

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Application Number: NDA 20758/S16**

**APPROVAL LETTER**



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration  
Rockville MD 20857

NDA 20-757/S-015  
NDA 20-758/S-016

MAY 9 2000

Bristol-Myers Squibb  
Attention: Mary Ellen Norvitch, Ph.D.  
P.O. Box 4000  
Princeton, New Jersey 08543-4000

Dear Dr. Norvitch:

Please refer to your supplemental new drug applications dated February 23, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Avapro (irbesartan) Tablets, 75, 150, 300 mg and Avalide (irbesartan/hydrochlorothiazide) Tablets, 75/12.5, 150/12.5, 300/12.5 mg.

We note that these supplements were submitted as a "Special Supplement – Changes Being Effected" under 21 CFR 314.70(c).

These supplemental new drug applications provide for final printed labeling revised as follows:

1. Under **ADVERSE REACTIONS**, the *Post-Marketing Experience* subsection has been changed to add hyperkalemia as follows:

The following adverse reactions have been reported in post-marketing experience: Rare cases of urticaria and angioedema (involving swelling of the face, lips, pharynx, and/or tongue); hyperkalemia.

2. The address information has been changed to reflect a new logo.

We have completed the review of these supplemental applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the final printed labeling included in your February 23, 2000 submissions. Accordingly, these supplemental applications are approved effective on the date of this letter.

NDA 20-757/S-015

NDA 20-758S-016

Page 2

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

Mr. Edward Fromm  
Regulatory Health Project  
(301) 594-5313

Sincerely,

*RS/* *5/9/00*  
Raymond J. Lipicky, M.D.  
Director  
Division of Cardio-Renal Drug Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: NDA 20758/S16**

**FINAL PRINTED LABELING**

APPROVED

1030329A1  
**AVALIDE®**  
(irbesartan-hydrochlorothiazide)  
Tablets



# AVALIDE®

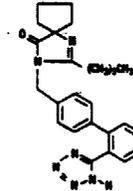
## (irbesartan-hydrochlorothiazide) Tablets

### USE IN PREGNANCY

When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, AVALIDE should be discontinued as soon as possible. (See WARNINGS: Fetal/Neonatal Morbidity and Mortality.)

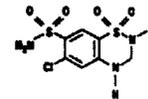
### DESCRIPTION

AVALIDE® (irbesartan-hydrochlorothiazide) Tablets is a combination of an angiotensin II receptor antagonist (AT<sub>1</sub> subtype), irbesartan, and a thiazide diuretic, hydrochlorothiazide (HCTZ). Irbesartan is a non-peptide compound, chemically described as a 2-butyl-3-[[2'-(1H-tetrazol-5-yl) [1,1'-biphenyl]-4-yl]methyl]-1,5-diazaspiro [4,4] non-1-en-4-one. Its empirical formula is C<sub>27</sub>H<sub>30</sub>N<sub>4</sub>O, and its structural formula is:



Irbesartan is a white to off-white crystalline powder with a molecular weight of 428.5. It is a nonpolar compound with a partition coefficient (octanol/water) of 10.1 at pH of 7.4. Irbesartan is slightly soluble in alcohol and methylene chloride and practically insoluble in water.

Hydrochlorothiazide is 6-chloro-3,4-dihydro-2H-1,2,4-benzothiazine-7-sulfonamide 1,1-dioxide. Its empirical formula is C<sub>7</sub>H<sub>8</sub>ClN<sub>2</sub>O<sub>4</sub>S<sub>2</sub> and its structural formula is:



Hydrochlorothiazide is a white, or practically white, crystalline powder with a molecular weight of 297.7. Hydrochlorothiazide is slightly soluble in water and freely soluble in sodium hydroxide solution.

AVALIDE is available for oral administration in tablets containing 150 mg of irbesartan combined with 12.5 mg of hydrochlorothiazide. Inactive ingredients include: lactose monohydrate, microcrystalline cellulose, pregelatinized starch, croscarmellose sodium, ferric oxide red, ferric oxide yellow, silicon dioxide, and magnesium stearate.

### CLINICAL PHARMACOLOGY

#### Mechanism Of Action

##### Irbesartan

Angiotensin II is a potent vasoconstrictor formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzyme (ACE, kininase II). Angiotensin II is the principal pressor agent of the renin-angiotensin system (RAS) and also stimulates aldosterone synthesis and secretion by adrenal cortex, cardiac contraction, renal reabsorption of sodium, activity of the sympathetic nervous system, and smooth muscle cell growth. Irbesartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively binding to the AT<sub>1</sub> angiotensin II receptor. There is also an AT<sub>2</sub> receptor in many tissues, but it is not involved in cardiovascular homeostasis.

Irbesartan is a specific competitive antagonist of AT<sub>1</sub> receptors with a much greater affinity (more than 8500-fold) for the AT<sub>1</sub> receptor than for the AT<sub>2</sub> receptor, and no agonist activity.

Blockade of the AT<sub>1</sub> receptor removes the negative feedback of angiotensin II on renin secretion, but the resulting increased plasma renin activity and circulating angiotensin II do not overcome the effects of irbesartan on blood pressure.

Irbesartan does not inhibit ACE or renin or affect other hormone receptors or ion channels known to be involved in the cardiovascular regulation of blood pressure and sodium homeostasis. Because irbesartan does not inhibit ACE, it does not affect the response to bradykinin; whether this has clinical relevance is not known.

##### Hydrochlorothiazide

Hydrochlorothiazide is a thiazide diuretic. Thiazides affect the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equivalent amounts. Indirectly, the diuretic action of hydrochlorothiazide reduces plasma volume, with consequent increases in plasma renin activity, increases in aldosterone secretion, increases in urinary potassium loss, and decreases in serum potassium. The renin-aldosterone link is mediated by angiotensin II, so coadministration of an angiotensin II receptor antagonist tends to reverse the potassium loss associated with these diuretics.

The mechanism of the antihypertensive effect of thiazides is not fully understood.

##### Pharmacokinetics

##### Irbesartan

Irbesartan is an orally active agent that does not require biotransformation into an active form. The oral absorption of irbesartan is rapid and complete with an average absolute bioavailability of 60-80%. Following oral administration of irbesartan, peak plasma concentrations of irbesartan are attained at 1.5-2 hours after dosing. Food does not affect the bioavailability of irbesartan.

Irbesartan exhibits linear pharmacokinetics over the therapeutic dose range.

The terminal elimination half-life of irbesartan averaged 11-15 hours. Steady-state concentrations are achieved within 3 days. Limited accumulation of irbesartan (<20%) is observed in plasma upon repeated once-daily dosing.

##### Hydrochlorothiazide

When plasma levels have been followed for at least 24 hours, the plasma half-life has been observed to vary between 5.8 and 14.8 hours.

\*Registered trademark of Sanofi

## Metabolism and Elimination

### Irbesartan

Irbesartan is metabolized via glucuronide conjugation and oxidation. Following oral or intravenous administration of <sup>14</sup>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 conjugate (approximately 6%). The remaining oxidative metabolites do not add appreciably to irbesartan's pharmacologic activity.

Irbesartan and its metabolites are excreted by both biliary and renal routes. Following either oral or intravenous administration of <sup>14</sup>C-labeled irbesartan, about 20% of radioactivity is recovered in the urine and the remainder in the feces, as irbesartan or irbesartan glucuronide.

*In vitro* studies of irbesartan oxidation by cytochrome P450 isoenzymes indicated irbesartan was oxidized primarily by 2C9; metabolism by 3A4 was negligible. Irbesartan was neither metabolized by, nor did it substantially induce or inhibit, isoenzymes commonly associated with drug metabolism (1A1, 1A2, 2A6, 2B6, 2C6, 2E1). There was no induction or inhibition of 3A4.

### Hydrochlorothiazide

Hydrochlorothiazide is not metabolized but is eliminated rapidly by the kidney. At least 61 percent of the oral dose is eliminated unchanged within 24 hours.

### Distribution

#### Irbesartan

Irbesartan is 90% bound to serum proteins (primarily albumin and  $\alpha_1$ -acid glycoprotein) with negligible binding to cellular components of blood. The average volume of distribution is 53–83 liters. Total plasma and renal clearances are in the range of 157–176 and 3.0–3.5 mL/min, respectively. With repetitive dosing, irbesartan accumulates to no clinically relevant extent.

Studies in animals indicate that radiolabeled irbesartan weakly crosses the blood brain barrier and placenta. Irbesartan is excreted in the milk of lactating rats.

#### Hydrochlorothiazide

Hydrochlorothiazide crosses the placental but not the blood-brain barrier and is excreted in breast milk.

### Special Populations

**Pediatric:** Irbesartan pharmacokinetics have not been investigated in patients <18 years of age.

**Gender:** No gender related differences in pharmacokinetics were observed in healthy elderly (age 65–80 years) or in healthy young (age 18–40 years) subjects. In studies of hypertensive patients, there was no gender difference in half-life or accumulation, but somewhat higher plasma concentrations of irbesartan were observed in females (11–44%). No gender-related dosage adjustment is necessary.

**Geriatric:** In elderly subjects (age 65–80 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 (age 18–40 years). No dosage adjustment is necessary in the elderly.

**Race:** In healthy black subjects, irbesartan AUC values were approximately 25% greater than whites; there were no differences in  $C_{max}$  values.

**Renal Insufficiency:** The pharmacokinetics of irbesartan were not altered in patients with renal impairment or in patients on hemodialysis. Irbesartan is not removed by hemodialysis. No dosage adjustment is necessary in patients with mild to severe renal impairment unless a patient with renal impairment is also volume depleted. (See WARNINGS: Hypotension in Volume- or Salt-depleted Patients and DOSAGE AND ADMINISTRATION.)

**Hepatic Insufficiency:** The pharmacokinetics of irbesartan following repeated oral administration were not significantly affected in patients with mild to moderate cirrhosis of the liver. No dosage adjustment is necessary in patients with hepatic insufficiency.

**Drug Interactions:** (See PRECAUTIONS: Drug Interactions.)

### Pharmacodynamics

#### Irbesartan

In healthy subjects, single oral irbesartan doses of up to 300 mg produced dose-dependent inhibition of the pressor effect of angiotensin II infusions. Inhibition was complete (100%) 4 hours following oral doses of 150 mg or 300 mg and partial inhibition was sustained for 24 hours (60% and 40% at 300 mg and 150 mg, 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, but serum potassium levels are not significantly affected at recommended doses.

In hypertensive patients, chronic oral doses of irbesartan (up to 300 mg) had no effect on glomerular filtration rate, renal plasma flow or filtration fraction. In multiple dose studies in hypertensive patients, there were no clinically important effects on fasting triglycerides, total cholesterol, HDL-cholesterol, or fasting glucose concentrations. There was no effect on serum uric acid during chronic oral administration and no uricosuric effect.

#### Hydrochlorothiazide

After oral administration of hydrochlorothiazide, diuresis begins within 2 hours, peaks in about 4 hours and lasts about 6 to 12 hours.

### Clinical Studies

#### Irbesartan

The antihypertensive effects of irbesartan were examined in seven (7) major placebo-controlled 8–12 week trials in patients with baseline diastolic blood pressures of 95–110 mmHg. Doses of 1–600 mg were included in these trials in order to fully explore the dose-range of irbesartan. These studies allowed a comparison of once- or twice-daily regimens at 150 mg/day, comparisons of peak and trough effects, and comparisons of response by gender, age, and race. Two of the seven placebo-controlled trials identified above and two additional placebo-controlled studies examined the antihypertensive effects of irbesartan and hydrochlorothiazide in combination.

The seven (7) studies of irbesartan monotherapy included a total of 1915 patients randomized to irbesartan (1–900 mg) and 611 patients randomized to placebo. Once-daily doses of 150 to 300 mg provided statistically and clinically significant decreases in systolic and diastolic blood pressure with trough (24 hour post-dose) effects after 6–12 weeks of treatment compared to placebo, of about 8–10/5–6 and 8–12/5–8 mmHg, respectively. No further increase in effect was seen at dosages greater than 300 mg. The dose-response relationships for effects on systolic and diastolic pressure are shown in Figures 1 and 2.

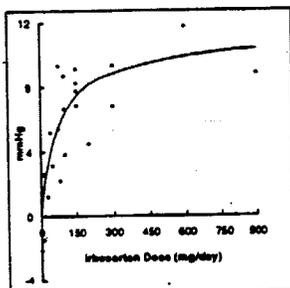


Figure 1. Placebo-subtracted reduction in trough SeDBP: integrated analysis

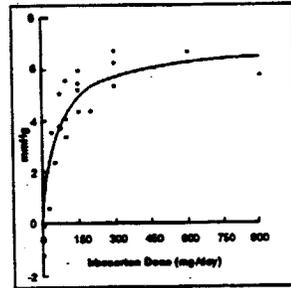


Figure 2. Placebo-subtracted reduction in trough SeDBP: integrated analysis

Once-daily administration of therapeutic doses of irbesartan gave peak effects at around 3–6 hours and, in one continuous ambulatory blood pressure monitoring study, and again around 14 hours. This was seen with both once-daily and twice-daily dosing. Trough-to-peak ratios for systolic and diastolic response were generally between 60–70%. In a continuous ambulatory blood pressure monitoring study, once-daily dosing at 150 mg gave trough and mean 24-hour responses similar to those observed in patients receiving twice-daily dosing at the same total daily dose.

Analysis of age, gender, and race subgroups of patients showed that men and women, and patients over and under 65 years of age, had generally similar responses. Irbesartan was effective in reducing blood pressure regardless of race, although the effect was somewhat less in blacks (usually a low-renin population). Black patients typically show an improved response with the addition of a low dose diuretic (e.g., 12.5 mg hydrochlorothiazide).

The effect of irbesartan is apparent after the first dose and is close to the full observed effect at 2 weeks. At the end of the 8-week exposure, about 2/3 of the antihypertensive effect was still present 1 week after the last dose. Rebound hypertension was not observed. There was essentially no change in average heart rate in irbesartan-treated patients in controlled trials.

### Irbesartan-Hydrochlorothiazide

The antihypertensive effects of AVALIDE (irbesartan-hydrochlorothiazide) Tablets were examined in 4 placebo-controlled studies of 8–12 weeks in patients with mild-to-moderate hypertension. These trials included 1914 patients randomized to fixed doses of irbesartan (37.5 to 300 mg) and concomitant hydrochlorothiazide (6.25 to 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.

### INDICATIONS AND USAGE

AVALIDE (irbesartan-hydrochlorothiazide) Tablets is indicated for the treatment of hypertension. This fixed dose combination is not indicated for initial therapy (see DOSAGE AND ADMINISTRATION).

### CONTRAINDICATIONS

AVALIDE is contraindicated in patients who are hypersensitive to any component of this product.

Because of the hydrochlorothiazide component, this product is contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs.

### WARNINGS

#### Fetal/Neonatal Morbidity and Mortality

Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature in patients who were taking angiotensin converting enzyme inhibitors. When pregnancy is detected, AVALIDE (irbesartan-hydrochlorothiazide) Tablets should be discontinued as soon as possible.

The use of drugs that act directly on the renin-angiotensin system during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug.

These adverse effects do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester.

Mothers whose embryos and fetuses are exposed to an angiotensin II receptor antagonist only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should have the patient discontinue the use of AVALIDE as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to a drug acting on the renin-angiotensin system will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intraamniotic environment.

If oligohydramnios is observed, AVALIDE (irbesartan-hydrochlorothiazide) Tablets should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to an angiotensin II receptor antagonist 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 or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal function.

When pregnant rats were treated with irbesartan from day 0 to day 20 of gestation (oral doses of 50, 180, and 650 mg/kg/day), increased incidences of renal pelvic cavitation, hydroureter and/or absence of renal papilla were observed in fetuses at doses  $\geq 50$  mg/kg/day (approximately equivalent to the maximum recommended human dose (MRHD), 300 mg/day, on a body surface area basis). Subcutaneous edema was observed in fetuses at doses  $\geq 180$  mg/kg/day (about 4 times the MRHD on a body surface area basis). As these anomalies were not observed in rats in which irbesartan exposure (oral doses of 50, 150 and 450 mg/kg/day) was limited to gestation days 6–15, they appear to reflect late gestational effects of the drug. In pregnant rabbits, oral doses of 30 mg irbesartan/kg/day were associated with maternal mortality and abortion. Surviving females receiving this dose (about 1.5 times the MRHD on a body surface area basis) had a slight increase in early resorptions and a corresponding decrease in live fetuses. Irbesartan was found to cross the placental barrier in rats and rabbits.

Radioactivity was present in the rat and rabbit fetus during late gestation and in rat milk following oral doses of radiolabeled irbesartan.

Studies in which hydrochlorothiazide was administered to pregnant mice and rats during their respective periods of major organogenesis at doses up to 3000 and 1000 mg/kg/day, respectively, provided no evidence of harm to the fetus.

A development toxicity study was performed in rats with doses of 50/50 and 150/150 mg/kg/day irbesartan-hydrochlorothiazide. Although the high dose combination appeared to be more toxic to the dams than either drug alone, there did not appear to be an increase in toxicity to the developing embryos.

Thiazides cross the placental barrier and appear in cord blood. There is a risk of fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions that have occurred in adults.

#### Hypotension in Volume- or Salt-depleted Patients

Excessive reduction of blood pressure was rarely seen in patients with uncomplicated hypertension treated with irbesartan alone (<0.1%) or with irbesartan-hydrochlorothiazide (approximately 1%). Initiation of antihypertensive therapy may cause symptomatic hypotension in patients with intravascular volume- or sodium-depletion, e.g., in patients treated vigorously with diuretics or in patients on dialysis. Such volume depletion should be corrected prior to administration of antihypertensive therapy.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty once the blood pressure has stabilized.

### Hydrochlorothiazide

#### Hepatic Impairment

Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

#### Hypersensitivity Reaction

Hypersensitivity reactions to hydrochlorothiazide may occur in patients with or without a history of allergy or bronchial asthma, but are more likely in patients with such a history.

#### Systemic Lupus Erythematosus

Thiazide diuretics have been reported to cause exacerbation or activation of systemic lupus erythematosus.

#### Lithium Interaction

Lithium generally should not be given with thiazides (see PRECAUTIONS: Drug Interactions; Hydrochlorothiazide, Lithium).

### PRECAUTIONS

#### General

##### Irbesartan-Hydrochlorothiazide

In double-blind clinical trials of various doses of irbesartan and hydrochlorothiazide, the incidence of hypertensive patients who developed hypokalemia (serum potassium <3.5 mEq/L) was 7.5% versus 6.0% for placebo; the incidence of hyperkalemia (serum potassium >5.7 mEq/L) was <1.0% versus 1.7% for placebo. No patient

discontinued due to increases or decreases in serum potassium. Overall, the combination of irbesartan and hydrochlorothiazide had no effect on serum potassium. Higher doses of irbesartan ameliorated the hypokalemic response to hydrochlorothiazide.

#### Hydrochlorothiazide

Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance: hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance, irrespective of cause, include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, confusion, seizures, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Hypokalemia may develop, especially with brisk diuresis, when severe cirrhosis is present, or after prolonged therapy.

Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia may cause cardiac arrhythmia and may also sensitize or exaggerate the response of the heart to the toxic effects of digitalis (e.g., increased ventricular irritability).

Although any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease), chloride replacement may be required in the treatment of metabolic alkalosis.

Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy. In diabetic patients dosage adjustments of insulin or oral hypoglycemic agents may be required. Hyperglycemia may occur with thiazide diuretics. Thus latent diabetes mellitus may become manifest during thiazide therapy.

The antihypertensive effects of the drug may be enhanced in the post-sympathetic patient.

If progressive renal impairment becomes evident consider withholding or discontinuing diuretic therapy.

Thiazides have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia.

Thiazides may decrease urinary calcium excretion. Thiazides may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function. Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.

#### Impaired Renal Function

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (e.g., patients with severe congestive heart failure), treatment with angiotensin converting enzyme inhibitors has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. Irbesartan would be expected to behave similarly. In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or BUN have been reported. There has been no known use of irbesartan in patients with unilateral or bilateral renal artery stenosis, but a similar effect should be anticipated.

Thiazides should be used with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.

#### Information for Patients

**Pregnancy:** Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to drugs that act on the renin-angiotensin system, and they should also be told that these consequences do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

**Symptomatic Hypotension:** A patient receiving AVALIDE (irbesartan-hydrochlorothiazide) Tablets should be cautioned that lightheadedness can occur, especially during the first days of therapy, and that it should be reported to the prescribing physician. The patient should be told that if syncope occurs, AVALIDE should be discontinued until the physician has been consulted.

All patients should be cautioned that inadequate fluid intake, excessive perspiration, diarrhea, or vomiting can lead to an excessive fall in blood pressure, with the same consequences of lightheadedness and possible syncope.

#### Drug Interactions

##### Irbesartan

No significant drug-drug pharmacokinetic (or pharmacodynamic) interactions have been found in interaction studies with hydrochlorothiazide, digoxin, warfarin, and nifedipine.

*In vitro* studies show significant inhibition of the formation of oxidized irbesartan metabolites with the known cytochrome CYP 2C9 substrates/inhibitors sulfaphenazole, tolbutamide and nifedipine. However, in clinical studies the consequences of concomitant irbesartan on the pharmacodynamics of warfarin were negligible. Concomitant nifedipine or hydrochlorothiazide had no effect on irbesartan pharmacokinetics. Based on *in vitro* data, no interaction would be expected with drugs whose metabolism is dependent upon cytochrome P450 isozymes 1A1, 1A2, 2A6, 2B6, 2D6, 2E1, or 3A4.

In separate studies of patients receiving maintenance doses of warfarin, hydrochlorothiazide, or digoxin, irbesartan administration for 7 days had no effect on the pharmacodynamics of warfarin (prothrombin time) or the pharmacokinetics of digoxin. The pharmacokinetics of irbesartan were not affected by coadministration of nifedipine or hydrochlorothiazide.

##### Hydrochlorothiazide

When administered concurrently the following drugs may interact with thiazide diuretics:

- Alcohol, Barbiturates, Or Narcotics**—potentiation of orthostatic hypotension may occur.
- Antidiabetic Drugs** (oral agents and insulin)—dosage adjustment of the antidiabetic drug may be required.
- Other Antihypertensive Drugs**—additive effect or potentiation.
- Cholestyramine And Colestipol Resins**—absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85 and 43 percent, respectively.
- Corticosteroids, ACTH**—intensified electrolyte depletion, particularly hypokalemia.
- Pressor Amines (e.g., Norepinephrine)**—possible decreased response to pressor amines but not sufficient to preclude their use.
- Skeletal Muscle Relaxants, Nondepolarizing (e.g., Tubocurarine)**—possible increased responsiveness to the muscle relaxant.

**Lithium**—should not generally be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity. Refer to the package insert for lithium preparations before use of such preparations with AVALIDE.

**Non-steroidal Anti-inflammatory Drugs**—in some patients, the administration of a non-steroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics. Therefore, when AVALIDE (irbesartan-hydrochlorothiazide) and non-steroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

#### Carcinogenesis, Mutagenesis, Impairment Of Fertility

##### 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 lymphocytes assay; *in vivo*-mouse micronucleus study). The combination of irbesartan and hydrochlorothiazide has not been evaluated in definitive studies of fertility.

##### 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 up to two years. For male and female rats, 500 mg/kg/day provided an average systemic exposure to irbesartan (AUC<sub>0-24h</sub>, bound plus unbound) about 3 and 11 times, respectively, the average systemic exposure in humans receiving the maximum recommended dose (MRD) of 300 mg irbesartan/day, whereas 1000 mg/kg/day (administered to females only) provided an average systemic exposure about 21 times that reported for humans at the MRD. For male and female mice, 1000 mg/kg/day provided an exposure to irbesartan about 3 and 5 times, respectively, the human exposure at 300 mg/day. 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 lymphocytes assay; *in vivo*-mouse micronucleus study).

Irbesartan had no adverse effects on fertility or mating of male or female rats at oral doses ≤550 mg/kg/day, the highest dose providing a systemic exposure to irbesartan (AUC<sub>0-24h</sub>, bound plus unbound) about 5 times that found in humans receiving the maximum recommended dose of 300 mg/day.

#### Hydrochlorothiazide

Two-year feeding studies in mice and rats conducted under the auspices of the National Toxicology Program (NTP) uncovered no evidence of a carcinogenic potential of hydrochlorothiazide in female mice (at doses of up to approximately 600 mg/kg/day) or in male and female rats (at doses of up to approximately 100 mg/kg/day). The NTP, however, found equivocal evidence for hepatocarcinogenicity in male mice.

Hydrochlorothiazide was not genotoxic *in vitro* in the Ames mutagenicity assay of *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 and in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations, or *in vivo* in assays using mouse germinal cell chromosomes, Chinese hamster bone marrow chromosomes, and the *Drosophila* sex-linked recessive lethal trait gene. Positive test results were obtained only in the *in vitro* CHO Sister Chromatid Exchange (clastogenicity) and in the Mouse Lymphoma Cell (mutagenicity) assays, using concentrations of hydrochlorothiazide from 43 to 1300 µg/mL, and in the *Aspergillus nidulans* non-disjunction assay at an unspecified concentration.

Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed, via their diet, to doses of up to 100 and 4 mg/kg, respectively, prior to mating and throughout gestation.

#### Pregnancy

**Pregnancy Categories C (first trimester) and D (second and third trimesters)**

(See WARNINGS: Fetal/Neonatal Morbidity and Mortality.)

#### Nursing Mothers

It is not known whether irbesartan is excreted in human milk, but irbesartan or some metabolite of irbesartan is secreted at low concentration in the milk of lactating rats. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Thiazides appear in human milk. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

#### Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

#### Geriatric Use

Of the total number of patients in controlled clinical studies of hypertension with AVALIDE, 143 patients (16.0%) were 65 years and over, while 21 (2.3%) were 75 years and over. No overall differences in effectiveness or safety were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

#### ADVERSE REACTIONS

##### Irbesartan-hydrochlorothiazide

AVALIDE (irbesartan-hydrochlorothiazide) Tablets has been evaluated for safety in 896 patients treated for essential hypertension. In clinical trials with AVALIDE, no adverse experiences peculiar to this combination drug product have been observed. Adverse experiences have been limited to those that were reported previously with irbesartan and/or hydrochlorothiazide (HCTZ). The overall incidence of adverse experiences reported with the combination was comparable to placebo. In general, treatment with AVALIDE was well tolerated. For the most part, adverse experiences have been mild and transient in nature and have not required discontinuation of therapy. In controlled clinical trials, discontinuation of AVALIDE therapy due to clinical adverse experiences was required in only 3.6%. This incidence was significantly less ( $p=0.023$ ) than the 6.8% of patients treated with placebo who discontinued therapy.

In these double-blind controlled clinical trials, the following adverse experiences reported with AVALIDE occurred in ≥1% of patients, and more often on the irbesartan-hydrochlorothiazide combination than on placebo, regardless of drug relationship:

	Irbesartan/HCTZ (n=896) (%)	Placebo (n=236) (%)	Irbesartan (n=400) (%)	HCTZ (n=380) (%)
<b>Body as a Whole</b>				
Chest Pain	2	1	2	2
Fatigue	7	3	4	3
Influenza	3	1	2	2
<b>Cardiovascular</b>				
Edema	3	3	2	2
Tachycardia	1	0	1	1
<b>Gastrointestinal</b>				
Abdominal Pain	2	1	2	2
Dyspepsia/heartburn	2	1	0	2
Nausea/vomiting	3	0	2	0
<b>Immunology</b>				
Allergy	1	0	1	1
<b>Musculoskeletal</b>				
Musculoskeletal Pain	7	5	6	10
<b>Nervous System</b>				
Dizziness	8	4	6	5
Dizziness Orthostatic	1	0	1	1
<b>Renal/Genitourinary</b>				
Abnormality Urination	2	1	1	2

The following adverse events were also reported at a rate of 1% or greater, but were as, or more, common in the placebo group: headache, sinus abnormality, cough, URI, pharyngitis, diarrhea, rhinitis, urinary tract infection, rash, anxiety/nervousness, and muscle cramp.

Adverse events occurred at about the same rates in men and women, older and younger patients, and black and non-black patients.

##### Irbesartan

Other adverse experiences that have been reported with irbesartan, without regard to causality are listed below:

- Body as a Whole:** fever, chills, orthostatic effects, facial edema, upper extremity edema
- Cardiovascular:** flushing, hypertension, cardiac murmur, myocardial infarction, angina pectoris, hypotension, syncope, arrhythmic/conduction disorder, cardio-respiratory arrest, heart failure, hypertensive crisis
- Dermatologic:** pruritus, dermatitis, ecchymosis, erythema face, urticaria
- Endocrine/Metabolic/Electrolyte Imbalances:** sexual dysfunction, libido change, gout
- Gastrointestinal:** diarrhea, constipation, gastroenteritis, flatulence, abdominal distention
- Musculoskeletal/Connective Tissue:** musculoskeletal trauma, extremity swelling, muscle cramp, arthritis, muscle ache, musculoskeletal chest pain, joint stiffness, bursitis, muscle weakness
- Nervous System:** anxiety/nervousness, sleep disturbance, numbness, somnolence, vertigo, emotional disturbance, depression, parosmia, tremor, transient ischemic attack, cerebrovascular accident
- Renal/Genitourinary:** prostate disorder
- Respiratory:** cough, upper respiratory infection, epistaxis, tracheobronchitis, congestion, pulmonary congestion, dyspnea, wheezing
- Special Senses:** vision disturbance, hearing abnormality, ear infection, ear pain, conjunctivitis.

##### Hydrochlorothiazide

Other adverse experiences that have been reported with hydrochlorothiazide, without regard to causality, are listed below:

- Body As A Whole:** weakness
- Digestive:** pancreatitis, jaundice (intrahepatic cholestatic jaundice), sialadenitis, cramping, gastric irritation
- Hematologic:** aplastic anemia, agranulocytosis, leukopenia, hemolytic anemia, thrombocytopenia
- Hypersensitivity:** purpura, photosensitivity, urticaria, necrotizing angitis (vasculitis and cutaneous vasculitis), fever, respiratory distress including pneumonitis and pulmonary edema, anaphylactic reactions
- Metabolic:** hyperglycemia, glycosuria, hyperuricemia
- Musculoskeletal:** muscle spasm
- Nervous System/Psychiatric:** restlessness
- Renal:** renal failure, renal dysfunction, interstitial nephritis

**Skin:** erythema multiforme including Stevens-Johnson syndrome, exfoliative dermatitis including toxic epidermal necrolysis

**Special Senses:** transient blurred vision, xanthopsia.

**Post-Marketing Experience**

The following adverse reactions have been reported in post-marketing experience: Rare cases of urticaria and angioedema (involving swelling of the face, lips, pharynx, and/or tongue); hyperkalemia.

**Laboratory Test Findings**

In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with administration of AVALIDE (irbesartan-hydrochlorothiazide) Tablets.

**Creatinine, Blood Urea Nitrogen:** Minor increases in blood urea nitrogen (BUN) or serum creatinine were observed in 2.3 and 1.1 percent, respectively, of patients with essential hypertension treated with AVALIDE alone. No patient discontinued taking AVALIDE due to increased BUN. One patient discontinued taking AVALIDE due to a minor increase in serum creatinine.

**Hemoglobin:** Mean decreases of approximately 0.2 g/dL occurred in patients treated with AVALIDE alone, but were rarely of clinical importance. This compared to a mean of 0.4 g/dL in patients receiving placebo. No patients were discontinued due to anemia.

**Liver Function Tests:** Occasional elevations of liver enzymes and/or serum bilirubin have occurred. In patients with essential hypertension treated with AVALIDE alone, one patient was discontinued due to elevated liver enzymes.

**Serum Electrolytes:** (See PRECAUTIONS.)

**OVERDOSAGE**

**Irbesartan**

No data are available in regard to overdosage in humans. However, daily doses of 900 mg for 8 weeks were well-tolerated. The most likely manifestations of overdosage are expected to be hypotension and tachycardia; bradycardia might also occur from overdose. Irbesartan is not removed by hemodialysis.

To obtain up-to-date information about the treatment of overdosage, a good resource is a certified Regional Poison-Control Center. Telephone numbers of certified poison-control centers are listed in the *Physicians' Desk Reference* (PDR). In managing overdosage, consider the possibilities of multiple-drug interactions, drug-drug interactions, and unusual drug kinetics in the patient.

Laboratory determinations of serum levels of irbesartan are not widely available, and such determinations have, in any event, no established role in the management of irbesartan overdosage.

Acute oral toxicity studies with irbesartan in mice and rats indicated acute lethal doses were in excess of 2000 mg/kg, about 25- and 50-fold the maximum recommended human dose (300 mg) on a mg/m<sup>2</sup> basis, respectively.

**Hydrochlorothiazide**

The most common signs and symptoms of overdose observed in humans are those caused by electrolyte depletion (hypokalemia, hypochloremia, hyponatremia) and dehydration resulting from excessive diuresis. If digoxin has also been administered, hypokalemia may accentuate cardiac arrhythmias. The degree to which hydrochlorothiazide is removed by hemodialysis has not been established. The oral LD<sub>50</sub> of hydrochlorothiazide is greater than 10 g/kg in both mice and rats.

**DOSAGE AND ADMINISTRATION**

The recommended initial dose of irbesartan is 150 mg once daily. Patients requiring further reduction in blood pressure should be titrated to 300 mg once daily.

A lower initial dose of irbesartan (75 mg) is recommended in patients with depletion of intravascular volume (e.g., patients treated vigorously with diuretics or on hemodialysis) (see **WARNINGS: Hypotension in Volume- or Salt-depleted Patients**). Patients not adequately treated by the maximum dose of 300 mg once daily are unlikely to derive additional benefit from a higher dose or twice-daily dosing.

Hydrochlorothiazide is effective in doses of 12.5 to 50 mg once daily.

To minimize dose-independent side effects, it is usually appropriate to begin combination therapy only after a patient has failed to achieve the desired effect with monotherapy.

The side effects (see **WARNINGS**) of irbesartan are generally rare and apparently independent of dose; those of hydrochlorothiazide are a mixture of dose-dependent (primarily hypokalemia) and dose-independent phenomena (e.g., pancreatitis), the former much more common than the latter. Therapy with any combination of irbesartan and hydrochlorothiazide will be associated with both sets of dose-independent side effects.

AVALIDE may be administered with other antihypertensive agents.

AVALIDE may be administered with or without food.

**Replacement Therapy**

The combination may be substituted for the titrated components.

**Dose Titration by Clinical Effect**

A patient whose blood pressure is inadequately controlled by irbesartan or hydrochlorothiazide alone may be switched to once daily AVALIDE. Recommended doses of AVALIDE, in order of increasing mean effect, are (irbesartan-hydrochlorothiazide) 150/12.5 mg, 300/12.5 mg, and 300/25 mg (two 150/12.5 mg tablets). The largest incremental effect will likely be in the transition from monotherapy to 150/12.5 mg. (See **CLINICAL PHARMACOLOGY: Clinical Studies**). It takes 2-4 weeks for the blood pressure to stabilize after a change in the dose of AVALIDE.

The usual dose of AVALIDE is one tablet once daily. More than two tablets once daily is not recommended. The maximal antihypertensive effect is attained about 2-4 weeks after initiation of therapy.

**Use in Patients with Renal Impairment**

The usual regimen of therapy with AVALIDE may be followed as long as the patient's creatinine clearance is >30 mL/min. In patients with more severe renal impairment, loop diuretics are preferred to thiazides, so AVALIDE is not recommended.

**Patients with Hepatic Impairment**

No dosage adjustment is necessary in patients with hepatic impairment.

**HOW SUPPLIED**

AVALIDE® (irbesartan-hydrochlorothiazide) Tablets are peach, biconvex, and oval with a heart debossed on one side and 2775 or 2776 on the reverse, supplied as follows:

Irbesartan (mg)	HCTZ (mg)	NDC 0067-XXXX-XX for unit of use			
		Bottle of			B blister of
		30	90	500	100
150	12.5	2775-31	2775-32	2775-15	2775-35
300	12.5	2776-31	2776-32	2776-15	2776-35

**Storage**

Store at a temperature between 15° C and 30° C (59° F and 86° F) [See USP].

Manufactured and Distributed by:  
Bristol-Myers Squibb Company  
Princeton, NJ 08543-4500  
Cocomarketed by:  
Sanofi-Synthelabo Inc.  
New York, NY 10016

**Bristol-Myers  
Squibb Company**

**sanofi-synthelabo**

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: NDA 20758/S16**

**ADMINISTRATIVE DOCUMENTS**

