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® (irbesartan) tablets, for oral use

Initial U.S. Approval: 1997

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>

DOSE FORMS AND STRENGTHS

- Tablets: 75 mg, 150 mg, 300 mg (3)

CONTRAINDICATIONS

- Hypersensitivity to any component of this product. (4)
- Coadministration 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

- Lithium: Risk of lithium toxicity. (7)
- Non-Steroidal Anti-inflammatory Drugs (NSAIDs) and COX-2 inhibitors: Increased risk of renal impairment. (7)

DRUG INTERACTIONS

- 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 infants. (8.3)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 07/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

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FULL PRESCRIBING INFORMATION

WARNING: FETAL TOXICITY

- When pregnancy is detected, discontinue AVAPRO as soon as possible.
- Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus [see Warnings and Precautions (5.1)]

1 INDICATIONS AND USAGE

1.1 Hypertension

AVAPRO® is indicated for the treatment of hypertension, to lower blood pressure. Lowering blood pressure lowers the risk of fatal and nonfatal cardiovascular (CV) events, primarily strokes and myocardial infarction. These benefits have been seen in controlled trials of antihypertensive drugs from a wide variety of pharmacologic classes including this drug.

Control of high blood pressure should be part of comprehensive cardiovascular risk management, including, as appropriate, lipid control, diabetes management, antithrombotic therapy, smoking cessation, exercise, and limited sodium intake. Many patients will require more than 1 drug to achieve blood pressure goals. For specific advice on goals and management, see published guidelines, such as those of the National High Blood Pressure Education Program’s Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC). Numerous antihypertensive drugs, from a variety of pharmacologic classes and with different mechanisms of action, have been shown in randomized controlled trials to reduce cardiovascular morbidity and mortality, and it can be concluded that it is blood pressure reduction, and not some other pharmacologic property of the drugs, that is largely responsible for those benefits. The largest and most consistent cardiovascular outcome benefit has been a reduction in the risk of stroke, but reductions in myocardial infarction and cardiovascular mortality also have been seen regularly. Elevated systolic or diastolic pressure causes increased cardiovascular risk, and the absolute risk increase per mm Hg is greater at higher blood pressures, so that even modest reductions of severe hypertension can provide substantial benefit. Relative risk reduction from blood pressure reduction is similar across populations with varying absolute risk, so the absolute benefit is greater in patients who are at higher risk independent of their hypertension (for example, patients with diabetes or hyperlipidemia), and such patients would be expected to benefit from more aggressive treatment to a lower blood pressure goal. Some antihypertensive drugs have smaller blood pressure effects as monotherapy in black patients, and many antihypertensive drugs have additional approved indications and effects (e.g., on angina, heart failure, or diabetic kidney disease). These considerations may guide selection of therapy.
AVAPRO may be coadministered 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 450 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 dehydration or with intravascular volume or salt depletion (e.g., patients treated vigorously with diuretics or on hemodialysis) [see Warnings and Precautions (5.2)].

3 DOSAGE FORMS AND STRENGTHS
AVAPRO 75 mg is a white to off-white biconvex oval tablet debossed with a heart on one side and “2871” on the other.

AVAPRO 150 mg is a white to off-white biconvex oval tablet debossed with a heart on one side and “2872” on the other.

AVAPRO 300 mg is a white to off-white biconvex oval tablet debossed with a heart on one side and “2873” 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 Pediatrie 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 mortality. Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, renal dysfunction, hypotension, 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), symtomatic hypotension may occur after initialization 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 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 is not always representative of rates observed in clinical practice. However, adverse reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate reliably their frequency or to establish a causal relationship to drug exposure. The following adverse events were considered by the investigator to be drug related.

Hypertension
AVAPRO has been evaluated for safety in more than 4300 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=1965) and at a higher incidence versus placebo (n=461), excluding those too general to be informative and those not reasonably associated with the use of drug because they were associated with concomitant administration being treated as common in the treated population: include: diarrhea (3% vs 2%), dyspepsia/heartburn (2% vs 1%), and fatigue (4% vs 3%).

Infrequent adverse effects on the nursing infant, discontinue nursing or discontinue AVAPRO.

7.1 Agents Increasing Serum Potassium
Coadministration of AVAPRO with other drugs that raise serum potassium levels may result in hyperkalemia, some adverse effects on the nursing infant, discontinue nursing or discontinue AVAPRO.

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

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

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 mortality. 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 use of these drugs in the second and third trimesters 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 intra-amniotic environment. If oligohydramnios is observed, discontinue AVAPRO, unless it is considered lifesaving for the mother. Fetal testing may be appropriate, based on the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury. Closely observe infants of mothers who received AVAPRO in pregnancy for hypotension, oliguria, and hyperkalemia [see Use in Specific Populations (8.4)].

Infants cross the placenta in rabbits and rabbits. In pregnant rats given ibesartan at doses greater than the maximum recommended human dose (MRHD), fetuses showed increased incidences of renal pelvic cast formation, hydronephrosis and renal papilla. Subcutaneous edema also occurred in fetuses of rats given doses about 4 to 5 times the MRHD (based on body surface area). These anomalies occurred when pregnant rats received ibesartan 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. Following oral doses of ibesartan 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 decreasing proportion 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 ibesartan.

8.3 Nursing Mothers
It is not known whether ibesartan is excreted in human milk, but ibesartan or some metabolite of ibesartan is secreted at low concentration in the milk of lactating rats. Because of the potential for adverse effects on the nursing infant, discontinue nursing or discontinue AVAPRO.

8.4 Pediatric Use
In infants with histories of in utero exposure to an angiotensin II receptor antagonist observe 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.

Ibesartan, in a study at a dose of up to 4.5 mg/kg/day, once daily, did not appear to lower blood pressure effectively in pediatric patients ages 6 to 16 years. AVAPRO has not been studied in pediatric patients less than 6 years old.

8.5 Geriatric Use
In clinical studies of hypertension, AVAPRO was effective in older patients ages 65 and over, while 150 (3.0%) were 75 years and over. No overall differences in effectiveness or safety were observed between these subjects and younger subjects, but greater sensitivity of some older individuals cannot be ruled out. See (Clinical Pharmacology (12.3) and Clinical Studies (14.1)) for information on geriatric dosing.

9.2 Overdosage
No data are available in regard to overdosage in humans. However, daily doses of 900 mg for 8 weeks in rats given oral doses of ibesartan 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 decreasing proportion in live fetuses [see Nonclinical Toxicology (13.2)].

30.1 DESCRIPTION
Ibesartan is a nonpolar compound with a molecular weight of 436.5. It is not soluble in alcohol and practically insoluble in water.

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

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

Ibesartan 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. Ibesartan 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 the active ingredient Ibesartan. Inactive ingredients include lactose, microcrystalline cellulose, pregelatinized starch, croscarmellose sodium, poloxamer 188, silicon dioxide, and magnesium stearate.

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 vasoactive hormone of the renin-angiotensin system, and an important component in the pathophysiology of hypertension. It also stimulates aldosterone secretion by the adrenal cortex. Ibesartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively binding to the AT1 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.

Ibesartan 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 Ibesartan on blood pressure.

Ibesartan 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 Ibesartan doses of up to 300 mg produced dose-dependent inhibition of the pressor effect of angiotensin II infusions. Inhibition was complete (100%) 4 hours following oral doses of 150 mg or 300 mg and partial inhibition was sustained for 24 hours (60% and 40% at 300 mg and 150 mg, respectively).

In hypertensive patients, angiotensin II receptor inhibition following chronic administration of Ibesartan 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 Ibesartan administration, but serum potassium levels are not significantly affected at recommended doses.

In hypertensive patients, chronic oral doses of Ibesartan (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 fibrinogen. In elderly subjects (age 65–80 years), irbesartan 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, Ibesartan AUC values are approximately 25% greater than whites; there is no difference in Cmax values.

Renal impairment
The pharmacokinetics of Ibesartan is not altered in patients with renal impairment or in patients on hemodialysis. Ibesartan 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).

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
No evidence of carcinogenicity was observed when Ibesartan 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 Ibesartan (AUC, bound plus unbound) about 3 and 11 times, respectively, the average systemic exposure in humans receiving the maximum recommended dose (MRD) of 300 mg Ibesartan/d. Although 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 Ibesartan about 3 and 5 times, respectively, the human exposure at 300 mg/day.

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

Ibesartan had no adverse effects on fertility or mating of male or female rats at oral doses ≤565 mg/kg/day, the highest dose providing a systemic exposure to Ibesartan (AUC, 0–24 hr 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 were treated with Ibesartan from Day 0 to Day 20 of gestation (oral doses of 50, 150, and 450 mg/kg/day), increased incidences of renal pelvic cavitation, hydroureter 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 Ibesartan 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 Ibesartan/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. Ibesartan 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 of 95 to 110 mmHg. Doses of 1 to 300 mg were included in these trials in order to fully explore the dose range of Ibesartan. 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 Ibesartan and hydrochlorothiazide in combination.

The 7 studies of Ibesartan monotherapy included a total of 1915 patients randomized to Ibesartan (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 hour blood pressure reductions of 10–15/6–12 mmHg and ≥12/7–8 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.

Geriatrics
In elderly subjects (age 65–80 years), Ibesartan 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, Ibesartan AUC values are approximately 25% greater than whites; there is no difference in Cmax values.

Renal impairment
The pharmacokinetics of Ibesartan is not altered in patients with renal impairment or in patients on hemodialysis. Ibesartan 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 Ibesartan following repeated oral administration are not significantly affected in patients with mild to moderate cirrhosis of the liver. No dosage adjustment is necessary in patients with hepatic insufficiency.

Drug-Drug Interactions
In vitro studies show significant inhibition of the formation of oxidized Ibesartan metabolites with the known cytochrome CYP2C9 substrates/inhibitors sulphasalazine, tolbutamide and nifedipine. However, in clinical studies the consequences of concomitant Ibesartan on the pharmacodynamics of warfarin were negligible. Based on in vitro data, no interaction would be expected with drugs whose metabolism is dependent upon cytochrome P450 isoenzymes 1A1, 1A2, 2A6, 2C9, 2C19, or 3A4. In separate studies of patients receiving maintenance doses of warfarin, hydrochlorothiazide, or digoxin, Ibesartan administration for 7 days has no effect on the pharmacodynamics of warfarin (prothrombin time) or pharmacokinetics of digoxin. The pharmacokinetics of Ibesartan are not affected by coadministration of nifedipine or hydrochlorothiazide.

15 ADVERSE REACTIONS
The most common adverse reactions were generally mild to moderate in severity and reversible upon discontinuation of therapy. They included headache, dizziness, and dizziness.

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The most common adverse reactions were generally mild to moderate in severity and reversible upon discontinuation of therapy. They included headache, dizziness, and dizziness.
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, amiodipine 2.5 mg, or matching placebo once-daily. Patients were titrated to a maintenance dose of AVAPRO 300 mg, or amiodipine 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 amiodipine, 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 (38%), but had no significant effect on ESRD alone and no effect on overall mortality (see Table 1).

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

### Table 1: IDNT: Components of Primary Composite Endpoint

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>AVAPRO N=579 (%)</th>
<th>Placebo N=569 (%)</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>Amiodipine N=567 (%)</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>
<td>41.1</td>
<td>0.77</td>
<td>0.63-0.93</td>
</tr>
<tr>
<td>Breakdown of first occurring event contributing to primary endpoint</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2x creatinine</td>
<td>14.2</td>
<td>19.5</td>
<td>---</td>
<td>---</td>
<td>22.8</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>ESRD</td>
<td>7.4</td>
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<td>---</td>
<td>---</td>
<td>8.8</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Death</td>
<td>11.1</td>
<td>11.2</td>
<td>---</td>
<td>---</td>
<td>9.5</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>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2x creatinine</td>
<td>16.9</td>
<td>23.7</td>
<td>0.67</td>
<td>0.52-0.87</td>
<td>25.4</td>
<td>0.63</td>
<td>0.49-0.81</td>
</tr>
</tbody>
</table>

### Table 1: IDNT: Components of Primary Composite Endpoint (continued)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>AVAPRO N=579 (%)</th>
<th>Placebo N=569 (%)</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>Amiodipine N=567 (%)</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESRD</td>
<td>14.2</td>
<td>17.8</td>
<td>0.77</td>
<td>0.57-1.03</td>
<td>18.3</td>
<td>0.77</td>
<td>0.57-1.03</td>
</tr>
<tr>
<td>Death</td>
<td>15.0</td>
<td>16.3</td>
<td>0.92</td>
<td>0.69-1.23</td>
<td>14.6</td>
<td>1.04</td>
<td>0.77-1.40</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 2: IDNT: Primary Efficacy Outcome Within Subgroups

<table>
<thead>
<tr>
<th>Baseline Factors</th>
<th>AVAPRO N=579 (%)</th>
<th>Placebo N=569 (%)</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>Amlodipine N=567 (%)</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>27.5</td>
<td>36.7</td>
<td>0.68</td>
<td>0.53-0.88</td>
<td>25.4</td>
<td>0.63</td>
<td>0.49-0.81</td>
</tr>
<tr>
<td>Female</td>
<td>42.3</td>
<td>44.6</td>
<td>0.98</td>
<td>0.72-1.34</td>
<td>43.5</td>
<td>0.95</td>
<td>0.67-1.34</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>29.5</td>
<td>37.3</td>
<td>0.75</td>
<td>0.60-0.95</td>
<td>46.2</td>
<td>0.95</td>
<td>0.67-1.34</td>
</tr>
<tr>
<td>Non-White</td>
<td>42.6</td>
<td>43.5</td>
<td>0.95</td>
<td>0.60-0.95</td>
<td>35.1</td>
<td>0.88</td>
<td>0.61-1.29</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></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>35.1</td>
<td>0.88</td>
<td>0.61-1.29</td>
</tr>
<tr>
<td>≥65</td>
<td>35.1</td>
<td>36.8</td>
<td>0.88</td>
<td>0.62-0.97</td>
<td>35.1</td>
<td>0.88</td>
<td>0.61-1.29</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>Bottles</th>
</tr>
</thead>
<tbody>
<tr>
<td>75 mg</td>
<td>0024-5850-90</td>
</tr>
<tr>
<td>150 mg</td>
<td>0024-5851-30</td>
</tr>
<tr>
<td>300 mg</td>
<td>0024-5852-30</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
Advising 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
Advising 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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Rx Only