**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 non-fatal cardiovascular events, primarily strokes and myocardial infarctions. (1.1)
- **Treatment of diabetic 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)

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**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)

**ADVERSE REACTIONS**

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 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: 07/2016

**DOSAGE FORMS AND STRENGTHS**

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

**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)

**7.1 Agents Increasing Serum Potassium**

**7.2 Lithium**

**7.3 Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) Including Selective Cyclooxygenase-2 Inhibitors (COX-2 Inhibitors)**

**7.4 Dual Blockade of the Renin-Angiotensin System (RAS)**

**17 PATIENT COUNSELING INFORMATION**

- 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 mmHg 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., for angina, heart failure, or diabetic kidney disease). These considerations may guide selection of therapy.
Nephropathy in Type 2 Diabetic Patients

AVAPRO may be used alone or in combination with other antihypertensive agents. 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.

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 depletion of intravascular volume or salt (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 “287” on the other.

AVAPRO 150 mg is a white to off-white biconvex oval tablet debossed with a heart on one side and “287Z” on the other.

4. CONTRAINDICATIONS

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 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 [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 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, volume or urine 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)].

5.4 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 may not reflect the rates observed in practice. The adverse reaction information from clinical trials does not always reflect the rates observed in practice because:
- 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.
- Urticaria; angioedema (including swelling of the face, lips, pharynx, or tongue); increased liver function tests; jaundice; hepatic hyperplasia; thymoblast hyperplasia, increased COPK, tinnitus.

6.2 Post-Marketing Experience

The following adverse reactions have been identified during post-approval use of AVAPRO. Because these 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.

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 Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) including Selective Cyclooxygenase-2 Inhibitors (COX-2 Inhibitors)

In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, co-administration 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, more frequently in patients treated with irbesartan compared to placebo. 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 an increased risk of hypotension, 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 co-administer 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 shown a statistically significant increase in major birth defects. Studies in rats and rabbits have shown embryo-fetal toxicity when maternal doses greater than 10 times the human dose were used. There are no adequate and well controlled studies in pregnant women. No data are available in regard to overdosage in humans. However, daily doses of 900 mg for 8 weeks in pregnant rabbits produced 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)].

Radioactivity was present in the rat and rabbit fetus during late gestation and in rat milk following oral administration. These anomalies occurred when pregnant rabbits received irbesartan 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. Irbesartan was not associated with an increased incidence of dry croush, as is typically associated with ACE inhibitor use. In placebo-controlled studies, the incidence of cough in irbesartan-treated patients was 2.8% versus 2.7% in patients receiving placebo.

5.6.1 Pregnancy

Irbesartan crosses the placenta in rats and rabbits. In pregnant rats given irbesartan at doses greater than the maximum recommended human dose (MRHD), fetuses showed increased incidences of renal pelvis and ureteral agenesis, renal agenesis, and some skeletal anomalies. In pregnant rabbits given oral doses of irbesartan equivalent to 1.5 times the MRHD, radioactivity was present in the rat and rabbit fetus during late gestation and in rat milk following oral doses of radiolabeled irbesartan.

8.3.1 Nursing Mothers

It is not known whether irbesartan is excreted in human milk, but irbesartan or some metabolite of irbesartan 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.

Irbesartan, 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

Of 4925 subjects receiving AVAPRO in controlled clinical studies of hypertension, 911 (18.5%) were 65 years and over, and 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).]

8.6 OVERDOSAGE

No data are available regarding overdosage in humans. However, daily doses of 900 mg for 8 weeks were well-tolerated. The most likely manifestations of overdosage are expected to be hypotension and tachycardia; bradycardia might also occur from overdose. Irbesartan is not removed by hemodialysis. Acute oral toxicity studies with irbesartan in mice and rats indicated acute lethal doses were in excess of 69 mg/kg, at least 25- and 50-fold the MRHD (300 mg) on a mg/m2 basis, respectively.

11 DESCRIPTION

AVAPRO (irbesartan) is an angiotensin II receptor (AT, subtype) antagonist. Irbesartan is a non-peptide compound, chemically described as 2-buty1-3H-[1-(3-nitrobenzyl)-5-ylpheny1]-3,1-diazaspiro[4,4]non-1-ene-4-one.
Ibesartan is a white to off-white crystalline powder with a molecular weight of 426.5. It is a nonpolar compound with a partition coefficient (octanol/water) of 10.1 at pH of 7.4. Ibesartan is slightly soluble in alcohol and methylene chloride and practically insoluble in water.

AVAPRO is available for oral administration in uncoated tablets containing 75 mg, 150 mg, or 300 mg of 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 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. 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 hypertensive 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- to 2-fold rise in angiotensin II plasma concentration and a 2- to 3-fold increase in plasma aldosterone 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 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 ibesartan is rapid and complete with an average absolute bioavailability of 60% to 80%. Following oral administration of AVAPRO, peak plasma concentrations of ibesartan are attained at 1.5 to 2 hours after dosing. Food does not affect the bioavailability of ibesartan.

Ibesartan exhibits linear pharmacokinetics over the therapeutic dose range.

Distribution

Ibesartan 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 ibesartan weakly crosses the blood-brain barrier and placenta. Ibesartan 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 ibesartan averages 11 to 15 hours. Steady-state concentrations are achieved within 3 days. Limited accumulation of ibesartan (≤20%) is observed in plasma upon repeated once-daily dosing and is not clinically relevant.

Metabolism

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

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

Excretion

Ibesartan and its metabolites are excreted by both biliary and renal routes. Following either oral or intravenous administration of 14C-labeled ibesartan, about 20% of radioactivity is recovered in the urine and the remainder in the feces, as ibesartan or ibesartan 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 ibesartan are observed in females (11%–44%). No sex-related dosage adjustment is necessary.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence of carciogenicity was observed when ibesartan was administered at doses 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) 6 to 14-fold 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/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 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 in assessing chromosomal aberrations (in vitro—human lymphocyte assay, in vivo—mouse micronucleus study).

Ibesartan had no adverse effects on fertility or mating of male or female rats at oral doses ≤50 mg/kg/day, the highest dose providing a systemic exposure to ibesartan (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 treated with ibesartan 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 caudation, hydrourereter and/or absence of renal papilla were observed in fetuses at doses ≥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 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 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 900 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 and 300 mg provided statistically and clinically significant decreases in systolic and diastolic blood pressure with trough-to-peak-dose ratios of 1.2 and 1.0 respectively. No effect on increase in weight 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 1/3 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.

The Irbesartan Diabetic Nephropathy Trial (IDNT) was a randomized, placebo- and active-controlled, 14.2 Nephropathy in Type 2 Diabetic Patients change in average heart rate in irbesartan-treated patients in controlled trials.

## 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, hyperten-

## Secondary Endpoint of the Study

The secondary endpoint of the study was a composite of cardiovascular mortality and morbidit

## Breakdown of First Occurring Event Contributing to Primary Endpoint

### Breakdown of First Occurring Event Contributing to Primary Endpoint

<table>
<thead>
<tr>
<th>Event</th>
<th>AVAPRO N=579 (%)</th>
<th>Placebo N=589 (%)</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>Amlopidine 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</td>
<td>0.66–0.97</td>
<td>0.63</td>
<td></td>
</tr>
<tr>
<td>Death</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>
<td>8.3</td>
<td>---</td>
<td>---</td>
<td>8.8</td>
<td>---</td>
<td>---</td>
</tr>
</tbody>
</table>

Table 1: Components of Primary Composite Endpoint

<table>
<thead>
<tr>
<th>Incident of Total Events Over Entire Period of Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>2x creatinine</td>
</tr>
<tr>
<td>16.9</td>
</tr>
<tr>
<td>23.7</td>
</tr>
<tr>
<td>0.52–0.97</td>
</tr>
</tbody>
</table>

Table 2: Components of Primary Composite Endpoint (continued)

<table>
<thead>
<tr>
<th>Event</th>
<th>AVAPRO N=579 (%)</th>
<th>Placebo N=589 (%)</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>Amlopidine N=567 (%)</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<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>

Table 2: Primary Efficacy Outcome Within Subgroups

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

- **AVAPRO** (irbesartan) is available as white to off-white biconvex oval tablets, deboosed 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:

- **Debossing**
  - 75 mg: 2871
  - 150 mg: 2872
  - 300 mg: 2873

- **Bottle of 30**
  - 0024-5850-30
  - 0024-5851-30
  - 0024-5852-30

- **Bottle of 90**
  - 0024-5850-90
  - 0024-5851-90
  - 0024-5852-90

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

#### Potassium Supplements

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

- **sanofi-aventis U.S. LLC**
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