**AVAPRO**

**HIGHLIGHTS OF PRESCRIBING INFORMATION**

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

**AVAPRO® (irbesartan) tablets, for oral use**

Initial U.S. Approval: 1997

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**WARNING: FETAL TOXICITY**

See full prescribing information for complete boxed warning.

- 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)

**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)

**DOSE 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>

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*Sections or subsections omitted from the full prescribing information are not listed*
AVAPRO may be used alone or in combination with other antihypertensive agents.

1.2 Nephropathy in Type 2 Diabetic Patients

AVAPRO is indicated for the treatment of diabetic nephropathy in patients with type 2 diabetes and hypertension, an elevated serum creatinine, and proteinuria (>300 mg/day). In this population, AVAPRO reduces the rate of progression of nephropathy as measured by the occurrence of doubling of serum creatinine or end-stage renal disease (need for dialysis or renal transplantation) [see Clinical Studies (14.2)].

2 DOSAGE AND ADMINISTRATION

2.1 General Considerations

AVAPRO may be administered with other antihypertensive agents and with or without food.

2.2 Hypertension

The recommended initial dose of AVAPRO is 150 mg once daily. The dosage can be increased to a maximum dose of 300 mg once daily as needed to control blood pressure [see Clinical Studies (14.1)].

2.3 Nephropathy in Type 2 Diabetic Patients

The recommended dose is 300 mg once daily [see Clinical Studies (14.2)].

2.4 Dose Adjustment in Volume and Salt-Depleted Patients

The recommended initial dose is 75 mg once daily in patients with depletion of intravascular volume or [e.g., patients treated vigorously with diuretics or on hemodialysis] [see Warnings and Precautions (5.2)].

3 DOSE FORMS AND STRENGTHS

AVAPRO 75 mg is a white to off-white, biconvex oval, film-coated, tablet debossed with a heart on one side and “2B7” on the other.

AVAPRO 150 mg is a white to off-white, biconvex oval, film-coated, tablet debossed with a heart on one side and “2B7Z” on the other.

AVAPRO 300 mg is a white to off-white, biconvex oval, film-coated, tablet debossed with a heart on one side and “2B7Z” on the other.

4 CONTRAINDICATIONS

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

Do not coadminister aliskiren with AVAPRO in patients with diabetes.

5 WARNINGS AND PRECAUTIONS

5.1 Fetal Toxicity

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 [see Use in Specific Populations (8.4)].

5.2 Hypotension in Volume or Salt-Depleted Patients

In patients with an associated 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 initiation 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 heart failure, or volume depletion) may be at particular risk of developing acute renal failure or death on AVAPRO. Monitor renal function periodically in these patients. Consider withholding or discontinuing therapy in patients who develop a clinically significant decrease in renal function on AVAPRO [see Drug Interactions (7.3)].

6 ADVERSE REACTIONS

The following important adverse reactions are described elsewhere in the labeling:

• Hypotension in Volume or Salt-Depleted Patients [see Warnings and Precautions (5.2)]
• Impaired Renal Function [see Warnings and Precautions (5.3)]

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.

Hypertension

AVAPRO has been evaluated for safety in more than 4030 patients with hypertension and about 5000 subjects overall. This experience includes 1303 patients treated for over 6 months and 407 patients for 1 year or more. In placebo-controlled clinical trials, the following adverse reactions were reported in at least 1% of patients treated with AVAPRO (n=1665) and at a higher incidence versus placebo (n=641), excluding those too general to be informative and those not reasonably associated with the use of drug because they were associated with noncompliance or were not at all related to the condition being treated or were not at all related to the activity of the renin-angiotensin system.

Table: Absolute Incidence of Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>AVAPRO 150 mg</th>
<th>AVAPRO 300 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bradycardia</td>
<td>5.5%</td>
<td>2.3%</td>
<td>3.1%</td>
</tr>
<tr>
<td>Hypotension</td>
<td>6.1%</td>
<td>3.7%</td>
<td>1.5%</td>
</tr>
<tr>
<td>Oliguria</td>
<td>4.6%</td>
<td>4.4%</td>
<td>0.4%</td>
</tr>
</tbody>
</table>

7 DRUG INTERACTIONS

7.1 Agents Increasing Serum Potassium

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

7.2 Lithium

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

7.3 Dual Blockade of Renin-Angiotensin System (RAS) Inhibitors

In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, coadministration of NSAIDs, including selective COX-2 inhibitors, with angiotensin II receptor antagonists (including irbesartan) may result in deterioration of renal function, including possible acute renal failure. Therefore, use irbesartan in these patients only if the benefit outweighs the risk and monitor renal function periodically in patients receiving irbesartan and NSAID therapy.

The antihypertensive effect of angiotensin II receptor antagonists, including irbesartan, may be attenuated by NSAIDs including selective COX-2 inhibitors.

7.4 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 hyperkalemia, hyperkalemia, and changes in renal function (including acute renal failure) compared to monotherapy. Most patients receiving the combination of two RAS inhibitors do not obtain any additional benefit compared to monotherapy. In general, avoid combined use of RAS inhibitors. Closely monitor blood pressure, renal function and electrolytes in patients on AVAPRO and other agents that affect the RAS.

Avoid concomitant use of AVAPRO in patients with diabetes. Avoid use of aliskiren with AVAPRO in patients with renal impairment (GFR <60 mL/min).
Ibopenatran 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 7.4. Ibopenatran is slightly soluble in alcohol and methylene chloride and practically insoluble in water. Avalpro is available for oral administration in unscored, film-coated tablets containing 75 mg, 150 mg, or 300 mg of ibopenatran. Inactive ingredients include: camphora wax, crocetin cellulose, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, silicon dioxide, and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Angiotensin II is a potent vasoconstrictor formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzyme (ACE, kininase II). Angiotensin II is the primary vasopressive hormone of the renin-angiotensin system, and an important component in the pathophysiology of hypertension. It also stimulates aldosterone secretion by the adrenal cortex. Ibopenatran blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively binding to the AT₁ receptor. Angiotensin II receptor found in many tissues (e.g., vascular smooth muscle, adrenal gland). There is also an AT₂ receptor in many tissues, but it is not involved in cardiovascular homeostasis. Ibopenatran is a specific competitive antagonist of AT₁ receptors with a much greater affinity (more than 8500-fold) for the AT₁ receptor than for the AT₂ receptor and no agonist activity. Blockade of the AT₁ receptor removes the negative feedback of angiotensin II on renin secretion, but the resulting increased plasma renin activity and circulating angiotensin II do not overcome the effects of ibopenatran on blood pressure.

Ibopenatran does not inhibit ACE or renin or affect other hormone receptors or ion channels known to be involved in the cardiovascular regulation of blood pressure and sodium homeostasis.

12.2 Pharmacodynamics

In healthy subjects, single oral ibopenatran doses of up to 300 mg produced dose-dependent inhibition of the preosor effect of angiotensin II infusions. Inhibition was complete (100%) 4 hours following oral doses of 150 mg or 300 mg and partial inhibition was sustained for 24 hours (40% and 300 mg and 150 mg, respectively).

In hypertensive patients, angiotensin II receptor inhibition following chronic administration of ibopenatran causes a 1.5-fold to 2-fold rise in angiotensin II plasma concentration and a 2-fold to 3-fold increase in plasma renin levels. Aldosterone plasma concentrations generally decline following ibopenatran administration, but there were no clinically important effects on total tryglolycerides, total cholesterol, LDL-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 ibopenatran is rapid and complete with an average absolute bioavailability of 60% to 80%. Following oral administration of Avalpro, peak plasma concentrations of ibopenatran are attained at 1.5 to 2 hours after dosing. Food does not affect the bioavailability of ibopenatran.

Ibopenatran exhibits linear pharmacokinetics over the therapeutic dose range.

Distribution

Ibopenatran 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.

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

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 ibopenatran averages 11 to 15 hours. Steady-state concentrations are achieved within 3 days. Limited accumulation of ibopenatran (<20%) is observed in plasma upon repeated once-daily dosing and is not clinically relevant.

Metabolism

Ibopenatran is an orally active agent that does not require biotransformation into an active form. Ibopenatran is metabolized via glucuronide conjugation and oxidation. Following oral or intravenous administration of 14C-labeled ibopenatran, more than 80% of the circulating plasma radioactivity is attributable to unchanged ibopenatran. The primary circulating metabolite is the inactive ibopenatran glucuronide conjugate (approximately 6%). The remaining oxidative metabolites do not add appreciably to ibopenatran's pharmacologic activity.

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

Excretion

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

Specific Populations

Sex

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

Geriatrics

In elderly subjects (age 65–80 years), ibopenatran elimination half-life is not significantly altered, but AUC and Cₘax values are about 20% to 50% greater than those of young subjects (age 18–40 years). No dosage adjustment is necessary in the elderly.

Race/ethnicity

In healthy black subjects, ibopenatran AUC values are approximately 25% greater than whites; there is no difference in Cₘax values.

Renal impairment

The pharmacokinetics of ibopenatran is not altered in patients with renal impairment or in patients on hemodialysis. Ibopenatran 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) and Dosage and Administration (2.4)).

Hepatic insufficiency

The pharmacokinetics of ibopenatran following repeated oral administration are not significantly affected in patients with mild to moderate hepatic insufficiency.

Drug–drug interactions

In vitro studies show significant inhibition of the formation of oxidized ibopenatran metabolites with the known cytochrome P450 substrates/inhibitors sulfinpyrazone, tolbutamide and nifedipine. However, in clinical studies the consequences of concomitant ibopenatran on the pharmacodynamics of warfarin were negligible. Based on in vivo data, no interaction would be expected with drugs whose metabolism is dependent upon cytochrome P450 isoenzymes 1A1, 1A2, 2A6, 2C8, 2C9, 2E1, or 3A4.

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence of carcinogenicity was observed when ibopenatran 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 an average systemic exposure to ibopenatran (AUC₀–24 hour bound plus unbound) about 3 and 11 times, respectively, the average systemic exposure in humans receiving the maximum recommended dose (MRD) of 300 mg/ibopenatran/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 ibopenatran about 3 and 5 times, respectively, the human exposure at 300 mg/day.

Ibopenatran 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). Ibopenatran was negative in several tests for induction of chromosomal aberrations (in vivo—human lymphocyte assay, in vivo—mouse micronucleus study).

Ibopenatran had no adverse effects on fertility or mating of male or female rats at oral doses ≤550 mg/kg/day, the highest dose providing a systemic exposure to ibopenatran (AUC₀–24 hour 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 pregnant rats that were treated with ibopenatran from Day 9 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 cavitation, hydropyocoele and/or absence of renal papilla were observed in fetuses at dosages ≥50 mg/kg/day (approximately equivalent to the maximum recommended human dose [MRHD], 300 mg/day, on a body surface area basis). Subcutaneous edema was observed in fetuses at dosages ≥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 ibopenatran 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 ibopenatran/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. Ibopenatran was found to cross the placental barrier in rats and rabbits.

14 CLINICAL STUDIES

14.1 Hypertension

The antihypertensive effects of Avalpro were examined in 7 placebo-controlled B-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 ibopenatran. 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 ibopenatran and hydrochlorothiazide in combination.

The 7 studies of ibopenatran monotherapy included a total of 1915 patients randomized to ibopenatran (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/peak percentage decreases after 6 to 12 weeks of treatment compared to placebo, of about 8–10/5–6 mmHg and 8–12/5–8 mmHg, respectively. No further increase in effect was seen at dosages greater than 300 mg. The dose-response relationships for effects on systolic and diastolic pressure are shown in Figures 1 and 2.

Figure 1. Placebo-subtracted reduction in trough SBP/DBP, integrated analysis

Figure 2. Placebo-subtracted reduction in trough SBP/DBP, integrated analysis
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% and 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 (SeSBP >135 mmHg or 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/day). 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 4.5%). 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 ≥6 mg/dL, dialysis, or renal transplantation), or death. Treatment with AVAPRO resulted in a 20% risk reduction versus placebo (p=0.0234) (see Figure 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).

Figure 3: IDNT: Kaplan-Meier Estimates of Primary Endpoint (Doubling of Serum Creatinine, End-Stage Renal Disease or All-Cause Mortality)

The percentages of patients experiencing an event during the course of the study can be seen in Table 1 below:

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>AVAPRO Placebo</th>
<th>Hazard Ratio 95% CI</th>
<th>Amlodipine Placebo</th>
<th>Hazard Ratio 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Composite Endpoint</td>
<td>32.6</td>
<td>0.80</td>
<td>0.66–0.97 (p=0.0234)</td>
<td>41.1</td>
</tr>
<tr>
<td>Breakdown of first occurring event contributing to primary endpoint</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2× creatinine</td>
<td>14.2</td>
<td>19.5</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>ESRD</td>
<td>7.4</td>
<td>8.3</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Death</td>
<td>11.1</td>
<td>11.2</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Incidence of total events over entire period of follow-up</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2× creatinine</td>
<td>16.9</td>
<td>23.7</td>
<td>0.67</td>
<td>0.52–0.87</td>
</tr>
</tbody>
</table>

The secondary endpoint of the study was a composite of cardiovascular mortality and morbidity (myocardial infarction, hospitalization for heart failure, stroke with permanent neurological deficit, amputation). There were no statistically significant differences among treatment groups in these endpoints. Compared with placebo, AVAPRO significantly reduced proteinuria by about 27%, an effect that was evident within 3 months of starting therapy. AVAPRO significantly reduced the rate of loss of renal function (glomerular filtration rate), as measured by the reciprocal of the serum creatinine concentration, by 18.2%.

Table 2 presents results for demographic subgroups. Subgroup analyses are difficult to interpret, and it is not known whether these observations represent true differences or chance effects. For the primary endpoint, AVAPRO’s favorable effects were seen in patients also taking other antihypertensive medications (angiotensin II receptor antagonists, angiotensin-converting-enzyme inhibitors, and calcium channel blockers were not allowed), oral hypoglycemic agents, and lipid-lowering agents.

<table>
<thead>
<tr>
<th>Table 2: IDNT: Primary Efficacy Outcome Within Subgroups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline Factors</td>
</tr>
<tr>
<td>------------------</td>
</tr>
<tr>
<td>Sex</td>
</tr>
<tr>
<td>Race</td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
</tbody>
</table>

16 HOW SUPPLIED/STORAGE AND HANDLING

AVAPRO (irbesartan) is available as white to off-white, biconvex oval, film-coated 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 film-coated tablets as follows:

- 75 mg
- 150 mg
- 300 mg

Bottle of 30: 0024-5851-30
Bottle of 90: 0024-5850-90
Bottle of 180: 0024-5852-30

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)].

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