AVAPRO® (irbesartan) tablets, for oral use

Initial U.S. Approval: 1997

**INDICATIONS AND USAGE**

AVAPRO is an angiotensin II receptor blocker (ARB) indicated for:

- Treatment of hypertension, to lower blood pressure. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions. (1.1)
- Treatment of diabetic nephropathy in hypertensive patients with type 2 diabetes, an elevated serum creatinine, and proteinuria. (1.2)

**DOSAGE AND ADMINISTRATION**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension (2.2)</td>
<td>150 to 300 mg once daily</td>
</tr>
<tr>
<td>Diabetic Nephropathy (2.3)</td>
<td>300 mg once daily</td>
</tr>
</tbody>
</table>

**WARNING: FETAL TOXICITY**

When pregnancy is detected, discontinue AVAPRO 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)

**CONTRAINDICATIONS**

- Hypersensitivity to any component of this product. (4)
- Co-administration with aliskiren in patients with diabetes. (4)

**WARNINGS AND PRECAUTIONS**

Hypotension: Correct volume or salt depletion prior to administration. (5.2)

Monitor renal function and serum potassium. (5.3)

**ADVERSE REACTIONS**

- Nephropathy in type 2 diabetic patients: The most common adverse reactions which were more frequent than placebo were hyperkalemia, dizziness, orthostatic dizziness, and orthostatic hypotension. (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.

**DRUG INTERACTIONS**

- Lithium: Risk of lithium toxicity (7)
- Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) and COX-2 inhibitors: Increased risk of renal impairment. Reduced antihypertensive effects. (7)
- Dual blockade of the renin-angiotensin system: Increased risk of renal impairment, hypotension, and hyperkalemia. (7)

**USE IN SPECIFIC POPULATIONS**

- Nursing Mothers: Potential for adverse effects in infant. (8.3)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 02/2016
hypoplasia, anuria, hypotension, renal failure, and death. When pregnancy is detected, hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull

5.2 Hypotension in Volume- or Salt-Depleted Patients

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

Do not co-administer aliskiren with AVAPRO in patients with diabetes.

5 Warnings and Precautions

5.1 Fetal Toxicity

Use of drugs that affect 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 AVAPRO as soon as possible [see Use in Specific Populations (8.1)].

5.2 Hypotension in Volume- or Salt-Depleted Patients

In patients with an activated renin-angiotensin system, such as volume- or salt-depleted patients (e.g., those being treated with high doses of diuretics), symptomatic hypotension may occur after initial normalization of treatment with AVAPRO. Correct volume or salt depletion prior to administration of AVAPRO or use a lower starting dose [see Dosage and Administration (2.4)].

5.3 Impaired Renal Function

Changes in renal function including acute renal failure can be caused by drugs that inhibit the renin-angiotensin system. Patients whose renal function may depend in part on the activity of the renin-angiotensin system (e.g., patients with renal artery stenosis, chronic kidney disease, severe hepatorenal syndrome (Irish type), or tomato syndrome may be at particular risk of developing acute renal failure or death on AVAPRO. Monitor renal function periodically in patients receiving AVAPRO and In general, avoid combined use of RAS inhibitors. 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 intra-amniotic environment. If oligohydramnios is observed, discontinue AVAPRO, unless it is considered to be a necessary treatment for the mother, and the patient is otherwise stable. If premature labor occurs or if the mother develops complications of prolonged uterine activity, deliver the neonate. The neonate, born to mothers who received angiotensin-converting enzyme (ACE) inhibitors in the second and third trimesters of pregnancy, should be observed for hypotension, oliguria, and hyperkalemia. If the neonate experiences respiratory distress, treat with positive pressure ventilation and/or respiratory support as indicated.

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 AVAPRO as soon as possible. These adverse outcomes are usually associated with the use of drugs that act on the renin-angiotensin system near or at the time of delivery. Infants born to mothers who received irbesartan in the second and third trimesters of pregnancy may present with hypotension and oliguria, which may respond to volume expansion and diuresis with a solution containing sodium and chloride. If not responsive to these measures, direct medical attention at once. Observe infants born to mothers who received irbesartan near or at delivery for hypotension, oliguria, and hyperkalemia. If oliguria occurs, support blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function.

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

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www.ibrinedicare.com
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.

Avapro is available for oral administration in unscored tablets containing 75 mg, 150 mg, or 300 mg of irbesartan. Inactive ingredients include: lactose, microcrystalline cellulose, pregelatinized starch, croscarmellose sodium, poloxamer 188, silicon dioxide, and magnesium stearate.

12.1 Mechanism of Action
Irbesartan is a non-peptide compound, chemically described as a 2-butyl-3-[p-[o-(1H-tetrazol-5-yl)phenyl]benzyl]-1,3-diazaspiro[4.4]non-1-en-4-one. Its empirical formula is C28H31N3O, and the structural formula:

\[
\text{C}-\text{N} - \text{N} - \text{C} - \text{N} - \text{H} - \text{CH}_3
\]

Irbesartan is an orally active agent that does not require biotransformation into an active metabolite. It is eliminated primarily by the kidneys. Irbesartan is excreted in the milk of lactating rats.

12.2 Pharmacodynamics

In healthy subjects, single oral doses of up to 300 mg produced dose-dependent inhibition of the pressor effect of AngII infusions. Inhibition was complete (100%) 4 hours following oral doses of 150 mg or 300 mg and partial inhibition was sustained for 24 hours (80% 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- to 2-fold rise in AngII plasma concentration and a 2- to 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.

12.3 Pharmacokinetics

Absorption
The oral absorption of irbesartan is rapid and complete with an average absolute bioavailability of 60% to 80%. Following oral administration of AVAPRO, 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.

Distribution
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 to 93 liters.

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

10 OVERDOSAGE
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 acute oral toxicity studies with irbesartan in mice and rats indicated acute lethal doses in excess of 2000 mg/kg, about 25- and 50-fold the MRHD (300 mg) on a mg/m² basis, respectively.

11 DESCRIPTION

AVAPRO (irbesartan) is an angiotensin II receptor (AT₁ subtype) antagonist. Irbesartan is a non-peptide compound, chemically described as a 2-buty-3-[p-[o-(1H-tetrazol-5-yl)phenyl]benzyl]-1,3-diazaspiro[4.4]non-1-en-4-one. Its empirical formula is C28H31N3O, and the structural formula:

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Elimination
Total plasma and renal clearances are in the range of 157 to 176 mL/min and 3.0 to 3.5 mL/min, respectively. The terminal elimination half-life of irbesartan averages 11 to 15 hours, but steady-state concentrations are achieved within 3 days. Limited accumulations of irbesartan (<20%) is observed in plasma upon repeated once-daily dosing and is not clinically relevant.

Metabolism
Irbesartan is an orally active agent that does not require biotransformation into an active form. Irbesartan is metabolized via glucuronide conjugation and oxidation. Following oral or intravenous administration of \(^{14}\text{C}\)-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.

In vitro studies indicate irbesartan is oxidized primarily by CYP2C9; metabolism by CYP3A4 is negligible.

Excretion
Irbesartan and its metabolites are excreted by both biliary and renal routes. Following either oral or intravenous administration of \(^{14}\text{C}\)-labeled irbesartan, about 20% of radioactivity is recovered in the urine and the remainder in the feces, as irbesartan or irbesartan glucuronide.

Specific Populations

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
No evidence of carcinogenicity was observed when irbesartan was administered at dosages of up to 500/1000 mg/kg/day (males/females, respectively) in rats and 1000 mg/kg/day in mice for up to 2 years. For male and female rats, 500 mg/kg/day provided a marginal systemic exposure to irbesartan (AUC<sub>0–24 h</sub> of 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 indicated 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 lymphoma assay, V79 mammalian-cell forward 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 of ≤850 mg/kg/day, the highest dose providing a systemic exposure to irbesartan (AUC<sub>0–24 h</sub> of bound plus unbound) about 5 times that found in humans receiving the MRD of 300 mg/day.

13.2 Animal Toxicology and/or Pharmacology

In a repeat-dose study in rats (Day 0 to Day 20 of gestation) (oral doses of 50 mg/kg/day, 180 mg/kg/day, and 650 mg/kg/day), increased incidences of renal pelvic caviation, hydropureter and/or absence of renal papilla were observed in fetuses at doses 200 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 ≥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 to 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.

14 CLINICAL STUDIES

14.1 Hypertension

The antihypertensive effects of AVAPRO were examined in 7 placebo-controlled 8- to 12-week trials in patients with baseline diastolic blood pressures (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 comparison of once- or twice-daily regimens at 150 mg/day, comparisons of peak and trough effects, and comparisons of response by sex, age, and race. Two of the seven placebo-controlled trials identified above 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 (1–900 mg) and 611 patients randomized to placebo. Once-daily doses of 150 mg and 300 mg provided statistically and clinically significant decreases in systolic and diastolic blood pressure with trough (24 hours post-dose) effects after 6 to 12 weeks of treatment compared to placebo, of about 8–10/6–8 mmHg and 8–12/8–10 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.

Once-daily administration of therapeutic doses of irbesartan gave peak effects at around 3 to 6 hours and, in one ambulatory blood pressure monitoring study, 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% to 70%. 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.

In controlled trials, the addition of irbesartan to hydrochlorothiazide doses of 6.25 mg, 12.5 mg, or 25 mg produced further dose-related reductions in blood pressure similar to those achieved with the same monotherapy dose of irbesartan. HCTZ also had an approximately additive effect. Analysis of age, sex, 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). The effect of irbesartan is apparent after the first dose, and it is close to its full observed effect at 2 weeks. At the end of an 8-week exposure, about 2/3 of the antihypertensive effect was still present one 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 Nephropathy in Type 2 Diabetic Patients

The Irbesartan Diabetic Nephropathy Trial (IDNT) was a randomized, placebo- and active-controlled, double-blind, multicenter study conducted worldwide in 1715 patients with type 2 diabetes, hypertension (SeDBP ≥85 mmHg), and nephropathy (serum creatinine 1.0 to 3.0 mg/dL in females or 1.2 to 3.0 mg/dL in males and proteinuria ≥300 mg/dL). Patients were randomized to receive AVAPRO 75 mg, amlodipine 2.5 mg, or matching placebo once-daily. Patients were titrated to a maintenance dose of AVAPRO 300 mg, or amlodipine 10 mg, as tolerated. Additional antihypertensive agents (excluding ACE inhibitors, angiotensin II receptor antagonists and calcium channel blockers) were added as needed to achieve blood pressure goal (<135/85 or 10 mmHg reduction in systolic blood pressure if higher than 160 mmHg) for patients in all groups. The study population was 66.5% male, 72.9% below 65 years of age, and 72% White (Asian/Pacific Islander 5.0%, Black 13.3%, Hispanic 4.8%). The mean baseline seated systolic and diastolic blood pressures were 159 mmHg and 87 mmHg, respectively. The patients entered the trial with a mean serum creatinine of 1.7 mg/dL and mean proteinuria of 4144 mg/day.

The mean blood pressure achieved was 142/77 mmHg for AVAPRO, 142/76 mmHg for amlodipine, and 145/79 mmHg for placebo. Overall, 83.0% of patients received the target dose of irbesartan more than 50% of the time. Patients were followed for a mean duration of 2.6 years. The primary composite endpoint was the time to occurrence of any one of the following events: doubling of baseline serum creatinine, end-stage renal disease (ESRD; defined by serum creatinine ≥2.6 mg/dL, dialysis, or renal transplantation), or death. Treatment with AVAPRO resulted in a 20% risk reduction versus placebo (p=0.0234) (see Table 3 and Table 1). Treatment with AVAPRO also reduced the occurrence of sustained doubling of serum creatinine as a separate endpoint (33%), but had no significant effect on ESRD alone and no effect on overall mortality (see Table 1).

Table 1: IDNT: Components of Primary Composite Endpoint

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Placebo</th>
<th>AVAPRO N=579 (%)</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Composite Endpoint</td>
<td>32.6</td>
<td>39.0</td>
<td>0.80</td>
<td>0.66–0.97 (p=0.0234)</td>
</tr>
<tr>
<td>Comparison With Placebo</td>
<td>41.1</td>
<td>0.77</td>
<td>0.63–0.93</td>
<td></td>
</tr>
<tr>
<td>Comparison With Amlodipine</td>
<td>N=567 (%)</td>
<td>Hazard Ratio</td>
<td>95% CI</td>
<td></td>
</tr>
<tr>
<td>Primary Composite Endpoint</td>
<td>16.9</td>
<td>23.7</td>
<td>0.67</td>
<td>0.52–0.87</td>
</tr>
<tr>
<td>Comparison With Placebo</td>
<td>5.4</td>
<td>0.63</td>
<td>0.49–0.81</td>
<td></td>
</tr>
<tr>
<td>Comparison With Amlodipine</td>
<td>N=567 (%)</td>
<td>Hazard Ratio</td>
<td>95% CI</td>
<td></td>
</tr>
<tr>
<td>Primary Composite Endpoint</td>
<td>14.2</td>
<td>17.8</td>
<td>0.77</td>
<td>0.57–1.03</td>
</tr>
<tr>
<td>Comparison With Placebo</td>
<td>8.3</td>
<td>0.77</td>
<td>0.57–1.03</td>
<td></td>
</tr>
<tr>
<td>Comparison With Amlodipine</td>
<td>N=567 (%)</td>
<td>Hazard Ratio</td>
<td>95% CI</td>
<td></td>
</tr>
<tr>
<td>Primary Composite Endpoint</td>
<td>15.0</td>
<td>16.3</td>
<td>0.92</td>
<td>0.69–1.23</td>
</tr>
<tr>
<td>Comparison With Placebo</td>
<td>14.6</td>
<td>1.04</td>
<td>0.77–1.40</td>
<td></td>
</tr>
</tbody>
</table>

Table 2: IDNT: Primary Efficacy Outcome Within Subgroups

<table>
<thead>
<tr>
<th>Factors</th>
<th>AVAPRO N=579 (%)</th>
<th>Placebo N=569 (%)</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Male</td>
<td>27.5</td>
<td>36.7</td>
<td>0.68</td>
</tr>
<tr>
<td>Female</td>
<td>42.3</td>
<td>44.6</td>
<td>0.98</td>
<td>0.72–1.34</td>
</tr>
<tr>
<td>Race</td>
<td>White</td>
<td>29.5</td>
<td>37.3</td>
<td>0.75</td>
</tr>
<tr>
<td>Non-White</td>
<td>42.6</td>
<td>43.5</td>
<td>0.95</td>
<td>0.67–1.34</td>
</tr>
</tbody>
</table>
### Table 2: IDNT: Primary Efficacy Outcome Within Subgroups (continued)

<table>
<thead>
<tr>
<th>Baseline Factors</th>
<th>AVAPRO N=579 (%)</th>
<th>Comparison With Placebo</th>
<th>Placebo N=569 (%)</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65</td>
<td>31.8</td>
<td>39.9</td>
<td>0.77</td>
<td>0.62–0.97</td>
<td></td>
</tr>
<tr>
<td>≥65</td>
<td>35.1</td>
<td>36.8</td>
<td>0.88</td>
<td>0.61–1.29</td>
<td></td>
</tr>
</tbody>
</table>

### 16 HOW SUPPLIED/STORAGE AND HANDLING

AVAPRO (irbesartan) is available as white to off-white biconvex oval tablets, debossed with a heart shape on one side and a code on the other (see Table below). Unit-of-use bottles contain 30 or 90 tablets as follows:

<table>
<thead>
<tr>
<th>Strength</th>
<th>Debossing</th>
<th>Bottle of 30</th>
<th>Bottle of 90</th>
</tr>
</thead>
<tbody>
<tr>
<td>75 mg</td>
<td>2871</td>
<td>0024-5850-30</td>
<td>0024-5850-90</td>
</tr>
<tr>
<td>150 mg</td>
<td>2872</td>
<td>0024-5851-30</td>
<td>0024-5851-90</td>
</tr>
<tr>
<td>300 mg</td>
<td>2873</td>
<td>0024-5852-30</td>
<td>0024-5852-90</td>
</tr>
</tbody>
</table>

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**

Advise female patients of childbearing age about the consequences of exposure to AVAPRO during pregnancy. Discuss treatment options with women planning to become pregnant. Patients should be asked to report pregnancies to their physicians as soon as possible.

**Potassium Supplements**

Advise patients receiving AVAPRO not to use potassium supplements or salt substitutes containing potassium without consulting their healthcare provider [see Drug Interactions (7.1)].