo was added on a background of 25 mg hydrochlorothiazide in patients not adequately controlled (SeDBP 93–120 mmHg) on hydrochlorothiazide (25 mg) alone. The addition of irbesartan (75–150 mg) gave an additive effect (systolic/diastolic) at trough (24 hours post-dosing) of 11/7 mmHg.

There was no difference in response for men and women or in patients over or under 65 years of age. Black patients had a larger response to hydrochlorothiazide than non-black patients and a smaller response to irbesartan. The overall response to the combination was similar for black and non-black patients.

Severe Hypertension

The efficacy of AVALIDE as initial therapy for severe hypertension (defined as a mean seated diastolic blood pressure (SeDBP) ≥110 mmHg confirmed on 2 separate occasions off all antihypertensive therapy) was studied in a 7-week, double-blind, randomized, multicenter study. Patients were randomized to either irbesartan and hydrochlorothiazide (150/12.5 mg) or to irbesartan (150 mg) once daily and followed for blood pressure response. These initial study regimens were increased at 1 week to irbesartan 300 mg/HCTZ 25 mg or to irbesartan 300 mg, respectively. The primary endpoint was a comparison at 5 weeks of the proportion of patients who achieved through SeDBP <90 mmHg. An additional supportive endpoint compared the proportion of subjects in each treatment group whose blood pressure was controlled, defined as simultaneous SeDBP <90 mmHg and SeSBP <140 mmHg.

Study demographics and trial design

The study randomized 697 patients, in a 2:1 ratio to receive either combination therapy (irbesartan plus HCTZ, N=468) or irbesartan monotherapy (N=229), and included 296 (42%) females, 101 (14%) blacks, and 92 (13%) ≥65 years of age. The mean age was 52 years. The mean blood pressure at baseline for the total population was 172/113 mmHg.