HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use AVALIDE safely and effectively. See full prescribing information for AVALIDE.

VALIDE® (irbesartan and hydrochlorothiazide) tablets, for oral use

Initial U.S. Approval: 1997

WARNING: FETAL TOXICITY

See full prescribing information for complete boxed warning.

• When pregnancy is detected, discontinue AVALIDE as soon as possible. (5.1)
• Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus. (5.1)

INDICATIONS AND USAGE

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

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

1. Replacement therapy: May be substituted for titrated components. (2.3)
2. Initiate with 150/12.5 mg. Titrate to 300/12.5 mg then 300/25 mg if needed. (2.2)
3. Renal impairment: Not recommended for patients with severe renal impairment (creatinine clearance <30 mL/min). (2.1, 5.6)

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)

DOSAGE FORMS AND STRENGTHS

• 150 mg irbesartan/12.5 mg hydrochlorothiazide tablets (3)
• 300 mg irbesartan/12.5 mg hydrochlorothiazide tablets (3)

DRUG INTERACTIONS

• NSAIDs and selective COX-2 inhibitors: Can reduce diuretic, natriuretic of diuretic, may lead to increased risk of renal impairment and reduced antihypertensive 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)

ADVERSE REACTIONS

Most common adverse events (≥5% on AVALIDE and more often than on placebo) are dizziness, fatigue, and musculoskeletal pain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact sanofi-aventis U.S. LLC at 1-800-633-1610 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

See 17 for PATIENT COUNSELING INFORMATION

Revised: 06/2017

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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)
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1 INDICATIONS AND USAGE

AVALIDE® (irbesartan-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 HCTZ monotherapy. The relationship between baseline blood pressure and achievement of a SeSBP <140 or <130 mmHg or SeDBP <80 mmHg in patients treated with AVALIDE compared to patients treated with irbesartan or HCTZ monotherapy are shown in Figures 1a through 2b.

Figure 1a: Probability of Achieving SBP <140 mmHg in Patients from Initial Therapy Studies V (Week 8) and VI (Week 7)*

Figure 1b: Probability of Achieving SBP <130 mmHg in Patients from Initial Therapy Studies V (Week 8) and VI (Week 7)*

*For all probability curves, patients without blood pressure measurements at Week 7 (Study VI) and Week 8 (Study V) were counted as not reaching goal (intent-to-treat analysis).

The above graphs provide a rough approximation of the likelihood of reaching a targeted blood pressure goal (e.g., Week 8 sitting systolic blood pressure <140 mmHg) for the treatment groups. The curve of each treatment group in each study was estimated by logistic regression modeling from all available data of that treatment group. The estimated likelihood at the right tail of each curve is less reliable due to small numbers of subjects with high baseline blood pressures.

For example, a patient with a blood pressure of 180/105 mmHg has about a 25% likelihood of achieving a goal of <140 mmHg (systolic) and 50% likelihood of achieving <90 mmHg (diastolic) on irbesartan alone (and lower still likelihoods on HCTZ alone).

The likelihood of achieving these goals on AVALIDE rises to about 40% (systolic) or 70% (diastolic) on irbesartan alone (and lower still likelihoods on HCTZ alone).

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.

Rapid Improvement

The usual regimens 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 effect, are (irbesartan-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)]

3 DOSAGE FORMS AND STRENGTHS

AVALIDE® (irbesartan-hydrochlorothiazide) 150/12.5 mg and 300/12.5 mg film-coated tablets are peach, biconvex, and oval with a heart debossed on one side and “2875” or “2876” on the reverse side, respectively.

4 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.

• Do not coadminister aliskiren with AVALIDE in patients with diabetes [see Drug Interactions (7)].

5 WARNINGS AND PRECAUTIONS

5.1 Fetal Toxicity

Pregnancy Category D

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, hypotension, renal failure, and death. When pregnancy is detected, discontinue AVALIDE as soon as possible [see Use in Specific Populations (8.1)].

Thiazides cross the placenta. The placenta, and use of thiazides during pregnancy is associated with a 5% risk of fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions that have occurred in adults.

5.2 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.

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-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 change in serum potassium was 0.1 mEq/L. Irbesartan and hydrochlorothiazide had no effect on serum potassium. Higher doses of irbesartan ameliorated the hypokalemic response to hydrochlorothiazide.

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

Hydrochlorothiazide

Hydrochlorothiazide can cause hypokalemia and hyponatremia. Hypomagnesemia can appear during thiazide therapy.

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-sympathectomy 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 Myopia and Secondary Angle-Closure Glaucoma
Sulfonamide or sulfonamide derivative drugs, such as hydrochlorothiazide, can cause an idiosyncratic reaction, resulting in transient myopia and acute angle-closure glaucoma. 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 can lead to 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 intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy.

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 a drug cannot be directly compared to rates 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 rates.

Irbesartan-Hydrochlorothiazide
AVALIDE tablets have been evaluated for safety in 1964 patients treated for essential hypertension in 6 clinical trials. In Studies I through IV with AVALIDE, no adverse events peculiar to this combination drug product have been observed. Adverse events have been limited to those that were reported previously with irbesartan or hydrochlorothiazide (HCTZ). The overall incidence of adverse events was similar with the combination and placebo. In general, treatment with AVALIDE was well tolerated. For the most part, adverse events 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 events 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 events reported with AVALIDE and placebo and, more often on the irbesartan-hydrochlorothiazide combination than on placebo, regardless of drug relationship:

<table>
<thead>
<tr>
<th></th>
<th>Irbesartan/ HCTZ (n=398) (%)</th>
<th>Placebo (n=236) (%)</th>
<th>Irbesartan (n=400) (%)</th>
<th>HCTZ (n=380) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Body as a Whole</strong></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>Influenza</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td><strong>Cardiovascular</strong></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><strong>Gastrointestinal</strong></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>
<tr>
<td>Nausea/vomiting</td>
<td>3</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td><strong>Immunology</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allergy</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>Musculoskeletal</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal Pain</td>
<td>6</td>
<td>5</td>
<td>6</td>
<td>10</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.

**Irbesartan**
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, 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, paresthesia, tremor, transient ischemic attack, cerebrovascular accident
Renal/Glomerulonephritis: 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 events that have been reported with hydrochlorothiazide, without regard to causality, are listed below:

Body as a Whole: weakness
Digestive: pancreatitis, jaundice (intrahepatic cholestatic jaundice), saliadenitis, cramping, gastrointestinal
Gastrointestinal: anaphylactic anemia, agranulocytosis, leukopenia, hemolytic anemia, thrombocytopenia
Hypersensitivity: purpura, photosensitivity, urticaria, necrotizing angiitis (vasculitis and cutaneous vasculitis), fever, respiratory distress including pneumonitis and pulmonary edema, anaphylactic reactions
Metabolic: hyperglycemia, glycosuria, hyperuricemia
Musculoskeletal/muscle spasm
Psychiatric/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

**Initial Therapy**
In the moderate hypertension Study V (mean SeDBP between 90 and 110 mmHg), the types and incidences of adverse events reported for patients treated with AVALIDE were similar to the adverse event profile in patients on initial irbesartan or HCTZ monotherapy. There were no reported events of syncope in the AVALIDE treatment group. In Study IV, there was one reported event in the HCTZ treatment group. The incidences of pre-specified adverse events on AVALIDE, irbesartan, and HCTZ, respectively, were: 0.9%, 0%, and 0% for hypotension; 3.0%, 3.8%, and 1.0% for dizziness; 5.5%, 3.8%, and 4.8% for headache; 1.2%, 0%, 0% for hypertension; 0.9%, 0%, and 0% for hypokalemia. The rates of discontinuation due to adverse events on AVALIDE, irbesartan alone, and HCTZ alone were 6.7%, 3.8%, and 4.8%.

In the severe hypertension (SeDBP ≥110 mmHg) Study VI, the overall pattern of adverse events consistently reported through 7 weeks of follow-up was similar in patients treated with AVALIDE as initial therapy and in patients treated with irbesartan as initial therapy. The incidences of the pre-specified adverse events on AVALIDE and irbesartan, respectively, were: 0% and 0% for syncope; 0.6% and 0% for hypotension; 3.6% and 4.0% for dizziness; 4.3% and 6.6% for headache; 0.2% and 0% for hypokalemia; and 0.6% and 0.4% for hypokalemia. The rates of discontinuation due to adverse events were 2.1% and 2.2%.

**Post-Marketing Experience**

The following adverse reactions have been identified during post-approval 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. Decisions to include these reactions in labeling are typically
based on one or more of the following factors: (1) seriousness of the reaction, (2) frequency of reporting, or (3) strength of causal connection to AVALIDE. The following have been very rarely reported with irbesartan and hydrochlorothiazide monotherapy: urticaria, jaundice, hepatitis, thrombocytopenia, and impaired renal function including renal failure. The following have been reported with irbesartan monotherapy: tinnitus, hyperkalemia, angioedema (involving swelling of the face, lips, pharynx, and/or tongue), and increased CPK. The following have been reported with hydrochlorothiazide monotherapy: secondary acute angle-closure glaucoma, acute myopia.

6.3 Laboratory Abnormalities

In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with administration of AVALIDE.

Creatinine, Blood Urea Nitrogen: Minor increases in blood urea nitrogen (BUN) or serum creatinine were observed in 2.3% and 1.1%, 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. These adverse effects are usually reversible. Therefore, monitor renal function and blood pressure periodically in patients receiving irbesartan and NSAID therapy.

Hydrochlorothiazide

Administration of a non-steroidal 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-hydrochlorothiazide) tablets 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.

7. Dual Blockade of the Renin-Angiotensin System (RAS)

Dual blockade of the RAS with angiotensin II receptor antagonists, ACE inhibitors, or aliskiren, and the angiotensin-converting enzyme (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.

7.3 Agents Increasing Serum Potassium

Coadministration of AVALIDE with other drugs that raise serum potassium levels may result in hyperkalemia, sometimes severe. Monitor serum potassium in such patients.

7.4 Antidiabetic Drugs (oral agents and insulin)

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

7.5 Cholestyramine and Colestipol Resins

Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Stagger the dosages of hydrochlorothiazide and the resin such that AVALIDE is administered at least 4 hours before or 4 to 6 hours after the administration of the resin.

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 hypoglycemia. Monitor electrolytes during concomitant use.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D

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, hypotension, renal failure, and death. When pregnancy is detected, discontinue AVALIDE as soon as possible. These adverse outcomes are usually associated with use of these drugs in the second and third trimester of pregnancy. 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. Appropriate management of maternal hypertension during pregnancy is important to optimize outcomes for both mother and fetus.

In the unusual case that there is no appropriate alternative to therapy with drugs affecting the renin-angiotensin system for a particular patient, apprise the mother of the potential risk to the fetus. Perform serial ultrasound examinations to assess the intraamniotic environment. If oligohydramnios is observed, discontinue AVALIDE, unless it is considered necessary to continue the drug therapy in order to provide benefit to the mother. Fetal testing should be appropriate, based on the maternal indications for drug therapy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury. Closely observe infants with histories of in utero exposure to AVALIDE for hypotension, oliguria, and hyperkalemia [see Use in Specific Populations (8.4)].

Ibersen crosses the placenta in rats and rabbits. In pregnant rats given ibersenaten at doses greater than the maximum recommended human dose (MRHD), fetuses showed increased incidences of renal pelvic cavitation, hydroureret and/or absence of renal papilla. Subcutaneous edema also occurred in fetuses at doses of about 4 times the MRHD (based on body surface area). These anomalies occurred when pregnant rats received ibersenaten through Day 20 of gestation but not when drug was stopped on gestation Day 15. The observed effects are believed to be late gestational effects of the drug. Pregnant rabbits given oral doses of ibersenaten equivalent to 1.5 times the MRHD experienced a high rate of maternal mortality and abortion. Surviving females had a slight increase in early abortions and a corresponding decrease in live fetuses [see Nonclinical Toxicology (13.2)].

Radioactivity was present in the rat and rabbit fetus during late gestation and in rat milk following oral doses of radiolabeled ibersenaten. When pregnant mice and rats were given hydrochlorothiazide at doses up to 3000 and 1000 mg/kg/day, respectively (about 600 and 400 times the MRHD) during their respective periods of major organogenesis, there was no evidence of fetal harm. A development toxicity study was performed in rats with doses of 50/50 mg/kg/day and 150/150 mg/kg/day ibersenaten-hydrochlorothiazide. Although the high dose combination appeared to be more toxic to the dam than either drug alone, there did not appear to be an increase in toxicity to the developing embryos.

8.3 Nursing Mothers

It is not known whether ibersenaten is excreted in human milk, but ibersenaten or some metabolite of ibersenaten is secreted at low concentration in the milk of lactating rats. 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.

8.4 Pediatric Use

Neonates with a history of in utero exposure to AVALIDE:

If oliguria or hypotension occurs, direct attention toward support of blood pressure and renal perfusion. Exchange transfusions or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal function.

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Of 1694 patients receiving AVALIDE in controlled clinical studies of hypertension, 264 (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)].

9. OVERDOSAGE

Ibersenaten

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

To obtain up-to-date information about the treatment of overdose, 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 overdose, consider the possibilities of multiple-drug interactions, drug-drug interactions, and unusual drug kinetics in the patient. Laboratory determinations of serum levels of ibersenaten are not widely available, and such determinations have, in any event, no established role in the management of ibersenaten overdose.

Acute oral toxicity studies with ibersenaten in mice and rats indicated acute lethal doses were in excess of 2000 mg/kg, about 25- and 50-fold the MRHD (300 mg) on a mg/m2 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 digitalis has also been administered, hypokalemia may accentuate cardiac arrhythmias. The degree to which hydrochlorothiazide is removed by hemodialysis has not been established. The oral LD50 of hydrochlorothiazide is greater than 10 g/kg in both mice and rats.

10. DESCRIPTION

IVALIDE (irbesartan-hydrochlorothiazide) tablets are a combination of an angiotensin II receptor antagonist (AT1 subtype), ibersenaten, and a thiazide diuretic, hydrochlorothiazide (HCTZ).

Irbesartan is a non-peptide compound, chemically described as a 2-butyl-3-[p-[1H-tetrazol-5-ylphenyl]-1,3-diazaspiro[4.4]non-1-en-4-one. Its empirical formula is C2HNO, and its structural formula is:

![Structural formula of irbesartan](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 sodium hydroxide solution.

Irbesartan is an orally active agent that does not require biotransformation into an active metabolite. Its empirical formula is C_{16}H_{17}N_{2}O_{5}S and its structural formula is:

\[ \text{H}_{2}\text{N} - \text{CH} - \text{CH} - \text{CH}_{2} \text{S} - \text{O} - \text{C} = \text{O} \]

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; 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.

Hydrochlorothiazide is metabolized via glucuronide conjugation and oxidation. Following 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 glucuronide.

In vitro studies of irbesartan oxidation by cytochrome P450 isoforms indicated irbesartan was oxidized primarily by CYP2C9. Metabolism by CYP3A4 was negligible. Irbesartan was neither metabolized by, nor did it substantially induce or inhibit, isoforms commonly associated with drug metabolism (1A1, 1A2, 2A6, 2B6, 2D6, 2E1). There was no induction of P450.

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

The combination of irbesartan and hydrochlorothiazide has not been evaluated in definitive clinical trials in hypertensive patients.

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.
mice for up to 2 years. For male and female rats, 500 mg/kg/day provided an average systemic exposure to irbesartan (AUC0–24 hours, 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.

Iburesartan 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), Iburesartan was negative in several tests for induction of chromosomal aberrations (in vivo—human lymphocyte assay; in vivo—mouse micronucleus study). Iburesartan had no adverse effects on fertility or mating of male or female rats at oral doses ≤850 mg/kg/day, the highest dose providing a systemic exposure to irbesartan (AUC0–24 hours, bound plus unbound) about 5 times that found in humans receiving the MRD 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. Two of these studies are included in the NTP database. 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 μM/L, 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.

13.2 Animal Toxicology and/or Pharmacology

Reproductive Toxicology Studies

When pregnant rats were treated with iburesartan from Day 0 to Day 20 of gestation (oral doses of 50, 180, and 650 mg/kg/day), increased incidences of renal pelvic cavitation, hydroureret, and/or absence of renal papilla were observed in fetuses at doses ≥50 mg/kg/day (approximately equivalent to the MRHD, 300 mg/day, on a body surface area basis). Subcutaneous edema was observed in fetuses at doses ≥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 iburesartan exposure (oral doses of 50, 150, and 450 mg/kg/day) was limited to gestation days 6 to 15, they appear to reflect late gestational effects of the drug. In pregnant rabbits, oral doses of 30 mg iburesartan/kg/day were associated with maternal mortality and abortion. Surviving females recovering the 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. Iburesartan was found to cross the placental barrier in rats and rabbits.

14 CLINICAL STUDIES

14.1 Iburesartan Monotherapy

The antihypertensive effects of iburesartan 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 iburesartan. These studies allowed a comparison of once- or twice-daily regimens at 150 mg hydrochlorothiazide. Study I was a factorial study that compared all combinations of iburesartan (37.5 mg, 100 mg, and 300 mg or placebo) and hydrochlorothiazide (6.25 mg, 12.5 mg, and 25 mg or placebo).

Study II compared the iburesartan-hydrochlorothiazide combinations of 75/12.5 mg and 150/25 mg to their individual components and placebo.

Study III investigated the ambulatory blood pressure responses to iburesartan-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 iburesartan (75 or 150 mg) in patients not controlled (SeSBP 9–120 mmHg) on hydrochlorothiazide (25 mg) alone. In Studies I–III, the addition of iburesartan 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 10/6 mmHg, similar to those achieved with the same monotherapy dose of iburesartan. The addition of hydrochlorothiazide to iburesartan 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), also similar to effects achieved with hydrochlorothiazide alone. Once-daily dosing with 150 mg iburesartan and 12.5 mg hydrochlorothiazide, or 300 mg iburesartan and 25 mg hydrochlorothiazide produced mean placebo-adjusted blood pressure reductions at trough (24 hours post-dosing) of about 13 to 15/7 to 9 mmHg, 14/9 to 12 mmHg, and 21 to 11/12 mmHg, respectively. Peak effects occurred at 3 to 6 hours, with the trough-to-peak ratios >65%.

In Study IV, the addition of iburesartan (75–150 mg) gave an additive effect (synergistic) at trough (24 hours post-dosing) of 11.7 mmHg.

Initial Therapy

Studies V and VI had no placebo group, so effects described below are not attributable to iburesartan or HCTZ.

Study V was conducted in patients with a mean baseline blood pressure of 162/98 mmHg and patients were randomized to be randomized to 1 of 3 drug regimens: irbesartan and hydrochlorothiazide, or irbesartan and enalapril, or irbesartan and placebo. Withdrawal rates were 3.8% on iburesartan, 4.8% on HCTZ, and 6% on placebo.

Study VI was conducted in patients with a mean baseline blood pressure of 172/113 mmHg and compared trough SeSBP at 5 weeks between the combination group (iburesartan and HCTZ 150/12.5 mg) and iburesartan (150 mg). These initial study regimens were increased at 2 weeks to AVALIDE 300/25 mg, iburesartan 300 mg, or to HCTZ 25 mg, respectively.

Mean reductions from baseline for SeSBP and SeSBP at trough were 14.6 mmHg and 27.1 mmHg for patients treated with AVALIDE, 11.6 mmHg and 22.1 mmHg for patients treated with iburesartan, 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 SeSBP was 5.0 mmHg lower (p=0.0016) compared to patients treated with iburesartan, 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 iburesartan, 4.8% on HCTZ, and 6% on placebo.

Study VII was conducted in patients with a mean baseline blood pressure of 172/113 mmHg and compared trough SeSBP at 5 weeks between the combination group (iburesartan and HCTZ 150/12.5 mg) and iburesartan (150 mg). These initial study regimens were increased at 1 week to AVALIDE 300/25 mg or to iburesartan 300 mg, respectively. At 5 weeks, mean reductions from baseline for SeSBP and SeSBP 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 iburesartan, respectively. The mean SeSBP 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 iburesartan. Patients treated with AVALIDE achieved more rapid blood pressure control with significantly lower SeSBP 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 iburesartan and 3.1% 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 iburesartan. 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-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/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 Bottles of 90</td>
<td>0024-5855-30 0024-5855-90</td>
</tr>
<tr>
<td>300 mg/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 Bottles of 90</td>
<td>0024-5856-30 0024-5856-90</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, 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 myopia and secondary angle-closure glaucoma
Advise patients to discontinue AVALIDE and seek immediate medical attention if they experience symptoms of Acute Myopia or Secondary Angle-Closure Glaucoma [see Warnings and Precautions (5.8)].