**INDICATIONS AND USAGE**

AVALIDE is a combination of irbesartan, an angiotensin II receptor antagonist, and hydrochlorothiazide, a thiazide diuretic, indicated for hypertension:

- In patients not adequately controlled with monotherapy. (1)
- As initial therapy in patients likely to need multiple drugs to achieve their blood pressure goals. (1)

**DOSE AND ADMINISTRATION**

**General Considerations**

- Maximum effects within 2 to 4 weeks after dose change. (2.1)
- Renal impairment: Not recommended for patients with severe renal impairment (creatinine clearance <30 mL/min). (2.1, 5.8)

**Hypertension**

- Initiate with 150/12.5 mg. Titrate to 300/12.5 mg then 300/25 mg if needed. (2.2)
- Replacement therapy: May be substituted for titrated components. (2.3)

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**CONTRAINDICATIONS**

- Hypersensitivity to any component of this product. (4)
- Anuria. (4)
- Hypersensitivity to sulfonamide-derived drugs. (4)
- Do not coadminister aliskiren with AVALIDE in patients with diabetes. (4)

**WARNINGS AND PRECAUTIONS**

- Hypotension: Correct volume depletion prior to administration. (5.2)
- Impaired renal function. (5.7)
- Thiazide diuretics may cause an exacerbation or activation of systemic lupus erythematosus. (5.4)
- Acute angle-closure glaucoma, acute myopia, and choroidal effusion. (5.8)

**ADVERSE REACTIONS**

Most common adverse events (≥5% on AVALIDE and more often than on placebo) are:

- Dizziness, fatigue, and musculoskeletal pain. (6.1)

**DRUG INTERACTIONS**

- NSAIDs and selective COX-2 inhibitors: Can reduce diuretic, natriuretic or diuretic, effect. Monitor renal function periodically. (7)
- Dual blockade of the renin-angiotensin system: Increased risk of renal impairment, hypotension, and hyperkalemia. (7)
- Antidiabetic drugs: Dosage adjustment of antidiabetic may be required. (7)
- Cholestyramine and colestipol: Reduced absorption of thiazides. (7)
- Lithium: Increases in serum lithium concentrations and lithium toxicity. (7)
- Carbamazepine: Increased risk of hyponatremia. (7)

**USE IN SPECIFIC POPULATIONS**

- Lactation: Potential for adverse effects in infant. (8.2)

**PATIENT COUNSELING INFORMATION**

- Antidiabetic Drugs (oral agents and insulin)
- Cholestyramine and Colestipol Resins
- Lithium
- Carbamazepine

**OVERDOSAGE**

- 16.2 Storage
- 16.1 How Supplied

**CLINICAL PHARMACOLOGY**

- 12.2 Pharmacodynamics
- 12.1 Mechanism of Action

**NONCLINICAL TOXICITY**

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

**CLINICAL STUDIES**

- 14.1 Irbesartan Monotherapy
- 14.2 Irbesartan and Hydrochlorothiazide

**SUPPLIED/STORAGE AND HANDLING**

- 16.1 How Supplied
- 16.2 Storage

**PATIENT COUNSELING INFORMATION**

- *Sections or subsections omitted from the full prescribing information are not listed*
1 INDICATIONS AND USAGE

AVALIDE® (irbesartan and hydrochlorothiazide) tablets are indicated for the treatment of hypertension.

AVALIDE may be used in patients whose blood pressure is not adequately controlled on monotherapy. AVALIDE may also be used as initial therapy in patients who are likely to need multiple drugs to achieve their blood pressure goals.

The choice of AVALIDE as initial therapy for hypertension should be based on an assessment of potential benefits and risks. Patients with stage 2 (moderate or severe) hypertension are at relatively high risk for cardiovascular events (such as strokes, heart attacks, and heart failure), kidney failure, and vision problems, so prompt treatment is clinically relevant. The decision to use a combination as initial therapy should be individualized and may be shaped by considerations such as the baseline blood pressure, the target goal, and the incremental likelihood of achieving goal with a combination compared with monotherapy.

Data from Studies V and VI [see Clinical Studies (14.2)] provide estimates of the probability of reaching a blood pressure goal with AVALIDE compared to irbesartan or hydrochlorothiazide (HCTZ) monotherapy. The relationship between baseline blood pressure and achievement of a SeSBP <140 or <130 mmHg or SeDBP <90 or <80 mmHg in patients treated with AVALIDE compared to patients treated with irbesartan or HCTZ monotherapy are shown in Figures 1a through 2b.

2 DOSAGE AND ADMINISTRATION

2.1 General Considerations

The side effects 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. [See Adverse Reactions (6.1)]. Maximum antihypertensive effects are attained within 2 to 4 weeks after a change in dose. AVALIDE may be administered with or without food. AVALIDE may be administered with other antihypertensive agents.

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.

Hepatic Impairment

No dosage adjustment is necessary in patients with hepatic impairment.

2.2 Add-On Therapy

In patients not controlled on monotherapy with irbesartan or hydrochlorothiazide, the recommended doses of AVALIDE, in order of increasing mean effects, are irbesartan and hydrochlorothiazide 150/12.5 mg, 300/12.5 mg, and 300/25 mg. The largest incremental effect will likely be in the transition from monotherapy to 150/12.5 mg. [See Clinical Studies (14.2)].

2.3 Replacement Therapy

AVALIDE may be substituted for the titrated components.

2.4 Initial Therapy

The usual starting dose is AVALIDE 150/12.5 mg once daily. The dosage can be increased after 1 to 2 weeks of therapy to a maximum of 300/25 mg once daily as needed to control blood pressure [see Clinical Studies (14.2)]. AVALIDE is not recommended as initial therapy in patients with intravascular volume depletion [see Warnings and Precautions (5.2)].

2.4.1 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 hypokalemia to other sulfonamide-derived drugs.
• Do not administer aliskiren in patients with diabetes [see Drug Interactions (7)].

5 WARNINGS AND PRECAUTIONS

5.1 Fetal Toxicity

AVALIDE can cause fetal harm when administered to a pregnant woman. Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypoplasia of the lungs, hypoplasia of other organs and fractures, and the risk of fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions that have occurred in adults.

5.2 Hypotension in Volume or Salt-Deppleted Patients

Excessive reduction of blood pressure was rarely seen in patients with uncomplicated hypertension treated with irbesartan or hydrochlorothiazide (HCTZ) monotherapy. The relationship between baseline blood pressure and achievement of a SeSBP <140 or <130 mmHg or SeDBP <90 or <80 mmHg in patients treated with AVALIDE compared to patients treated with irbesartan or HCTZ monotherapy are shown in Figures 1a through 2b.

5.3 Hypersensitivity Reaction

Hydrochlorothiazide

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.

5.4 Systemic Lupus Erythematosus

Hydrochlorothiazide

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

5.5 Electrolyte and Metabolic Imbalances

Irbesartan and 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. On average, the combination of irbesartan and hydrochlorothiazide had no effect on serum potassium. Higher doses of irbesartan inactivated the hypokalemic response to hydrochlorothiazide.

Co-administration of AVALIDE with potassium-sparing diuretics, potassium supplement, potassium-containing salt substitutes or other drugs that raise serum potassium levels may result in hyperkalemia, sometimes severe. Monitor serum potassium in such patients.

Irbesartan

Hydrochlorothiazide

Hydrochlorothiazide can cause hypokalemia and hyponatremia. Hyponatremia can result in hypokalemia which appears difficult to treat despite potassium repletion. Drugs that inhibit the renin-angiotensin system can cause hyperkalemia. Monitor serum electrolytes periodically.
Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy. Hydrochlorothiazide may alter glucose tolerance and raise serum levels of cholesterol and triglycerides. The antihypertensive effects of the drug may be enhanced in the post-sympathetic patient. 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.  

5.6 Hepatic Impairment

Hydrochlorothiazide

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.

5.7 Impaired Renal Function

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals [see Drug Interactions (7)]. 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 ACE 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.

5.8 Acute Angle-Closure Glaucma, Acute Myopia, and Choroidal Effusion

Hydrochlorothiazide

Hydrochlorothiazide, a sulfonamide, can cause an idiosyncratic reaction resulting in acute angle-closure glaucoma and elevated intracocular pressure with or without a noticeable acute myopic shift and/or choroidal effusions. Cases of acute angle-closure glaucoma have been reported with hydrochlorothiazide. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma may result in permanent vision loss. The primary treatment is to discontinue drug intake as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intracocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating the rates on AVALIDE. Irbesartan tablets have been evaluated for safety in 1694 patients treated for essential hypertension in 8 clinical trials. In Studies I through IV with AVALIDE, no adverse events occurred at about the same rates in men and women, older and younger patients, and black and non-black patients. Adverse events in Studies V and VI were similar to those described above in Studies I through IV. Other adverse events 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, arrhythmia/conduction disorder, cardiorespiratory 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, extremy swelling, muscle cramp, articular, muscle ache, musculoskeletal chest pain, joint stiffness, bursitis, muscle weakness
Nervous System: anxiety/nervousness, sleep disturbance, numbness, somnolence, vertigo, emotional disturbance, depression, paresthesia, 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
Hypersensitivity: purpura, photosensitivity, urticaria, necrotizing angitis (vasculitis and cutaneous vasculitis), fever, respiratory distress including Stevens-Johnson syndrome, exfoliative dermatitis including toxic epidermal necrolysis
Metabolic: hyperglycemia, glycosuria, hyperuricemia
Musculoskeletal: muscle spasm
Nervous System/Psychiatric: restlessness
Renal: renal failure, renal dysfunction, interstitial nephritis
Skin: erythema multiforme including toxic epidermal necrolysis including toxic epidermal necrolysis
Systemic: exfoliative dermatitis, exfoliative dermatitis, exfoliative dermatitis, exfoliative dermatitis
Allergy: 1 0 1 1
Abnormality
Urination

<table>
<thead>
<tr>
<th>Event</th>
<th>Irbesartan/ HCTZ (n=898) (%)</th>
<th>Placebo (n=236) (%)</th>
<th>Irbesartan (n=400) (%)</th>
<th>HCTZ (n=380) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body as a Whole</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest Pain</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Fatigue</td>
<td>6</td>
<td>3</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Fluinfluenza</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Edema</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Dyspepsia/ heartburn</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

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. Adverse events in Studies V and VI were similar to those described above in Studies I through IV. Other adverse events that have been reported with irbesartan, without regard to causality, are listed below.

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of the prespecified adverse events on AVALIDE and irbesartan, respectively, were: 4% and 0% for systolic; 0.6% and 0.2% for diastolic; 2.9% and 2.7% for oliguria; 0.2% and 0% for proteinuria; 0% and 0% for anuria; 0.2% and 0% for hyperkalemia; 0.2% and 0% for hypokalemia; and 0% and 0% for hyponatremia. The rates of discontinuation due to adverse events were 2.1% and 2.2%. [See Clinical Studies (14.2).]

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of AVALIDE. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Therefore, it is not always possible to determine these reactions to be drug related or to establish their relative contributions due to the presence of concomitant disease or other drugs. The reactions are ordered by system organ class and dose-relatedAdverse reactions that are not related to system organ class are listed afterward. [See Adverse Reactions (6) and Clinical Pharmacology (12).]

6.3 Laboratory Abnormalities

Liver Function Tests: Elevated SGOT and/or SGPT levels were observed in 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.

Serum Electrolytes: [See Warnings and Precautions (5.2, 5.6).]

7.2 Dual Blockade of the Renin-Angiotensin System (RAS)

Dual blockade of the RAS with angiotensin-receptor blockers, ACE inhibitors, or aliskiren is associated with increased risks of hypotension, hyperkalemia, and changes in renal function (including acute renal failure) compared to monotherapy. Closely monitor blood pressure, renal function, and electrolytes in patients on AVALIDE and other agents that affect the RAS.

In most patients no benefit has been associated with using two RAS inhibitors concomitantly. In general, avoid combined use of RAS inhibitors.

Do not coadminister aliskiren with AVALIDE in patients with diabetes. Avoid use of aliskiren with AVALIDE in patients with renal impairment (GFR <60 mL/min).

7.4 Antidiabetic Drugs (oral agents and insulin)

Dosage adjustment of the antidiabetic drug may be required when coadministered with hydrochlorothiazide.

7.5 Cholesteryamine and Colestipol Resins

Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Stagger the dosage of hydrochlorothiazide and the resin such that AVALIDE is administered at least 4 hours before or 4 to 6 hours after the resin. [See Drug Interactions (7.1).]

7.6 Lithium

Increases in serum lithium concentrations and lithium toxicity have been reported with concomitant use of irbesartan or thiazide diuretics. Monitor lithium levels in patients receiving AVALIDE and lithium.

7.7 Carbamazepine

Concomitant use of carbamazepine and hydrochlorothiazide has been associated with the risk of symptomatic hyponatremia. Monitor electrolytes during concomitant use.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

AVALIDE can cause fetal harm when administered to a pregnant woman. Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death [see Clinical Considerations]. Most epidemiologic studies examining fetal abnormalities after exposure to antihypertensive use in the first trimester have not distinguished drugs affecting the renin-angiotensin system from other antihypertensive agents. When pregnancy is detected, discontinue AVALIDE as soon as possible. All pregnancies have the potential for adverse outcomes regardless of drug exposure. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. [See Clinical Considerations (7.3).]

6. Antidiabetic Drugs (oral agents and insulin)

7.4 Antidiabetic Drugs (oral agents and insulin)

Increase was approximately 1 additional SCC case for every 6,700 patients per year. [See Warnings and Precautions (5.3).]

6.6% for headache; 0.2% and 0% for hyperkalemia; and 0.6% and 0.4% for hypokalemia. Therefore, monitor renal function and blood pressure periodically in diabetic patients.

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7.1 Nonsteroidal Anti-inflammatory Agents Including Selective Cyclooxygenase-2 Inhibitors (COX-2 Inhibitors)

Irbesartan

Treated at least 4 hours before or 4 to 6 hours after the administration of the resin.

Inhibitors (COX-2 Inhibitors)

6.3 Laboratory Abnormalities

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 Warnings and Precautions (5.2, 5.6).]

7.2 Dual Blockade of the Renin-Angiotensin System (RAS)

Dual blockade of the RAS with angiotensin-receptor blockers, ACE inhibitors, or aliskiren is associated with increased risks of hypotension, hyperkalemia, and changes in renal function (including acute renal failure) compared to monotherapy. Closely monitor blood pressure, renal function, and electrolytes in patients on AVALIDE and other agents that affect the RAS.

In most patients no benefit has been associated with using two RAS inhibitors concomitantly. In general, avoid combined use of RAS inhibitors.

Do not coadminister aliskiren with AVALIDE in patients with diabetes. Avoid use of aliskiren with AVALIDE in patients with renal impairment (GFR <60 mL/min).

7.4 Antidiabetic Drugs (oral agents and insulin)

Dosage adjustment of the antidiabetic drug may be required when coadministered with hydrochlorothiazide.

7.5 Cholesteryamine and Colestipol Resins

Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Stagger the dosage of hydrochlorothiazide and the resin such that AVALIDE is adminis-

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Increases in serum lithium concentrations and lithium toxicity have been reported with concomitant use of irbesartan or thiazide diuretics. Monitor lithium levels in patients receiving AVALIDE and NSAID therapy.

Hydrochlorothiazide

Administration of a nonsteroidal anti-inflammatory agent, including a selective COX-2 inhibitor, can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing, and thiazide diuretics. Therefore, when AVALIDE (irbesartan and hydrochlorothiazide) tablets and nonsteroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is observed.

8.4 Pediatric Use

8.5 Geriatric Use

Of 1694 patients receiving AVALIDE in controlled clinical studies of hypertension, 294 (15.6%) were 65 years and over, while 45 (2.7%) were 75 years and over. No overall differences in safety or effectiveness were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out. [See Clinical Pharmacology (12.3) and Clinical Studies (14).]

10 OVERDOSAGE

Irbesartan

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

To obtain up-to-date information about the treatment of overdosage, a good resource is Physicians’ Desk Reference.

10.2 Lactation

There are no available data on the presence of irbesartan in human milk, effects on milk production, or the breastfed infant. Irbesartan or some metabolite of irbesartan is secreted in human milk. [See Data (5.1)].

10.3 Lactation

Inhibitors (COX-2 Inhibitors)

6.3 Laboratory Abnormalities

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.

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Concomitant use of carbamazepine and hydrochlorothiazide has been associated with the risk of symptomatic hyponatremia. Monitor electrolytes during concomitant use.

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Acute oral toxicity studies with irbesartan in mice and rats indicated acute lethal doses were in excess of 2000 mg/kg, about 25-fold and 50-fold the MRHD (300 mg) based on body surface area.

11 DESCRIPTION

Irbesartan is a non-peptide compound, chemically described as a 2-butyl-3-[p-(1H-tetrazol-5-yl)phenyl]benzyl]-1,3-diazaspiro[4.4]non-1-ene-4-one. Its empirical formula is C_{25}H_{28}N_{2}O_{5}, and its structural formula is:

![Chemical structure of irbesartan](image)

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-dihydropyridine-2,1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide. Its empirical formula is C_{12}H_{17}ClN_{2}O_{4}, and its structural formula is:

![Chemical structure of hydrochlorothiazide](image)

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 film-coated tablets containing either 150 mg or 300 mg of irbesartan combined with 12.5 mg of hydrochlorothiazide. All dosage strengths contain the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, hypromellose, magnesium stearate, silicon dioxide, and colloidal silicon dioxide. Its empirical formula is C_{25}H_{30}N_{2}O_{5}, and its structural formula is:

![Chemical structure of AVALIDE](image)

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Irbesartan 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 amines (e.g., norepinephrine): Possible decreased response to pressor amines but not sufficient to preclude their use.

12.3 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 50% to 80%. Following oral administration of irbesartan, peak plasma concentrations of irbesartan are attained at 1.5 to 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 to 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 5.6 and 14.8 hours.

Distribution

Irbesartan

Irbesartan is metabolized via glucuronide conjugation and oxidation. Following oral or intravenous administration of 14C-labeled irbesartan, more than 80% of the circulating plasma radioactivity is attributable to unchanged irbesartan. The primary circulating metabolite is the inactive irbesartan glucuronide 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 14C-labeled irbesartan, about 20% of radioactivity is recovered in the urine and the remainder in the feces, as irbesartan or irbesartan metabolites.

In vitro studies of irbesartan oxidation by cytochrome P450 isoenzymes indicated that 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, 2D6, 2E1). There was no induction or inhibition of 3A4.

Hydrochlorothiazide

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

Metabolism and Elimination

Irbesartan

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Hydrochlorothiazide

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

Distribution

Irbesartan

Irbesartan is 90% bound to serum proteins (primarily albumin and α1-acid glycoprotein) with negligible binding to cellular components of blood. The average volume of distribution is 53 to 93 liters. Total plasma and renal clearances are in the range of 157 to 176 mL/min and 3.0 to 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.

Specific Populations

Pediatric

Irbesartan and hydrochlorothiazide pharmacokinetics have not been investigated in patients <1 year of age.

Gender

No gender-related differences in pharmacokinetics were observed in healthy elderly (age 65 to 80 years) or in healthy young (age 18 to 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% to 44%). No gender-related dosage adjustment is necessary.

Geriatric

In elderly subjects (age 65 to 80 years), irbesartan elimination half-life was not significantly altered, but AUC and Cmax values were about 20% to 50% greater than those of young subjects (age 18 to 40 years). No dosage adjustment is necessary in the elderly.
In healthy black subjects, irbesartan AUC values were approximately 25% greater than whites; there were no differences in Cmax values.

Renal insufficiency

The pharmacokinetics of irbesartan were not altered in patients with renal impairment or in patients with 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 and Precautions (5.2).]

Hepatic insufficiency

The pharmacokinetics of irbesartan followed 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-Drug Interactions

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 CYP2C9 substrates/substrates inhibitors sulphenazole, tolbutamide, and nifedipine. However, in clinical studies the concomitant administration of nifedipine 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 isoenzymes 1A2, 2A6, 2B6, 2C9, 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.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Irbesartan and Hydrochlorothiazide

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

Irbesartan and hydrochlorothiazide was not mutagenic in standard in vitro tests (Ames microbial test and Chinese hamster mammalian-cell forward gene-mutation assay). Irbesartan and hydrochlorothiazide was negative in tests for induction of chromosomal aberrations (in vitro-human lymphocyte 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 5000/1000 mg/kg/day (males/females, respectively) in rats and 1000/500 mg/kg/day in mice for up to 2 years. For male and female rats, 500 mg/kg/day provided an average systemic exposure to irbesartan (AUC0–24 h, bound plus unbound) about 3 and 5 times, respectively, the average systemic exposure in humans receiving the maximum recommended human dose (MRHD) of 300 mg irbesartan/day; whereas 1000/500 mg/kg/day (administered to females only) provided an average systemic exposure about 21 times that reported for humans at the MRHD. 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 lymphocyte assay; in vivo-mouse micronucleus study).

Irbesartan had no adverse effects on fertility or mating of male or female rats at oral doses ≤500 mg/kg/day, the highest dose providing a systemic exposure to irbesartan (AUC0–24 h, bound plus unbound) about 5 times that found in humans receiving the MRHD 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 Orosomucoid sex-linked recessive lethal trait gene. Positive test results were obtained only in the in vitro mouse 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 has 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.

14 CLINICAL STUDIES

14.1 Initial Therapy

The antihypertensive effects of irbesartan were examined in 7 major placebo-controlled, 8 to 12-week trials in patients with baseline diastolic blood pressures of 95 to 110 mmHg. Doses of 1 to 900 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 7 placebo-controlled trials identified above and 2 additional placebo-controlled studies examined the antihypertensive effects of irbesartan and hydrochlorothiazide in combination.

The 7 studies of irbesartan monotherapy included a total of 1915 patients randomized to irbesartan (1 to 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 to 12 weeks of treatment compared to placebo, of about 8 to 10/5 to 6 mmHg and 8 to 12/5 to 8 mmHg, respectively. No further increase in effect was seen at dosages greater than 300 mg/day.

The dose-response relationships for effects on systolic and diastolic pressure are shown in Figures 3 and 4.

Once-daily administration of therapeutic doses of irbesartan gave peak effects at about 3 to 6 hours and, in one continuous ambulatory blood pressure monitoring study, again about 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% and 75%.

In a continuous ambulatory blood pressure monitoring study, once-daily dosing with 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.

14.2 Irbesartan and Hydrochlorothiazide

Initial Therapy

Study I compared the irbesartan and hydrochlorothiazide combinations of 75/12.5 mg and 150/25 mg to their individual components and placebo. Study II investigated the ambulatory blood pressure responses to irbesartan and hydrochlorothiazide (75/12.5 mg and 150/25 mg) and placebo after 8 weeks of dosing. Study IV investigated the effects of the addition of irbesartan (75 or 150 mg) in patients not controlled (SeDBP ≥110 mmHg) on hydrochlorothiazide (25 mg alone). In Studies III–V, the addition of irbesartan 150 to 300 mg to hydrochlorothiazide doses of 6.25, 12.5, or 25 mg produced further dose-related reductions in blood pressure at trough of 8 to 10 mmHg/3 to 6 mmHg, similar 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 to 6/2 to 3 mmHg (12.5 mg) and 7 to 11/4 to 5 mmHg (25 mg), similar to effects achieved with hydrochlorothiazide alone. Once-daily dosing with 150 mg irbesartan and 25 mg hydrochlorothiazide (AVALIDE 150/25 mg) and 150 mg irbesartan and 25 mg hydrochlorothiazide produced mean placebo-adjusted blood pressure reductions at trough (24 hours post dosing) of about 13 to 15/9 to 11 mmHg (150 mg), 9 to 12/4 to 5 mmHg (25 mg), and 21/11 to 12 mmHg, respectively. Peak effects occurred at 3 to 6 hours, with the elimination of the post-prandial peak response.

In Study IV, the addition of irbesartan (75–150 mg) gave an additive effect (systolic/ diastolic) at trough (24 hours post dosing) of 11/7 mmHg.

HCTZ

Study V and VI had no placebo group, so effects described below are not all attributable to irbesartan or HCTZ. Study V was conducted in patients with a mean baseline blood pressure of 162/98 mmHg and compared the change from baseline in SeSBP at 8 weeks between the combination group (irbesartan and HCTZ 150/25 mg), to irbesartan (150 mg) and to HCTZ (12.5 mg). These studies present 1 week after the last dose. Rebound hypertension was not observed. Peak effects occurred at 3 to 6 hours, with the elimination of the post-prandial peak response.

Mean reductions from baseline for SeDBP and SeSBP at trough were 14.6 mmHg and 22.1 mmHg for patients treated with irbesartan, and 7.3 mmHg and 15.7 mmHg for patients treated with HCTZ at 8 weeks, respectively. For patients treated with AVALIDE, the mean change from baseline in SeSBP was 3.0 mmHg lower (p=0.0013) and the mean change from baseline in SeDBP was 5.0 mmHg lower (p=0.0016) compared to patients treated with irbesartan, and 7.4...
mmHg lower (p<0.0001) and 11.3 mmHg lower (p<0.0001) compared to patients treated with HCTZ, respectively. Withdrawal rates were 3.8% on irbesartan, 4.8% on HCTZ, and 6.7% on AVALIDE.

Study VI was conducted in patients with a mean baseline blood pressure of 172/113 mmHg and compared trough SeDBP at 5 weeks between the combination group (irbesartan and HCTZ 150/12.5 mg) and irbesartan (150 mg). These initial study regimens were increased at 1 week to AVALIDE 300/25 mg or to irbesartan 300 mg, respectively. At 5 weeks, mean reductions from baseline for SeDBP and SeSBP at trough were 24.0 mmHg and 30.8 mmHg for patients treated with AVALIDE and 19.3 mmHg and 21.1 mmHg for patients treated with irbesartan, respectively. 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. Patients treated with AVALIDE achieved more rapid blood pressure control with significantly lower SeDBP and SeSBP and greater blood pressure control at every assessment (Week 1, Week 3, Week 5, and Week 7). Maximum effects were seen at Week 7.

Withdrawal rates were 2.2% on irbesartan and 2.1% on AVALIDE.

In Studies I–VI, 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.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

AVALIDE® (irbesartan and hydrochlorothiazide) film-coated tablets have markings on both sides and are available in the strengths and packages listed in the following table:

<table>
<thead>
<tr>
<th>Tablet Strength (irbesartan and hydrochlorothiazide)</th>
<th>Film-Coated Tablet Color/Shape</th>
<th>Tablet Markings</th>
<th>Package Size</th>
<th>NDC Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>150 mg and 12.5 mg</td>
<td>peach, biconvex, oval-shaped</td>
<td>heart debossed on one side and “2875” on the reverse</td>
<td>Bottles of 30</td>
<td>0024-5855-30</td>
</tr>
<tr>
<td>300 mg and 12.5 mg</td>
<td>peach, biconvex, oval-shaped</td>
<td>heart debossed on one side and “2876” on the reverse</td>
<td>Bottles of 30</td>
<td>0024-5856-30</td>
</tr>
</tbody>
</table>

16.2 Storage

Store at 25°C (77°F); excursions permitted to 15°C–30°C (59°F–86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Pregnancy

Tell female patients of childbearing age about the consequences of exposure to AVALIDE during pregnancy. Discuss treatment options with women planning to become pregnant. Ask patients to report pregnancies to their physician as soon as possible.

Symptomatic Hypotension

Tell patients using AVALIDE that they may feel lightheaded, especially during the first days of use. Tell patients to inform their physician if they feel lightheaded or faint. Tell the patient, if fainting occurs, to stop using AVALIDE and contact the prescribing doctor.

Tell patients using AVALIDE that getting dehydrated can lower their blood pressure too much and lead to lightheadedness and possible fainting. Dehydration may occur with excessive sweating, diarrhea, or vomiting and with not drinking enough liquids.

Potassium Supplements

Advise patients not to use potassium supplements or salt substitutes containing potassium without consulting their healthcare provider [see Drug Interactions (7.3)].

Acute Angle-Closure Glaucoma, Acute Myopia, and Choroidal Effusion

Advise patients to discontinue AVALIDE and seek immediate medical attention if they experience symptoms of acute angle-closure glaucoma, acute myopia, and choroidal effusion [see Warnings and Precautions (5.8)].

Non-melanoma Skin Cancer

Instruct patients taking hydrochlorothiazide to protect skin from the sun and undergo regular skin cancer screening.

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IRH-FPLR-SL-SEP21 Rx Only

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