

**CENTER FOR DRUG EVALUATION AND RESEARCH**

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**FINAL PRINTED LABELING**

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PRESCRIBING  
 INFORMATION

TV:L2A

## TEVETEN®

brand of

### eprosartan mesylate tablets

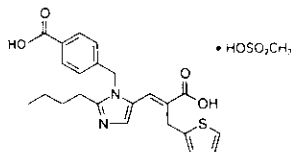
#### USE IN PREGNANCY

When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, Teveten should be discontinued as soon as possible. See WARNINGS: Fetal/Neonatal Morbidity and Mortality.

#### DESCRIPTION

Teveten (eprosartan mesylate) is a non-biphenyl non-tetrazole angiotensin II receptor (AT<sub>1</sub>) antagonist. A selective non-peptide molecule, Teveten is chemically described as the monomethanesulfonate of (E)-2-butyl-1-(p-carboxybenzyl)-α-2-thienylmethylimidazole-5-acrylic acid.

Its empirical formula is C<sub>23</sub>H<sub>24</sub>N<sub>2</sub>O<sub>4</sub>S•CH<sub>3</sub>O<sub>3</sub>S and molecular weight is 520.625. Its structural formula is



Eprosartan mesylate is a white to off-white free-flowing crystalline powder that is insoluble in water, freely soluble in ethanol, and melts between 248° and 250°C.

Teveten is available as aqueous film-coated, scored Tiltab® tablets containing eprosartan mesylate equivalent to 300 mg or 400 mg eprosartan zwitterion (white oval or pink oval tablets, respectively). **Inactive ingredients:** croscarmellose sodium, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, pregelatinized starch, titanium dioxide. Tablets may also contain one or more of the following agents: iron oxide red, iron oxide yellow, polysorbate 80.

#### CLINICAL PHARMACOLOGY

##### Mechanism of Action

Angiotensin II (formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzyme [kininase II]), a potent vasoconstrictor, is the principal pressor agent of the renin-angiotensin system. Angiotensin II also stimulates aldosterone synthesis and secretion by the adrenal cortex, cardiac contraction, renal resorption of sodium, activity of the sympathetic nervous system, and smooth muscle cell growth. Eprosartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT<sub>1</sub> receptor found in many tissues (e.g., vascular smooth muscle, adrenal gland). There is also an AT<sub>2</sub> receptor found in many tissues but it is not known to be associated with cardiovascular homeostasis. Eprosartan does not exhibit any partial agonist activity at the AT<sub>1</sub> receptor. Its affinity for the AT<sub>1</sub> receptor is

1,000 times greater than for the AT<sub>2</sub> receptor. *In vitro* binding studies indicate that eprosartan is a reversible, competitive inhibitor of the AT<sub>1</sub> receptor.

Blockade of the AT<sub>1</sub> 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 effect of eprosartan on blood pressure.

Teveten (eprosartan mesylate) does not inhibit kininase II, the enzyme that converts angiotensin I to angiotensin II and degrades bradykinin; whether this has clinical relevance is not known. It does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

#### Pharmacokinetics

##### General

Absolute bioavailability following a single 300 mg oral dose of eprosartan is approximately 13%. Eprosartan plasma concentrations peak at 1 to 2 hours after an oral dose in the fasted state. Administering eprosartan with food delays absorption, and causes variable changes (<25%) in C<sub>max</sub> and AUC values which do not appear clinically important. Plasma concentrations of eprosartan increase in a slightly less than dose-proportional manner over the 100 mg to 800 mg dose range. The terminal elimination half-life of eprosartan following oral administration is typically 5 to 9 hours. Eprosartan does not significantly accumulate with chronic use.

##### Metabolism and Excretion

Eprosartan is eliminated by biliary and renal excretion, primarily as unchanged compound. Less than 2% of an oral dose is excreted in the urine as a glucuronide. There are no active metabolites following oral and intravenous dosing with [<sup>14</sup>C] eprosartan in human subjects. Eprosartan was the only drug-related compound found in the plasma and feces. Following intravenous [<sup>14</sup>C] eprosartan, about 61% of the material is recovered in the feces and about 37% in the urine. Following an oral dose of [<sup>14</sup>C] eprosartan, about 90% is recovered in the feces and about 7% in the urine. Approximately 20% of the radioactivity excreted in the urine was an acyl glucuronide of eprosartan with the remaining 80% being unchanged eprosartan.

##### Distribution

Plasma protein binding of eprosartan is high (approximately 98%) and constant over the concentration range achieved with therapeutic doses.

The pooled population pharmacokinetic analysis from two Phase 3 trials of 299 men and 172 women with mild to moderate hypertension (aged 20 to 93 years) showed that eprosartan exhibited a population mean oral clearance (CL/F) for an average 60-year-old patient of 48.5 L/hr. The population mean steady-state volume of distribution (V<sub>ss</sub>/F) was 308 liters. Eprosartan pharmacokinetics were not influenced by weight, race, gender or severity of hypertension at baseline. Oral clearance was shown to be a linear function of age with CL/F decreasing 0.62 L/hr. for every year increase.

##### Special Populations

**Pediatric:** Eprosartan pharmacokinetics have not been investigated in patients younger than 18 years of age.

**Geriatric:** Following single oral dose administration of eprosartan to healthy elderly men (aged 68 to 78 years), AUC, C<sub>max</sub>, and T<sub>max</sub> eprosartan values increased, on average by approximately twofold, compared to healthy young men (aged 20 to 39 years) who received the same dose. The extent of plasma protein binding was not influenced by age.

**Gender:** There was no difference in the pharmacokinetics and plasma protein binding between men and women following single oral dose administration of eprosartan.

**Race:** A pooled population pharmacokinetic analysis of 442 Caucasian and 29 non-Caucasian hypertensive patients showed that oral clearance and steady-state volume of distribution were not influenced by race.

**Renal Insufficiency:** Following administration of eprosartan 200 mg b.i.d. for 7 days, patients with mild renal impairment (CL<sub>cr</sub> 60 to 80 mL/min.) showed mean

eprosartan  $C_{max}$  and AUC values similar to subjects with normal renal function. Compared to patients with normal renal function, mean AUC and  $C_{max}$  values were approximately 30% higher in patients with moderate renal impairment ( $CL_{cr}$  30 to 59 mL/min.) and 50% higher in patients with severe renal impairment ( $CL_{cr}$  5 to 29 mL/min.). The unbound eprosartan fraction was not influenced by mild to moderate renal impairment but increased approximately twofold in a few patients with severe renal impairment. No dosage adjustment is necessary for patients with renal impairment. Eprosartan was poorly removed by hemodialysis ( $CL_{HD}$  <1 L/hr.) (see DOSAGE AND ADMINISTRATION).

**Hepatic Insufficiency:** Eprosartan AUC (but not  $C_{max}$ ) values increased, on average, by approximately 40% in men with decreased hepatic function compared to healthy men after a single 100 mg oral dose of eprosartan. Hepatic disease was defined as a documented clinical history of chronic hepatic abnormality diagnosed by liver biopsy, liver/spleen scan or clinical laboratory tests. The extent of eprosartan plasma protein binding was not influenced by hepatic dysfunction. No dosage adjustment is necessary for patients with hepatic impairment (see DOSAGE AND ADMINISTRATION).

#### Drug Interactions

Concomitant administration of eprosartan and digoxin had no effect on single oral-dose digoxin pharmacokinetics. Concomitant administration of eprosartan and warfarin had no effect on steady-state prothrombin time ratios (INR) in healthy volunteers. Concomitant administration of eprosartan and glyburide in diabetic patients did not affect 24-hour plasma glucose profiles. Eprosartan pharmacokinetics were not affected by concomitant administration of ranitidine. Eprosartan did not inhibit human cytochrome P450 enzymes CYP1A, 2A6, 2C9/8, 2C19, 2D6, 2E and 3A *in vitro*. Eprosartan is not metabolized by the cytochrome P450 system; eprosartan steady-state concentrations were not affected by concomitant administration of ketoconazole or fluconazole, potent inhibitors of CYP3A and 2C9, respectively.

#### Pharmacodynamics and Clinical Effects

Eprosartan inhibits the pharmacologic effects of angiotensin II infusions in healthy adult men. Single oral doses of eprosartan from 10 mg to 400 mg have been shown to inhibit the vasopressor, renal vasoconstrictive and aldosterone secretory effects of infused angiotensin II with complete inhibition evident at doses of 350 mg and above. Eprosartan inhibits the pressor effects of angiotensin II infusions. A single oral dose of 350 mg of eprosartan inhibits pressor effects by approximately 100% at peak, with approximately 30% inhibition persisting for 24 hours. The absence of angiotensin II AT<sub>1</sub> agonist activity has been demonstrated in healthy adult men. In hypertensive patients treated chronically with eprosartan, there was a twofold rise in angiotensin II plasma concentration and a twofold rise in plasma renin activity, while plasma aldosterone levels remained unchanged. Serum potassium levels also remained unchanged in these patients.

Achievement of maximal blood pressure response to a given dose in most patients may take 2 to 3 weeks of treatment. Onset of blood pressure reduction is seen within 1 to 2 hours of dosing with few instances of orthostatic hypotension. Blood pressure control is maintained with once- or twice-daily dosing over a 24-hour period. Discontinuing treatment with eprosartan does not lead to a rapid rebound increase in blood pressure.

There was no change in mean heart rate in patients treated with eprosartan in controlled clinical trials.

Eprosartan increases mean effective renal plasma flow (ERPF) in salt-replete and salt-restricted normal subjects. A dose-related increase in ERPF of 25% to 30% occurred in salt-restricted normal subjects, with the effect plateauing between 200 mg and 400 mg doses. There was no change in ERPF in hypertensive patients and patients with renal insufficiency on normal salt diets. Eprosartan did not reduce glomerular filtration rate in patients with renal insufficiency or in patients with hypertension, after 7 days and 28 days of dosing, respectively. In hypertensive patients and patients with

chronic renal insufficiency, eprosartan did not change fractional excretion of sodium and potassium.

Eprosartan (1200 mg once daily for 7 days or 300 mg twice daily for 28 days) had no effect on the excretion of uric acid in healthy men, patients with essential hypertension or those with varying degrees of renal insufficiency.

There were no effects on mean levels of fasting triglycerides, total cholesterol, HDL cholesterol, LDL cholesterol or fasting glucose.

#### Clinical Trials

The safety and efficacy of Teveten (eprosartan mesylate) have been evaluated in controlled clinical trials worldwide that enrolled predominantly hypertensive patients with sitting DBP ranging from 95 mmHg to  $\leq 115$  mmHg. There is also some experience with use of eprosartan together with other antihypertensive drugs in more severe hypertension.

The antihypertensive effects of Teveten were demonstrated principally in five placebo-controlled trials (4 to 13 weeks' duration) including dosages of 400 mg to 1200 mg given once daily (two studies), 25 mg to 400 mg twice daily (two studies), and one study comparing total daily doses of 400 mg to 800 mg given once daily or twice daily. The five studies included 1,111 patients randomized to eprosartan and 395 patients randomized to placebo. The studies showed dose-related antihypertensive responses.

At study endpoint, patients treated with Teveten at doses of 600 mg to 1200 mg given once daily experienced significant decreases in sitting systolic and diastolic blood pressure at trough, with differences from placebo of approximately 5-10/3-6 mmHg. Limited experience is available with the dose of 1200 mg administered once daily. In a direct comparison of 200 mg to 400 mg b.i.d. with 400 mg to 800 mg o.d. of Teveten, effects at trough were similar. Patients treated with Teveten at doses of 200 mg to 400 mg given twice daily experienced significant decreases in sitting systolic and diastolic blood pressure at trough, with differences from placebo of approximately 7-10/4-6 mmHg.

Peak (1 to 3 hours) effects were uniformly, but moderately, larger than trough effects with b.i.d. dosing, with the trough-to-peak ratio for diastolic blood pressure 65% to 80%. In the once-daily dose-response study, trough-to-peak response of  $\leq 50\%$  were observed at some doses (including 1200 mg), suggesting attenuation of effect at the end of the dosing interval.

The antihypertensive effect of Teveten was similar in men and women, but was somewhat smaller in patients over 65. There were too few black subjects to determine whether their response was similar to Caucasians. In general, blacks (usually a low renin population) have had smaller responses to ACE inhibitors and angiotensin II inhibitors than Caucasian populations.

Angiotensin-converting enzyme (ACE) inhibitor-induced cough (a dry, persistent cough) can lead to discontinuation of ACE inhibitor therapy. In one study, patients who had previously coughed while taking an ACE inhibitor were treated with eprosartan, an ACE inhibitor (enalapril) or placebo for six weeks. The incidence of dry, persistent cough was 2.2% on eprosartan, 4.4% on placebo, and 20.5% on the ACE inhibitor;  $P=0.008$  for the comparison of eprosartan with enalapril. In a second study comparing the incidence of cough in 259 patients treated with eprosartan to 261 patients treated with the ACE inhibitor enalapril, the incidence of dry, persistent cough in eprosartan-treated patients (1.5%) was significantly lower ( $P=0.018$ ) than that observed in patients treated with the ACE inhibitor (5.4%). In addition, analysis of overall data from six double-blind clinical trials involving 1,554 patients showed an incidence of spontaneously reported cough in patients treated with eprosartan of 3.5%, similar to placebo (2.6%).

#### INDICATIONS AND USAGE

Teveten is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensives such as diuretics and calcium channel blockers.

## CONTRAINDICATIONS

*Teveten* is contraindicated in patients who are hypersensitive to this product or any of its components.

## WARNINGS

### Fetal/Neonatal Morbidity and Mortality

Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature in patients who were taking angiotensin-converting enzyme inhibitors. When pregnancy is detected, *Teveten* (eprosartan mesylate) should be discontinued as soon as possible.

The use of drugs that act directly on the renin-angiotensin system during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug.

These adverse effects do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to an angiotensin II receptor antagonist only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should advise the patient to discontinue the use of eprosartan as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to a drug acting on the renin-angiotensin system will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intra-amniotic environment.

If oligohydramnios is observed, *Teveten* should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a nonstress test (NST) or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to an angiotensin II receptor antagonist should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function.

Eprosartan mesylate has been shown to produce maternal and fetal toxicities (maternal and fetal mortality, low maternal body weight and food consumption, resorptions, abortions and litter loss) in pregnant rabbits given oral doses as low as 10 mg eprosartan/kg/day. No maternal or fetal adverse effects were observed at 3 mg/kg/day; this oral dose yielded a systemic exposure (AUC) to unbound eprosartan 0.8 times that achieved in humans given 400 mg b.i.d. No adverse effects on *in utero* or postnatal development and maturation of offspring were observed when eprosartan mesylate was administered to pregnant rats at oral doses up to 1000 mg eprosartan/kg/day (the 1000 mg eprosartan/kg/day dose in non-pregnant rats yielded systemic exposure to unbound eprosartan approximately 0.6 times the exposure achieved in humans given 400 mg b.i.d.).

### Hypotension in Volume- and/or Salt-Depleted Patients

In patients with an activated renin-angiotensin system, such as volume- and/or salt-depleted patients (e.g., those being treated with diuretics), symptomatic hypotension may occur. These conditions should be

corrected prior to administration of *Teveten*, or the treatment should start under close medical supervision. If hypotension occurs, the patient should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty once the blood pressure has stabilized.

## PRECAUTIONS

### Risk of Renal Impairment

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function have been reported in susceptible individuals treated with angiotensin II antagonists; in some patients, these changes in renal function were reversible upon discontinuation of therapy. In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (e.g., patients with severe congestive heart failure), treatment with angiotensin-converting enzyme inhibitors and angiotensin II receptor antagonists has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. *Teveten* (eprosartan mesylate) would be expected to behave similarly.

In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or BUN have been reported. Similar effects have been reported with angiotensin II antagonists; in some patients, these effects were reversible upon discontinuation of therapy.

### Information for Patients

**Pregnancy:** Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to drugs that act on the renin-angiotensin system, and they should also be told that these consequences do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible so that treatment may be discontinued under medical supervision.

### Drug Interactions

Eprosartan has been shown to have no effect on the pharmacokinetics of digoxin and the pharmacodynamics of warfarin and glyburide. Thus, no dosing adjustments are necessary during concomitant use with these agents. Because eprosartan is not metabolized by the cytochrome P450 system, inhibitors of CYP450 enzyme would not be expected to affect its metabolism, and ketoconazole and fluconazole, potent inhibitors of CYP3A and 2C9, respectively, have been shown to have no effect on eprosartan pharmacokinetics. Ranitidine also has no effect on eprosartan pharmacokinetics.

Eprosartan (up to 400 mg b.i.d. or 800 mg o.d.) doses have been safely used concomitantly with a thiazide diuretic (hydrochlorothiazide). Eprosartan doses of up to 300 mg b.i.d. have been safely used concomitantly with sustained-release calcium channel blockers (sustained-release nifedipine) with no clinically significant adverse interactions.

### Carcinogenesis, Mutagenesis, Impairment of Fertility

Eprosartan mesylate was not carcinogenic in dietary restricted rats or *ad libitum* fed mice dosed at 600 mg and 2000 mg eprosartan/kg/day, respectively, for up to 2 years. In male and female rats, the systemic exposure (AUC) to unbound eprosartan at the dose evaluated was only approximately 20% of the exposure achieved in humans given 400 mg b.i.d. In mice, the systemic exposure (AUC) to unbound eprosartan was approximately 25 times the exposure achieved in humans given 400 mg b.i.d.

Eprosartan mesylate was not mutagenic *in vitro* in bacteria or mammalian cells (mouse lymphoma assay). Eprosartan mesylate also did not cause structural chromosomal damage *in vivo* (mouse micronucleus assay). In human peripheral lymphocytes *in vitro*, eprosartan mesylate was equivocal for clastogenicity with metabolic activation, and was negative without

metabolic activation. In the same assay, eprosartan mesylate was positive for polyploidy with metabolic activation and equivocal for polyploidy without metabolic activation.

Eprosartan mesylate had no adverse effects on the reproductive performance of male or female rats at oral doses up to 1000 mg eprosartan/kg/day. This dose provided systemic exposure (AUC) to unbound eprosartan approximately 0.6 times the exposure achieved in humans given 400 mg b.i.d.

#### Pregnancy

**Pregnancy Category C (first trimester) and D (second and third trimesters):** See WARNINGS: Fetal/Neonatal Morbidity and Mortality.

#### Nursing Mothers

Eprosartan is excreted in animal milk; it is not known whether eprosartan is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from eprosartan, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

#### Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

#### Geriatric Use

Of the total number of patients receiving *Teveten* in clinical studies, 29% (681 of 2,334) were 65 years and over, while 5% (124 of 2,334) were 75 years and over. Based on the pooled data from randomized trials, the decrease in diastolic blood pressure and systolic blood pressure with *Teveten* was slightly less in patients ≥65 years of age compared to younger patients. In a study of only patients over the age of 65, *Teveten* at 200 mg twice daily (and increased optionally up to 300 mg twice daily) decreased diastolic blood pressure on average by 3 mmHg (placebo corrected). Adverse experiences were similar in younger and older patients.

#### ADVERSE REACTIONS

*Teveten* has been evaluated for safety in more than 3,300 healthy volunteers and patients worldwide, including more than 1,460 patients treated for more than 6 months, and more than 980 patients treated for 1 year or longer. *Teveten* was well tolerated at doses up to 1200 mg daily. Most adverse events were of mild or moderate severity and did not require discontinuation of therapy. The overall incidence of adverse experiences and the incidences of specific adverse events reported with eprosartan were similar to placebo.

Adverse experiences were similar in patients regardless of age, gender, or race. Adverse experiences were not dose-related.

In placebo-controlled clinical trials, about 4% of 1,202 of patients treated with *Teveten* discontinued therapy due to clinical adverse experiences, compared to 6.5% of 352 patients given placebo.

**Adverse Events Occurring at an Incidence of 1% or More Among Eprosartan-treated Patients:** The following table lists adverse events that occurred at an incidence of 1% or more among eprosartan-treated patients who participated in placebo-controlled trials of 8 to 13 weeks' duration, using doses of 25 mg to 400 mg twice daily, and 400 mg to 1200 mg once daily. The overall incidence of adverse events reported with *Teveten* (54.4%) was similar to placebo (52.8%).

**Table 1. Adverse Events Reported by ≥1% of Patients Receiving *Teveten* (eprosartan mesylate) and Were More Frequent on Eprosartan than Placebo**

| Event                  | Incidence                    |                         |
|------------------------|------------------------------|-------------------------|
|                        | Eprosartan<br>(n=1,202)<br>% | Placebo<br>(n=352)<br>% |
| <b>Body as a Whole</b> |                              |                         |
| Infection viral        | 2                            | 1                       |
| Injury                 | 2                            | 1                       |
| Fatigue                | 2                            | 1                       |

#### Gastrointestinal

Abdominal pain 2 1

#### Metabolic and Nutritional

Hypertriglyceridemia 1 0

#### Musculoskeletal

Arthralgia 2 1

#### Nervous System

Depression 1 0

#### Respiratory

Upper respiratory tract infection 8 5

Rhinitis 4 3

Pharyngitis 4 3

Coughing 4 3

#### Urogenital

Urinary tract infection 1 0

The following adverse events were also reported at a rate of 1% or greater in patients treated with eprosartan, but were as, or more, frequent in the placebo group: headache, myalgia, dizziness, sinusitis, diarrhea, bronchitis, dependent edema, dyspepsia, chest pain.

Facial edema was reported in 5 patients receiving eprosartan. Angioedema has been reported with other angiotensin II antagonists.

In addition to the adverse events above, potentially important events that occurred in at least two patients/subjects exposed to eprosartan or other adverse events that occurred in <1% of patients in clinical studies are listed below. It cannot be determined whether events were causally related to eprosartan.

**Body as a Whole:** alcohol intolerance, asthenia, substernal chest pain, peripheral edema, fatigue, fever, hot flushes, influenza-like symptoms, malaise, rigors, pain;

**Cardiovascular:** angina pectoris, bradycardia, abnormal ECG, specific abnormal ECG, extrasystoles, atrial fibrillation, hypotension, tachycardia, palpitations;

**Gastrointestinal:** anorexia, constipation, dry mouth, esophagitis, flatulence, gastritis, gastroenteritis, gingivitis, nausea, periodontitis, toothache, vomiting;

**Hematologic:** anemia, purpura;

**Liver and Biliary:** increased SGOT, increased SGPT;

**Metabolic and Nutritional:** increased creatine phosphokinase, diabetes mellitus, glycosuria, gout, hypercholesterolemia, hyperglycemia, hyperkalemia, hypokalemia, hyponatremia;

**Musculoskeletal:** arthritis, aggravated arthritis, arthrosis, skeletal pain, tendinitis, back pain;

**Nervous System/Psychiatric:** anxiety, ataxia, insomnia, migraine, neuritis, nervousness, paresthesia, somnolence, tremor, vertigo;

**Resistance Mechanism:** herpes simplex, otitis externa, otitis media, upper respiratory tract infection;

**Respiratory:** asthma, epistaxis;

**Skin and Appendages:** eczema, furunculosis, pruritus, rash, maculopapular rash, increased sweating;

**Special Senses:** conjunctivitis, abnormal vision, xerophthalmia, tinnitus;

**Urinary:** albuminuria, cystitis, hematuria, micturition frequency, polyuria, renal calculus, urinary incontinence;

**Vascular:** leg cramps, peripheral ischemia.

**Laboratory Test Findings:** In placebo-controlled studies, clinically important changes in standard laboratory parameters were rarely associated with administration of *Teveten* (eprosartan mesylate). Patients were rarely withdrawn from *Teveten* because of laboratory test results.

**Creatinine, Blood Urea Nitrogen:** Minor elevations in creatinine and in BUN occurred in 0.6% and 1.3%, respectively, of patients taking *Teveten* and 0.9% and 0.3%, respectively, of patients given placebo in controlled clinical trials. Two patients were withdrawn from clinical trials for elevations in serum creatinine and BUN, and three additional patients were withdrawn for increases in serum creatinine.

**Liver Function Tests:** Minor elevations of ALAT, ASAT, and alkaline phosphatase occurred for comparable percentages of patients taking Teveten (eprosartan mesylate) or placebo in controlled clinical trials. An elevated ALAT of  $>3.5 \times \text{ULN}$  occurred in 0.1% of patients taking Teveten (one patient) and in no patient given placebo in controlled clinical trials. Four patients were withdrawn from clinical trials for an elevation in liver function tests.

**Hemoglobin:** A greater than 20% decrease in hemoglobin was observed in 0.1% of patients taking Teveten (one patient) and in no patient given placebo in controlled clinical trials. Two patients were withdrawn from clinical trials for anemia.

**Leukopenia:** A WBC count of  $\leq 3.0 \times 10^3/\text{mm}^3$  occurred in 0.3% of patients taking Teveten and in 0.3% of patients given placebo in controlled clinical trials. One patient was withdrawn from clinical trials for leukopenia.

**Neutropenia:** A neutrophil count of  $\leq 1.5 \times 10^3/\text{mm}^3$  occurred in 1.3% of patients taking Teveten and in 1.4% of patients given placebo in controlled clinical trials. No patient was withdrawn from any clinical trials for neutropenia.

**Thrombocytopenia:** A platelet count of  $\leq 100 \times 10^9/\text{L}$  occurred in 0.3% of patients taking Teveten (one patient) and in no patient given placebo in controlled clinical trials. Four patients receiving Teveten in clinical trials were withdrawn for thrombocytopenia. In one case, thrombocytopenia was present prior to dosing with Teveten.

**Serum Potassium:** A potassium value of  $\geq 5.6 \text{ mmol/L}$  occurred in 0.9% of patients taking Teveten and 0.3% of patients given placebo in controlled clinical trials. One patient was withdrawn from clinical trials for hyperkalemia and three for hypokalemia.

#### OVERDOSAGE

Limited data are available regarding overdosage. Appropriate symptomatic and supportive therapy should be given if overdosage should occur. There was no mortality in rats and mice receiving oral doses of up to 3000 mg eprosartan/kg and in dogs receiving oral doses of up to 1000 mg eprosartan/kg.

#### DOSAGE AND ADMINISTRATION

The usual recommended starting dose of Teveten is 600 mg once daily when used as monotherapy in patients who are not volume-depleted (see WARNINGS, Hypotension in Volume- and/or Salt-Depleted Patients). Teveten can be administered once or twice daily with total daily doses ranging from 400 mg to 800 mg. There is limited experience with doses beyond 800 mg/day.

If the antihypertensive effect measured at trough using once-daily dosing is inadequate, a twice-a-day regimen at the same total daily dose or an increase in dose may give a more satisfactory response. Achievement of maximum blood pressure reduction in most patients may take 2 to 3 weeks.

Teveten may be used in combination with other antihypertensive agents such as thiazide diuretics or calcium channel blockers if additional blood-pressure-lowering effect is required. Discontinuation of treatment with eprosartan does not lead to a rapid rebound increase in blood pressure.

#### Elderly, Hepatically Impaired or Renally Impaired Patients:

No initial dosing adjustment is generally necessary for elderly or hepatically impaired patients or those with renal impairment.

Teveten may be taken with or without food.

#### HOW SUPPLIED

Teveten (eprosartan mesylate) is available as aqueous film-coated, scored Tiltab® tablets as follows:

300 mg white, oval tablets debossed with SB and 5043 on both sides of the tablet

NDC 0007-5043-18 (bottles of 60)

NDC 0007-5043-79 (bottles of 180)

NDC 0007-5043-60 SUP 60's (intended for institutional use only)

NDC 0007-5043-25 (bottles of 500)

400 mg pink, oval tablets debossed with SB and 5044 on both sides of the tablet

NDC 0007-5044-18 (bottles of 60)

NDC 0007-5044-79 (bottles of 180)

NDC 0007-5044-60 SUP 60's (intended for institutional use only)

NDC 0007-5044-25 (bottles of 500)

#### STORAGE

Store at controlled room temperature 20° to 25°C (68° to 77°F) [see USP].

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Printed in U.S.A.

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R<sub>x</sub> only



Plasma concentrations of angiotensin I, angiotensin II and plasma renin activity (PRA), increased in a dose dependent manner after single and repeated administration of candesartan cilexetil to healthy subjects and hypertensive patients. ACE activity was not altered in healthy subjects after repeated candesartan cilexetil administration. The once daily administration of up to 16 mg of candesartan cilexetil to healthy subjects did not influence plasma aldosterone concentrations, but a decrease in the plasma concentration of aldosterone was observed when 32 mg of candesartan cilexetil was administered to hypertensive patients. In spite of the effect of candesartan cilexetil on aldosterone secretion, very little effect on serum potassium was observed.

In multiple dose studies with hypertensive patients, there were no clinically significant changes in metabolic function including serum levels of total cholesterol, triglycerides, glucose, or uric acid. In a 12-week study of 161 patients with non-insulin dependent (type II) diabetes mellitus and hypertension, there was no change in the level of HbA<sub>1c</sub>.

The antihypertensive effects of ATACAND were examined in 14 placebo-controlled trials of 4 to 12 weeks duration, primarily at daily doses of 2 to 32 mg per day in patients with baseline diastolic blood pressures of 95-114 mmHg. Most of the trials were of candesartan cilexetil as a single agent but it was also studied as add-on to hydrochlorothiazide and amlodipine. These studies included a total of 2350 patients randomized to one of several doses of candesartan cilexetil and 1027 to placebo. Except for a study in diabetics, all studies showed significant effects, generally dose related, of 2-32 mg on trough (24 hour) systolic and diastolic pressures compared to placebo, with doses of 8-32 mg giving effects about 8-12/4-8 mmHg. There were no exaggerated first dose effects in these patients. Most of the antihypertensive effect was seen within two weeks of initial dosing, and the full effect in four weeks. With once daily dosing, blood pressure effects were maintained over 24 hours, with trough to peak ratios of blood pressure effect generally over 80%. Candesartan cilexetil had an additional blood pressure lowering effect when added to hydrochlorothiazide.

The antihypertensive effect was similar in men and women and in patients older and younger than 65. Candesartan was effective in reducing blood pressure regardless of race, although the effect was somewhat less in blacks (usually a low-renin population). This has been generally true for angiotensin II antagonists and ACE inhibitors.

In long-term studies of up to one year, the antihypertensive effectiveness of candesartan cilexetil was maintained and there was no rebound after abrupt withdrawal.

There were no changes in the heart rate of patients treated with candesartan cilexetil in controlled trials.

ATACAND is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.

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

### Fetal/Neonatal Morbidity and Mortality

Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature in patients who were taking angiotensin converting enzyme inhibitors. When pregnancy is detected, ATACAND should be discontinued as soon as possible.

The use of drugs that act directly on the renin-angiotensin system during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, in utero reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug.

These adverse effects do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to an angiotensin II receptor antagonist only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should have the patient discontinue the use of ATACAND as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to a drug acting on the renin-angiotensin system will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intra-uterine environment.

If oligohydramnios is observed, ATACAND should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a nonstress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be

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1. The first step in the process is to identify the problem or issue that needs to be addressed. This involves gathering information and understanding the context of the problem.

2. Once the problem is identified, the next step is to define the objectives and goals of the project. This helps to clarify what needs to be achieved and provides a clear direction for the team.

3. The third step is to develop a plan or strategy to address the problem. This involves breaking down the problem into smaller, manageable tasks and determining the resources needed to complete each task.

4. The fourth step is to implement the plan. This involves putting the strategy into action and monitoring progress regularly to ensure that the project is on track.

5. The final step is to evaluate the results of the project. This involves comparing the actual outcomes against the objectives and goals to determine the effectiveness of the project.

[illegible][illegible]

Infants with histories of *in utero* lithium receptor antagonist should be closely monitored for signs of oliguria, hyperkalemia, and hypotension. Management should be directed toward supporting renal perfusion. Exchange transfusion may be required as means of reversing hypocalcemia and hyperkalemia pending long-term management for disordered renal function.

There is no clinical experience with pregnant women. Oral doses of 2.1 kg/day administered to pregnant and continued through lactation reduced survival and an increase in the offspring. The 10 mg/kg daily 2.8 times the maximum recommended dose (MRHD) of 32 mg on a assumes human body weight of 5 given to pregnant rabbits at an (approximately 1.7 times the MRHD) maternal toxicity (decreased body weight, no external, visceral or maternal toxicity or adverse effects) were observed when oral doses of 10 mg/kg/day (approximately 1.7 times the MRHD) were administered to

In patients with an activated renin-angiotensin system (e.g., as volume- and/or salt-depleted or treated with diuretics), symptoms of hypotension may be exacerbated. These conditions should be corrected prior to treatment with ATACAND, or the treatment should be initiated under close medical supervision (see DOSAGE AND ADMINISTRATION).

If hypotension occurs, the patient is placed in the supine position and, if necessary, given a bolus of normal saline. A transient hypotension is a contraindication to further treatment. The patient is continued without difficulty once stabilized.

**Impaired Renal Function:** As the renin-angiotensin-aldosterone function may be anticipated in such patients with ATACAND. In patients whose renal function depends primarily upon the activity of the renin-angiotensin system, treatment with ATACAND (e.g., patients with severe congestive heart failure, patients treated with angiotensin converting enzyme inhibitors or angiotensin receptor antagonists has been associated with increased risk of hypotension and/or progressive azotemia and/or death. Similar results have been observed in patients treated with ATACAND. (See ADVERSE REACTIONS, Special Populations.)

In studies of ACE inhibitors in bilateral renal artery stenosis, increased blood urea nitrogen (BUN) have not been no long-term use of ATACAND or bilateral renal artery stenosis, is expected.

**Pregnancy:** Female patients of childbearing age should be told about the consequences of exposure to drugs that act on the nervous system, and they should also be told that the data available to date appear to have resulted from intrauterine exposure to drugs has been limited to the first trimester of pregnancy. Women should be asked to report pregnancies to their physicians as soon as possible.

No significant drug-interactions have been observed with doses of candesartan cilexetil given with food or without food. Candesartan cilexetil has no effect on the pharmacokinetics of nifedipine, digoxin, warfarin or oral contraceptives in healthy volunteers. Candesartan cilexetil is not metabolized by the cytochrome P450 system and has no effects on P450 enzymes, neither does it inhibit, or is metabolized by, those enzymes.

There was no evidence of carcinogenic activity in rats receiving the test article orally at doses up to 104 weeks at doses up to 3 mg/kg body weight, respectively. Rats received the drug by gavage (maximally tolerated) doses of 100 mg/kg body weight, which provided systemic exposures to candesartan in mice, approximately 7 times as high as the exposure in man at the recommended daily human dose (32 mg).

Candesartan cilexetil was not genotoxic in *in vivo* chromosomal aberration assays. In addition, candesartan was not genotoxic in microbial mutagenesis, mammalian *in vitro* and *in vivo* chromosome aberration assays.





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swers, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to an angiotensin II receptor antagonist should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function.

There is no clinical experience with the use of ATACAND in pregnant women. Oral doses of 10 mg candesartan cilexetil/kg/day administered to pregnant rats during late gestation and continued through lactation were associated with reduced survival and an increased incidence of hydronephrosis in the offspring. The 10 mg/kg/day dose in rats is approximately 2.8 times the maximum recommended daily human dose (MRHD) of 32 mg on a mg/m<sup>2</sup> basis (comparison assumes human body weight of 50 kg). Candesartan cilexetil given to pregnant rabbits at an oral dose of 3 mg/kg/day (approximately 1.7 times the MRHD on a mg/m<sup>2</sup> basis) caused maternal toxicity (decreased body weight and death) but, in surviving dams, had no adverse effects on fetal survival, fetal weight or on external, visceral or skeletal development. No maternal toxicity or adverse effects on fetal development were observed when oral doses up to 1000 mg candesartan cilexetil/kg/day (approximately 138 times the MRHD on a mg/m<sup>2</sup> basis) were administered to pregnant mice.

**Hypotension in Volume- and Salt-Depleted Patients**

In patients with an activated renin-angiotensin system, such as volume- and/or salt-depleted patients (e.g., those being treated with diuretics), symptomatic hypotension may occur. These conditions should be corrected prior to administration of ATACAND, or the treatment should start under close medical supervision (see DOSAGE AND ADMINISTRATION).

If hypotension occurs, the patients should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty once the blood pressure has stabilized.

**PRECAUTIONS**

**General**

**Impaired Renal Function:** As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals treated with ATACAND. In patients whose renal function may depend upon the activity of the renin-angiotensin-aldosterone system (e.g., patients with severe congestive heart failure), treatment with angiotensin converting enzyme inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. Similar results may be anticipated in patients treated with ATACAND. (See CLINICAL PHARMACOLOGY, Special Populations.)

In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen (BUN) have been reported. There has been no long-term use of ATACAND in patients with unilateral or bilateral renal artery stenosis, but similar results may be expected.

**Information for Patients**

**Pregnancy:** Female patients of childbearing age should be told about the consequences of second and third trimester exposure to drugs that act on the renin-angiotensin system, and they should also be told that these consequences do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

**Drug Interactions**

No significant drug-interactions have been reported in studies of candesartan cilexetil given with other drugs such as glyburide, nifedipine, digoxin, warfarin, hydrochlorothiazide and oral contraceptives in healthy volunteers. Because candesartan is not metabolized by the cytochrome P450 system and has no effects on P450 enzymes, interactions with drugs that inhibit, or are metabolized by, those enzymes would not be expected.

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

There was no evidence of carcinogenicity when candesartan cilexetil was orally administered to mice and rats for up to 104 weeks at doses up to 300 and 1000 mg/kg/day, respectively. Rats received the drug by gavage whereas mice received the drug by dietary administration. These (maximally tolerated) doses of candesartan cilexetil provided systemic exposures to candesartan (AUCs) that were, in mice, approximately 7 times and, in rats, more than 70 times the exposure in man at the maximum recommended daily human dose (32 mg).

Candesartan cilexetil was not genotoxic in the microbial mutagenesis and mammalian cell mutagenesis assays and in the *in vivo* chromosomal aberration and rat unscheduled DNA synthesis assays. In addition, candesartan was not genotoxic in the microbial mutagenesis, mammalian cell mutagenesis and *in vitro* and *in vivo* chromosome aberration assays.

Fertility and reproductive performance were not affected in studies with male and female rats given oral doses of up to

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300 mg/kg/day (83-times the maximum daily human dose of 32 mg on a body surface area basis).

**Pregnancy**

**Pregnancy Categories C (first trimester) and D (second and third trimesters).** See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

**Nursing Mothers**

It is not known whether candesartan is excreted in human milk, but candesartan has been shown to be present in rat milk. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

**Pediatric Use**

Safety and effectiveness in pediatric patients have not been established.

**Geriatric Use**

Of the total number of subjects in clinical studies of ATACAND, 21% were 65 and over, while 3% were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. In a placebo controlled trial of about 200 elderly hypertensive patients (ages 65 to 87 years), administration of candesartan cilexetil was well tolerated and lowered blood pressure by about 12.6 mmHg more than placebo.

**ADVERSE REACTIONS**

ATACAND has been evaluated for safety in more than 3600 patients/subjects including more than 3200 patients treated for hypertension. About 600 of these patients were studied for at least six months and about 200 for more than at least one year. In general, treatment with ATACAND was well-tolerated. The overall incidence of adverse events reported with ATACAND was similar to placebo.

The rate of withdrawals due to adverse events in all trials in patients (7510 total) was 3.3% of (i.e., 106 of 3260) patients treated with candesartan cilexetil as monotherapy and 3.5% of (i.e., 39 of 1106) patients treated with placebo. In placebo controlled trials, discontinuation of therapy due to clinical adverse events occurred in 2.4% of (i.e., 57 of 2350) patients treated with ATACAND and 3.4% of (i.e., 38 of 1027) patients treated with placebo.

The most common reasons for discontinuation of therapy with ATACAND were headache (0.6%) and dizziness (0.3%).

The adverse experiences that occurred in placebo-controlled clinical trials in at least 1% of patients treated with ATACAND and at a higher incidence in candesartan cilexetil (n=2350) than placebo (n=1027) patients included back pain (3% vs. 2%), dizziness (4% vs. 3%), upper respiratory tract infection (5% vs. 4%), pharyngitis (2% vs. 1%), and rhinitis (2% vs. 1%).

The following adverse experiences occurred in placebo-controlled clinical trials at a more than 1% rate but at about the same or greater incidence in patients receiving placebo compared to candesartan cilexetil: fatigue, peripheral edema, chest pain, headache, bronchitis, coughing, sinusitis, nausea, abdominal pain, diarrhea, vomiting, arthralgia, albuminuria.

Other potentially important adverse events that have been reported, whether or not attributed to treatment, with an incidence of 0.5% or greater from the more than 3200 patients worldwide treated with ATACAND are listed below. It cannot be determined whether these events were causally related to ATACAND. **Body as a Whole:** asthenia, fever; **Central and Peripheral Nervous System:** paresthesia, vertigo; **Gastrointestinal System Disorder:** dyspepsia, gastroenteritis; **Heart Rate and Rhythm Disorders:** tachycardia, palpitation; **Metabolic and Nutritional Disorders:** creatine phosphokinase increased, hyperglycemia, hypertriglyceridemia, hyperuricemia; **Musculoskeletal System Disorders:** myalgia; **Platelet/Bleeding Clotting Disorders:** epistaxis; **Psychiatric Disorders:** anxiety, depression, somnolence; **Respiratory System Disorders:** dyspnea; **Skin and Appendages Disorders:** rash, sweating increased; **Urinary System Disorders:** hematuria.

Other reported events seen less frequently included angina pectoris, myocardial infarction, and angioedema.

Adverse events occurred at about the same rates in men and women, older and younger patients, and black and non-black patients.

**Laboratory Test Findings**

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

**Creatinine, Blood Urea Nitrogen:** Minor increases in blood urea nitrogen (BUN) and serum creatinine were observed infrequently.

**Hyperuricemia:** Hyperuricemia was rarely found (19 or 0.8% of 3260 patients treated with candesartan cilexetil and 5 or 0.5% of 1106 patients treated with placebo).

**Hemoglobin and Hematocrit:** Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.2 grams/dL and 0.5 volume percent, respectively) were observed in patients treated with ATACAND alone, but were rarely of clinical importance. Anemia, leukopenia and throm-

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**(Candesartan Cilexetil)**  
**TABLETS**



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bocytopenia were associated with withdrawal of one patient each from clinical trials.

**Potassium:** A small increase (mean increase of 0.1 mEq/L) was observed in patients treated with ATACAND alone, but was rarely of clinical importance. One patient from a congestive heart failure trial was withdrawn for hyperkalemia (serum potassium = 7.5 mEq/L). This patient was also receiving spironolactone.

**Liver Function Tests:** Elevations of liver enzymes and/or serum bilirubin were observed infrequently. Five patients assigned to candesartan cilexetil in clinical trials were withdrawn because of abnormal liver chemistries. All had elevated transaminases. Two had mildly elevated total bilirubin but one of these patients was diagnosed with Hepatitis A.

### OVERDOSAGE

No lethality was observed in acute toxicity studies in mice, rats and dogs given single oral doses of up to 2000 mg/kg of candesartan cilexetil. In mice given single oral doses of the primary metabolite, candesartan, the minimum lethal dose was greater than 1000 mg/kg but less than 2000 mg/kg.

Limited data are available in regard to overdosage in humans. In one recorded case of an intentional overdose, a 43 year old female patient (Body Mass Index of 31 kg/m<sup>2</sup>) ingested an estimated 150 mg of candesartan cilexetil, in conjunction with multiple other pharmaceutical agents (ibuprofen, naproxen sodium, diphenhydramine hydrochloride and ketoprofen). Gastric lavage was performed, the patient was monitored in hospital for several days and was discharged without sequelae.

Candesartan cannot be removed by hemodialysis.

**Treatment:** To obtain up-to-date information about the treatment of overdose, consult your Regional Poison-Control Center. Telephone numbers of certified poison-control centers are listed in the Physicians' Desk Reference (PDR). In managing overdose, consider the possibilities of multiple-drug overdoses, drug-drug interactions, and altered pharmacokinetics in your patient.

The most likely manifestation of overdosage with ATACAND would be hypotension, dizziness and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted.

### DOSAGE AND ADMINISTRATION

Dosage must be individualized. Blood pressure response is dose-related over the range of 2-32 mg. The usual recommended starting dose of ATACAND is 16 mg once daily when it is used as monotherapy in patients who are not volume depleted. ATACAND can be administered once or twice daily with total daily doses ranging from 8 mg to 32 mg. Larger doses do not appear to have a greater effect and there is relatively little experience with such doses. Most of the antihypertensive effect is present within 2 weeks and maximal blood pressure reduction is generally obtained within four to six weeks of ATACAND treatment.

No initial dosage adjustment is necessary for elderly patients, for patients with mildly impaired renal function, or for patients with mildly impaired hepatic function (see CLINICAL PHARMACOLOGY, Special Populations). For patients with possible depletion of intravascular volume (e.g., patients treated with diuretics, particularly those with impaired renal function), ATACAND should be initiated under close medical supervision and consideration should be given to administration of a lower dose (see WARNINGS, Hypotension in Volume- and Salt-Depleted Patients).

ATACAND may be administered with or without food.

If blood pressure is not controlled by ATACAND alone, a diuretic may be added. ATACAND may be administered with other antihypertensive agents.

### NOW SUPPLIED

No. 3782 — Tablets ATACAND, 4 mg, are white to off-white, circular/biconvex shaped, non film-coated tablets, coded ACF on one side and 004 on the other. They are supplied as follows:

NDC 61113-004-31 unit of use bottles of 30  
NDC 61113-004-54 unit of use bottles of 90  
NDC 61113-004-28 unit dose packages of 100  
NDC 61113-004-82 bottles of 1000.

No. 3780 — Tablets ATACAND, 8 mg, are light pink, circular/biconvex shaped, non film-coated tablets, coded ACG on one side and 008 on the other. They are supplied as follows:

NDC 61113-008-31 unit of use bottles of 30  
NDC 61113-008-54 unit of use bottles of 90  
NDC 61113-008-28 unit dose packages of 100  
NDC 61113-008-82 bottles of 1000.

No. 3781 — Tablets ATACAND, 16 mg, are pink, circular/biconvex shaped, non film-coated tablets, coded ACH on one side and 016 on the other. They are supplied as follows:

NDC 61113-016-31 unit of use bottles of 30  
NDC 61113-016-54 unit of use bottles of 90  
NDC 61113-016-28 unit dose packages of 100  
NDC 61113-016-82 bottles of 1000.

No. 3791 — Tablets ATACAND, 32 mg, are pink, circular/biconvex shaped, non film-coated tablets, coded ACL on one side and 032 on the other. They are supplied as follows:

NDC 61113-032-31 unit of use bottles of 30  
NDC 61113-032-54 unit of use bottles of 90  
NDC 61113-032-28 unit dose packages of 100  
NDC 61113-032-82 bottles of 1000.

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### Storage

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



Manufactured by:

**ASTRA MERCK**

Weymouth, MA 01987, USA

### Packaged by:

Merck & Co., INC., West Point, PA 19380, USA



Manufactured under the license from Takeda Chemical Industries, Ltd., by: Astra AB, S-151 85 Södertälje, Sweden.

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## AVAPRO® (irbesartan) Tablets



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CAUTION: FEDERAL LAW PROHIBITS  
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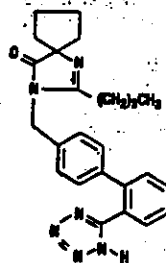
## AVAPRO® (irbesartan) Tablets

### USE IN PREGNANCY

When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, AVAPRO should be discontinued as soon as possible. See WARNINGS: Fetal/Neonatal Morbidity and Mortality.

### DESCRIPTION

AVAPRO® (irbesartan) is an angiotensin II receptor (AT<sub>1</sub> subtype) antagonist. Irbesartan is a non-peptide compound, chemically described as a 2-butyl-3-[[2'-(1*H*-tetrazol-5-yl) [1,1'-biphenyl]-4-yl]methyl]-1,3-diazaspiro [4,4] non-1-en-4-one. Its empirical formula is C<sub>25</sub>H<sub>28</sub>N<sub>4</sub>O, and the structural formula:



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.

### CLINICAL PHARMACOLOGY

#### 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 principal pressor agent of the renin-angiotensin system (RAS) and also stimulates aldosterone synthesis and secretion by adrenal cortex, cardiac contraction, renal resorption of sodium, activity of the sympathetic nervous system, and smooth muscle cell growth. Irbesartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively binding to the AT<sub>1</sub> angiotensin II receptor. There is also an AT<sub>2</sub> receptor in many tissues, but it is not involved in cardiovascular homeostasis.

Irbesartan is a specific competitive antagonist of AT<sub>1</sub> receptors with a much greater affinity (more than 8500-fold) for the AT<sub>1</sub> receptor than for the AT<sub>2</sub> receptor and no agonist activity.

Blockade of the AT<sub>1</sub> 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 irbesartan on blood pressure.

Irbesartan 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. Because irbesartan does not inhibit ACE, it does not affect the response to bradykinin; whether this has clinical relevance is not known.

#### Pharmacokinetics

Irbesartan is an orally active agent that does not require biotransformation into an active form. The oral absorption of irbesartan is rapid and complete with an average absolute bioavailability of 60–80%. Following oral administration of AVAPRO, peak plasma concentrations of irbesartan are attained at 1.5–2 hours after dosing. Food does not affect the bioavailability of AVAPRO.

Irbesartan exhibits linear pharmacokinetics over the therapeutic dose range.

The terminal elimination half-life of irbesartan averaged 11–15 hours. Steady-state concentrations are achieved within 3 days. Limited accumulation of irbesartan (<20%) is observed in plasma upon repeated once-daily dosing.

#### Metabolism and Elimination

Irbesartan is metabolized via glucuronide conjugation and oxidation. Following oral or intravenous administration of <sup>14</sup>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.

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

*In vitro* studies of irbesartan oxidation by cytochrome P450 isoenzymes indicated irbesartan was oxidized primarily by 2C9; metabolism by 3A4 was negligible. Irbesartan was neither metabolized by, nor did it substantially induce or inhibit, isoenzymes commonly associated with drug metabolism (1A1, 1A2, 2A6, 2B6, 2D6, 2E1). There was no induction or inhibition of 3A4.

#### Distribution

Irbesartan is 90% bound to serum proteins (primarily albumin and α<sub>1</sub>-acid glycoprotein) with negligible binding to cellular components of blood. The average

volume of distribution: the range of 157–311 L. Irbesartan accumulates in tissues. Studies in animal: brain barrier and placenta. Special Populations: Pediatric: Irbesartan years of age.

Gender: No gender healthy elderly (age in studies of hypertension accumulation, but observed in females).

Geriatric: In elderly was not significantly than those of young sary in the elderly.

Race: In healthy b greater than whites;

Renal insufficiency: with renal impairment: hemodialysis. No do renal impairment un (See WARNINGS: Hy AND ADMINISTRATION).

Hepatic insufficiency: oral administration w cirrhosis of the liver insufficiency.

#### Drug Interactions:

Pharmacodynamic: In healthy subjects, dependent inhibition complete (100%) 4 inhibition was susta respectively).

In hypertensive pa: Istration of irbesartar and a 2–3 fold incre: generally decline fol are not significantly

In hypertensive pa: effect on glomerular tiple dose studies i effects on fasting tri: concentrations. Ther: Istration, and no uric

#### Clinical Studies

The antihypertensive major placebo-cont: pressures of 95–110 order to fully explore ison of once- or twi: trough effects, and c seven placebo-cont: effects of irbesartan

The seven (7) stud randomized to irbes: Once-daily doses of decreases in systolic effects after 6–12 w and 8–12/5–8 mmHg greater than 300 m: diastolic pressure an



Figure 1. Placebo-s trough SeSP; Inseg

\*Registered trademark of Sanofi

volume of distribution is 53–83 liters. Total plasma and renal clearances are in the range of 157–176 and 3.0–3.6 mL/min, respectively. With repetitive dosing, irbesartan accumulates to no clinically relevant extent.

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

#### Special Populations

**Pediatric:** Irbesartan pharmacokinetics have not been investigated in patients <18 years of age.

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

**Geriatric:** In elderly subjects (age 65–80 years), irbesartan elimination half-life was not significantly altered, but AUC and  $C_{max}$  values were about 20–50% greater than those of young subjects (age 18–40 years). No dosage adjustment is necessary in the elderly.

**Race:** In healthy black subjects, irbesartan AUC values were approximately 25% greater than whites; there were no differences in  $C_{max}$  values.

**Renal Insufficiency:** The pharmacokinetics of irbesartan were not altered in patients with renal impairment or in patients on hemodialysis. Irbesartan 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: Hypotension in Volume- or Salt-depleted Patients and DOSAGE AND ADMINISTRATION.)

**Hepatic Insufficiency:** The pharmacokinetics of irbesartan following repeated oral administration were not significantly affected in patients with mild to moderate cirrhosis of the liver. No dosage adjustment is necessary in patients with hepatic insufficiency.

**Drug Interactions:** (See PRECAUTIONS: Drug Interactions.)

#### Pharmacodynamics

In healthy subjects, single oral irbesartan 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 irbesartan causes a 1.5–2 fold rise in angiotensin II plasma concentration and a 2–3 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.

#### Clinical Studies

The antihypertensive effects of AVAPRO (irbesartan) were examined in seven (7) major placebo-controlled 8–12 week trials in patients with baseline diastolic blood pressures of 95–110 mmHg. Doses of 1–800 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 gender, age, and race. Two of the seven placebo-controlled trials identified above examined the antihypertensive effects of irbesartan and hydrochlorothiazide in combination.

The seven (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 and 300 mg provided statistically and clinically significant decreases in systolic and diastolic blood pressure with trough (24 hours post-dose) effects after 6–12 weeks of treatment compared to placebo, of about 8–10/5–6 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.

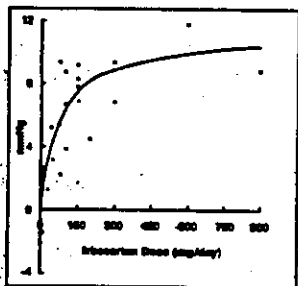


Figure 1. Placebo-subtracted reduction in trough SBP, integrated analysis

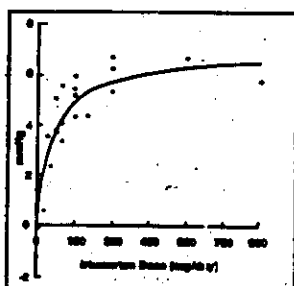


Figure 2. Placebo-subtracted reduction in trough DBP, integrated analysis

Once-daily administration of therapeutic doses of irbesartan gave peak effects at around 3–6 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 60–70%. 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, 12.5, 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, gender, 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.

#### INDICATIONS AND USAGE

AVAPRO (irbesartan) is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.

#### CONTRAINDICATIONS

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

#### WARNINGS

##### Fetal/Neonatal Morbidity and Mortality

Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature in patients who were taking angiotensin-converting-enzyme inhibitors. When pregnancy is detected, AVAPRO should be discontinued as soon as possible.

The use of drugs that act directly on the renin-angiotensin system during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug.

These adverse effects do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester.

Mothers whose embryos or fetuses are exposed to an angiotensin II receptor antagonist only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should have the patient discontinue the use of AVAPRO as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to a drug acting on the renin-angiotensin system will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intraamniotic environment.

If oligohydramnios is observed, AVAPRO should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to an angiotensin II receptor antagonist should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function.

When pregnant rats were treated with irbesartan from day 0 to day 20 of gestation (oral doses of 50, 180, and 650 mg/kg/day), increased incidences of renal pelvic cavitation, hydronephrosis and/or absence of renal papilla were observed in fetuses at doses  $\geq 50$  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  $\geq 180$  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 6–15, 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.

Radioactivity was present in the rat and rabbit fetus during late gestation and in rat milk following oral doses of radiolabeled irbesartan.

#### Hypotension in Volume- or Salt-depleted Patients

Excessive reduction of blood pressure was rarely seen (<0.1%) in patients with uncomplicated hypertension. Initiation of antihypertensive therapy may cause symptomatic hypotension in patients with intravascular volume- or sodium-depletion, e.g., in patients treated vigorously with diuretics or in patients on dialysis. Such volume depletion should be corrected prior to administration of AVAPRO (irbesartan), or a low starting dose should be used (see DOSAGE AND ADMINISTRATION).

If hypotension occurs, the patient should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty once the blood pressure has stabilized.

#### PRECAUTIONS

##### Impaired Renal Function

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (e.g., patients with severe congestive heart failure), treatment with angiotensin-converting-enzyme inhibitors has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. AVAPRO would be expected to behave similarly. In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or BUN have been reported. There has been no known use of AVAPRO in patients with unilateral or bilateral renal artery stenosis, but a similar effect should be anticipated.

##### Information for Patients

**Pregnancy:** Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to drugs that act on the renin-angiotensin system, and they should also be told that these consequences do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

##### Drug Interactions

No significant drug-drug pharmacokinetic (or pharmacodynamic) interactions have been found in interaction studies with hydrochlorothiazide, digoxin, warfarin, and nifedipine.

*In vitro* studies show significant inhibition of the formation of oxidized irbesartan metabolites with the known cytochrome CYP 2C9 substrates/inhibitors sulphenazole, tolbutamide and nifedipine. However, in clinical studies the consequences of concomitant irbesartan 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 isozymes 1A1, 1A2, 2A6, 2B6, 2D6, 2E1, or 3A4.

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

##### Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence of carcinogenicity was observed when irbesartan 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 two years. For male and female rats, 500 mg/kg/day provided an average systemic exposure to irbesartan ( $AUC_{0-24h}$ , bound plus unbound) about 3 and 11 times, respectively, the average systemic exposure in humans receiving the maximum recommended dose (MRD) of 300 mg irbesartan/day, whereas 1000 mg/kg/day (administered to females only) provided an average systemic exposure about 21 times that reported for humans at the MRD. For male and female mice, 1000 mg/kg/day provided an exposure to irbesartan about 3 and 5 times, respectively, the human exposure at 300 mg/day.

Irbesartan 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). 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  $\leq 650$  mg/kg/day, the highest dose providing a systemic exposure to irbesartan ( $AUC_{0-24h}$ , bound plus unbound) about 5 times that found in humans receiving the maximum recommended dose of 300 mg/day.

##### Pregnancy

**Pregnancy Categories C (first trimester) and D (second and third trimester).**

See WARNINGS: Fetal/Neonatal Morbidity and Mortality.

##### 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, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

##### Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

##### Geriatric Use

Of the total number of patients receiving AVAPRO (irbesartan) in controlled clinical studies, 911 patients (18.5%) were 65 years and over, while 150 patients (3.0%) were 75 years and over. No overall differences in effectiveness or safety were observed between these patients and younger patients, but greater sensitivity in some older individuals cannot be ruled out.

#### ADVERSE REACTIONS

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. Treatment with AVAPRO was well-tolerated, with an incidence of adverse events similar to placebo. These events generally were mild and transient with no relationship to the dose of AVAPRO.

In placebo-controlled clinical trials, discontinuation of therapy due to a clinically adverse event was required in 3.3 percent of patients treated with AVAPRO, versus 4.5 percent of patients given placebo.

In placebo-controlled clinical trials, the adverse event experiences that occurred in at least 1% of patients treated with AVAPRO ( $n=1965$ ) and at a higher incidence versus placebo ( $n=641$ ) included diarrhea (3% vs. 2%), dyspepsia/heartburn (2% vs. 1%), musculoskeletal trauma (2% vs. 1%), fatigue (4% vs. 3%), and upper respiratory infection (9% vs. 6%). None of these differences were significant.

The following adverse events occurred at an incidence of 1% or greater in patients treated with irbesartan, but were at least as frequent or more frequent in patients receiving placebo: abdominal pain, anxiety/nervousness, chest pain, dizziness, edema, headache, influenza, musculoskeletal pain, pharyngitis, nausea, vomiting, rash, rhinitis, sinus abnormality, tachycardia and urinary tract infection.

Irbesartan use was not associated with an increased incidence of dry cough, 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.

The incidence of hypotension or orthostatic hypotension was low in irbesartan treated patients (0.4%), unrelated to dosage, and similar to the incidence among placebo treated patients (0.2%). Dizziness, syncope, and vertigo were reported with equal or less frequency in patients receiving irbesartan compared with placebo.

In addition, the following potentially important events occurred in less than 1% of the 1965 patients and at least 5 patients (0.3%) receiving irbesartan in clinical studies, and those less frequent, clinically significant events (listed by body system) it cannot be determined whether these events were causally related to irbesartan:

**Body as a Whole:** fever, chills, facial edema, upper extremity edema;  
**Cardiovascular:** flushing, hypertension, cardiac murmur, myocardial infarction, angina pectoris, arrhythmic/conduction disorder, cardio-respiratory arrest, heart failure, hypertensive crisis;

**Dermatologic:** pruritus, dermatitis, ecchymosis, erythema face, urticaria;  
**Endocrine/Metabolic/Electrolyte Imbalances:** sexual dysfunction, libido change, gout;

**Gastrointestinal:** constipation, oral lesion, gastroenteritis, flatulence, abdominal distention;

**Musculoskeletal/Connective Tissue:** extremity swelling, muscle cramp, arthritis, muscle ache, musculoskeletal chest pain, joint stiffness, bursitis, muscle weakness;

**Nervous System:** sleep disturbance, numbness, somnolence, emotional disturbance, depression, paresthesia, tremor, transient ischemic attack, cerebrovascular accident;

**Renal/Genitourinary:** abnormal urination, prostate disorder;

**Respiratory:** epistaxis, tracheobronchitis, congestion, pulmonary congestion, dyspnea, wheezing;

**Special Senses:** vision disturbance, hearing abnormality, ear infection, ear pain, conjunctivitis, other eye disturbance, eyelid abnormality, ear abnormality.

##### Laboratory Test Findings

In controlled clinical trials, clinically important differences in laboratory tests were rarely associated with administration of AVAPRO.

**Creatinine, Blood Urea Nitrogen:** Minor increases in blood urea nitrogen (BUN) or serum creatinine were observed in less than 0.7% of patients with essential hypertension treated with AVAPRO alone versus 0.9% on placebo. (See PRECAUTIONS: Impaired Renal Function.)

**Hematologic:** Mean decreases in hemoglobin of 0.2 g/dL were observed in 0.2% of patients receiving AVAPRO compared to 0.3% of placebo treated patients. Neutropenia ( $<1000$  cells/mm<sup>3</sup>) occurred at similar frequencies among patients receiving AVAPRO (0.3%) and placebo treated patients (0.5%).

#### 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 expected to be hypotension and tachycardia; bradycardia might also occur from overdosage. Irbesartan is not removed by hemodialysis.

To obtain up-to-date information about the treatment of overdosage, a good resource is a certified Regional Poison-Control Center. Telephone numbers of certified poison-control centers are listed in the *Physicians' Desk Reference* (PDR). In managing overdosage, consider the possibilities of multiple-drug interactions.



drug-drug interactions, and unusual drug kinetics in the patient.

Laboratory determinations of serum levels of irbesartan are not widely available, and such determinations have, in any event, no known established role in the management of irbesartan overdose.

Acute oral toxicity studies with irbesartan in mice and rats indicated acute lethal doses were in excess of 2000 mg/kg, about 25- and 50-fold the maximum recommended human dose (300 mg) on a mg/m<sup>2</sup> basis, respectively.

#### DOSAGE AND ADMINISTRATION

The recommended initial dose of AVAPRO is 150 mg once daily. Patients requiring further reduction in blood pressure should be titrated to 300 mg once daily.

A low dose of a diuretic may be added, if blood pressure is not controlled by AVAPRO alone. Hydrochlorothiazide has been shown to have an additive effect (see CLINICAL PHARMACOLOGY: Clinical Studies). Patients not adequately treated by the maximum dose of 300 mg once daily are unlikely to derive additional benefit from a higher dose or twice-daily dosing.

No dosage adjustment is necessary in elderly patients, or in patients with hepatic impairment or mild to severe renal impairment.

AVAPRO may be administered with other antihypertensive agents.

AVAPRO may be administered with or without food.

#### Volume- and Salt-depleted Patients

A lower initial dose of AVAPRO (75 mg) is recommended in patients with depletion of intravascular volume or salt (e.g., patients treated vigorously with diuretics or on hemodialysis) (see WARNINGS: Hypotension in Volume- or Salt-depleted Patients).

#### HOW SUPPLIED

AVAPRO® (irbesartan) is available as white to off-white biconvex oval tablets, debossed with a heart shape on one side and a portion of the NDC code on the other. Unit-of-use bottles contain 30, 90, or 500 tablets and blister packs contain 100 tablets, as follows:

|                | 75 mg        | 150 mg       | 300 mg       |
|----------------|--------------|--------------|--------------|
| Debossing      | 2771         | 2772         | 2773         |
| Bottle of 30   | 0087-2771-31 | 0087-2772-31 | 0087-2773-31 |
| Bottle of 90   | 0087-2771-32 | 0087-2772-32 | 0087-2773-32 |
| Bottle of 500  | 0087-2771-15 | 0087-2772-15 | 0087-2773-15 |
| Blister of 100 | 0087-2771-35 | 0087-2772-35 | 0087-2773-35 |

#### Storage

Store at a temperature between 15° C and 30° C (59° F and 86° F) [USP].

Manufactured and Distributed by:  
Bristol-Myers Squibb Company  
Princeton, NJ 08543-4500

Comarketed by:  
Sanofi Pharmaceuticals, Inc.  
New York, NY 10016

# Diovan<sup>TM</sup>

C87-6 (Rev. 4/97)  
666751

valsartan

Capsules

Prescribing Information

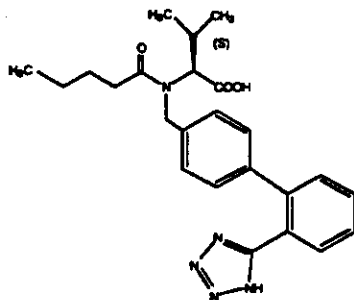
## USE IN PREGNANCY

When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, Diovan should be discontinued as soon as possible. See WARNINGS: Fetal/Neonatal Morbidity and Mortality.

## DESCRIPTION

Diovan (valsartan) is a nonpeptide, orally active, and specific angiotensin II antagonist acting on the AT<sub>1</sub> receptor subtype.

Valsartan is chemically described as *N*-(1-oxopentyl)-*N*-[2'-(1*H*-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl-L-valine. Its empirical formula is C<sub>26</sub>H<sub>29</sub>N<sub>5</sub>O<sub>3</sub>, its molecular weight is 435.5, and its structural formula is



Valsartan is a white to practically white fine powder. It is soluble in ethanol and methanol and slightly soluble in water.

Diovan is available as capsules for oral administration, containing either 80 mg or 160 mg of valsartan. The inactive ingredients of the capsules are cellulose compounds, crospovidone, gelatin, iron oxides, magnesium stearate, povidone, sodium lauryl sulfate, and titanium dioxide.

## CLINICAL PHARMACOLOGY

### Mechanism of Action

Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzyme (ACE, kininase II). Angiotensin II is the principal pressor agent of the renin-angiotensin system, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation, and renal reabsorption of sodium. Valsartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT<sub>1</sub> receptor in many tissues, such as vascular smooth muscle and the adrenal gland. Its action is therefore independent of the pathways for angiotensin II synthesis.

There is also an AT<sub>2</sub> receptor found in many tissues, but AT<sub>2</sub> is not known to be associated with cardiovascular homeostasis. Valsartan has much greater affinity (about 20,000-fold) for the AT<sub>1</sub> receptor than for the AT<sub>2</sub> receptor. The primary metabolite of valsartan is essentially inactive with an affinity for the AT<sub>1</sub> receptor about one 200th that of valsartan itself.

Blockade of the renin-angiotensin system with ACE inhibitors, which inhibit the biosynthesis of angiotensin II from angiotensin I, is widely used in the treatment of hypertension. ACE inhibitors also inhibit the degradation of bradykinin, a reaction also catalyzed by ACE. Because valsartan does not inhibit ACE (kininase II), it does not affect the response to bradykinin. Whether this difference has clinical relevance is not yet known. Valsartan does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

Blockade of the angiotensin II receptor inhibits the negative regulatory feedback of angiotensin II on renin secretion, but the resulting increased plasma renin activity and angiotensin II circulating levels do not overcome the effect of valsartan on blood pressure.

### Pharmacokinetics

Valsartan peak plasma concentration is reached 2 to 4 hours after dosing. Valsartan shows bi-exponential decay kinetics following intravenous administration, with an average elimination half-life of about 6 hours. Absolute bioavailability for the capsule formulation is about 25% (range 10%-35%). Food decreases the exposure (as measured by AUC) to valsartan by about 40% and peak plasma concentration (C<sub>max</sub>) by about 50%. AUC and C<sub>max</sub> values of valsartan increase approximately linearly with increasing dose over the clinical dosing range. Valsartan does not accumulate appreciably in plasma following repeated administration.

### Metabolism and Elimination

Valsartan, when administered as an oral solution, is primarily recovered in feces (about 83% of dose) and urine (about 13% of dose). The recovery is mainly as unchanged drug, with only about 20% of dose recovered as metabolites. The primary metabolite, accounting for about 9% of dose is valeryl 4-hydroxy valsartan. The enzyme(s) responsible for valsartan metabolism have not been identified but do not seem to be CYP 450 isozymes.

Following intravenous administration, plasma clearance of valsartan is about 2 L/h and its renal clearance is 0.62 L/h (about 30% of total clearance).

### Distribution

The steady state volume of distribution of valsartan after intravenous administration is small (17 L), indicating that valsartan does not distribute into tissues extensively. Valsartan is highly bound to serum proteins (95%), mainly serum albumin.

### Special Populations

**Pediatric:** The pharmacokinetics of valsartan have not been investigated in patients <18 years of age.

**Geriatric:** Exposure (measured by AUC) to valsartan is higher by 70% and the half-life is longer by 35% in the elderly than in the young. No dosage adjustment is necessary (see DOSAGE AND ADMINISTRATION).

**Gender:** Pharmacokinetics of valsartan does not differ significantly between males and females.

**Renal Insufficiency:** There is no apparent correlation between renal function (measured by creatinine clearance) and exposure (measured by AUC) to valsartan in patients with different degrees of renal impairment. Consequently, dose adjustment is not required in patients with mild-to-moderate renal dysfunction. No studies have been performed in patients with severe impairment of renal function (creatinine clearance < 10 mL/min). Valsartan is not removed from the plasma by hemodialysis. In the case of severe renal disease, exercise care with dosing of valsartan (see DOSAGE AND ADMINISTRATION).

**Hepatic Insufficiency:** On average, patients with mild-to-moderate chronic liver disease have twice the exposure (measured by AUC values) to valsartan of healthy volunteers (matched by age, sex and weight). In general, no dosage adjustment is needed in patients with mild-to-moderate liver disease. Care should be exercised in patients with liver disease (see DOSAGE AND ADMINISTRATION).

### Pharmacodynamics and Clinical Effects

Valsartan inhibits the pressor effect of angiotensin II infusions. An oral dose of 80 mg inhibits the pressor effect by about 80% at peak with approximately 30% inhibition persisting for 24 hours. No information on the effect of larger doses is available.

Removal of the negative feedback of angiotensin II causes a 2- to 3-fold rise in plasma renin and consequent rise in angiotensin II plasma concentration in hypertensive patients. Minimal decreases in plasma aldosterone were observed after administration of valsartan; very little effect on serum potassium was observed.

In multiple-dose studies in hypertensive patients with stable renal insufficiency and patients with renovascular hypertension, valsartan had no clinically significant effects on glomerular filtration rate, filtration fraction, creatinine clearance, or renal plasma flow.

In multiple-dose studies in hypertensive patients, valsartan had no notable effects on total cholesterol, fasting triglycerides, fasting serum glucose, or uric acid.

The antihypertensive effects of Diovan were demonstrated principally in 7 placebo-controlled, 4- to 12-week trials (one in patients over 65) of dosages from 10 to 320 mg/day in patients with baseline diastolic blood pressures of 95-115. The studies allowed comparison of once-daily and twice-daily regimens of 160 mg/day; comparison of peak and trough effects; comparison (in pooled

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data) of response by gender, age, and race; and evaluation of incremental effects of hydrochlorothiazide.

Administration of valsartan to patients with essential hypertension results in a significant reduction of sitting, supine, and standing systolic and diastolic blood pressure, usually with little or no orthostatic change.

In most patients, after administration of a single oral dose, onset of antihypertensive activity occurs at approximately 2 hours, and maximum reduction of blood pressure is achieved within 6 hours. The antihypertensive effect persists for 24 hours after dosing, but there is a decrease from peak effect at lower doses (40 mg) presumably reflecting loss of inhibition of angiotensin II. At higher doses, however (160 mg), there is little difference in peak and trough effect. During repeated dosing, the reduction in blood pressure with any dose is substantially present within 2 weeks, and maximal reduction is generally attained after 4 weeks. In long-term follow-up studies (without placebo control), the effect of valsartan appeared to be maintained for up to two years. The antihypertensive effect is independent of age, gender or race. The latter finding regarding race is based on pooled data and should be viewed with caution, because antihypertensive drugs that affect the renin-angiotensin system (that is, ACE inhibitors and angiotensin-II blockers) have generally been found to be less effective in low-renin hypertensives (frequently blacks) than in high-renin hypertensives (frequently whites). In pooled, randomized, controlled trials of Diovan that included a total of 140 blacks and 830 whites, valsartan and an ACE-inhibitor control were generally at least as effective in blacks as whites. The explanation for this difference from previous findings is unclear.

Abrupt withdrawal of valsartan has not been associated with a rapid increase in blood pressure.

The blood pressure lowering effect of valsartan and thiazide-type diuretics are approximately additive.

The 7 studies of valsartan monotherapy included over 2000 patients randomized to various doses of valsartan and about 800 patients randomized to placebo. Doses below 80 mg were not consistently distinguished from those of placebo at trough, but doses of 80, 160 and 320 mg produced dose-related decreases in systolic and diastolic blood pressure, with the difference from placebo of approximately 6-9/3-5 mmHg at 80-160 mg and 9/6 mmHg at 320 mg. In a controlled trial the addition of HCTZ to valsartan 80 mg resulted in additional lowering of systolic and diastolic blood pressure by approximately 6/3 and 12/5 mmHg for 12.5 and 25 mg of HCTZ, respectively, compared to valsartan 80 mg alone.

Patients with an inadequate response to 80 mg once daily were titrated to either 160 mg once daily or 80 mg twice daily, which resulted in a comparable response in both groups.

In controlled trials, the antihypertensive effect of once-daily valsartan 80 mg was similar to that of once-daily enalapril 20 mg or once-daily lisinopril 10 mg.

There was essentially no change in heart rate in valsartan-treated patients in controlled trials.

## INDICATIONS AND USAGE

Diovan is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.

## CONTRAINDICATIONS

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

## WARNINGS

### Fetal/Neonatal Morbidity and Mortality

Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature in patients who were taking angiotensin-converting enzyme inhibitors. When pregnancy is detected, Diovan should be discontinued as soon as possible.

The use of drugs that act directly on the renin-angiotensin system during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug.

These adverse effects do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to an angiotensin II receptor antagonist only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should advise the patient to discontinue the use of valsartan as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to a drug acting on the renin-angiotensin system will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intra-amniotic environment.

If oligohydramnios is observed, valsartan should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of in utero exposure to an angiotensin II receptor antagonist should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function.

No teratogenic effects were observed when valsartan was administered to pregnant mice and rats at oral doses up to 600 mg/kg/day and to pregnant rabbits at oral doses up to 10 mg/kg/day. However, significant decreases in fetal weight, pup birth weight, pup survival rate, and slight delays in developmental milestones were observed in studies in which parental rats were treated with valsartan at oral, maternally toxic (reduction in body weight gain and food consumption) doses of 600 mg/kg/day during organogenesis or late gestation and lactation. In rabbits, fetotoxicity (i.e., resorptions, litter loss, abortions, and low body weight) associated with maternal toxicity (mortality) was observed at doses of 5 and 10 mg/kg/day. The no observed adverse effect doses of 600, 200 and 2 mg/kg/day in mice, rats and rabbits represent 9, 6, and 0.1 times, respectively, the maximum recommended human dose on a mg/m<sup>2</sup> basis. (Calculations assume an oral dose of 320 mg/day and a 60-kg patient.)

### Hypotension in Volume- and/or Salt-Depleted Patients

Excessive reduction of blood pressure was rarely seen (0.1%) in patients with uncomplicated hypertension. In patients with an activated renin-angiotensin system, such as volume- and/or salt-depleted patients receiving high doses of diuretics, symptomatic hypotension may occur. This condition should be corrected prior to administration of Diovan, or the treatment should start under close medical supervision.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty once the blood pressure has stabilized.

## PRECAUTIONS

### General

**Impaired Hepatic Function:** As the majority of valsartan is eliminated in the bile, patients with mild-to-moderate hepatic impairment, including patients with biliary obstructive disorders, showed lower valsartan clearance (higher AUCs). Care should be exercised in administering Diovan to these patients.

**Impaired Renal Function:** As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (e.g., patients with severe congestive heart failure), treatment with angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. Diovan would be expected to behave similarly.

In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen have been reported. In a 4-day trial of valsartan in 12 patients with unilateral renal artery stenosis, no significant increases in serum creatinine or blood urea nitrogen were observed. There has been no long-term use of Diovan in patients with unilateral or bilateral renal artery stenosis, but an effect similar to that seen with ACE inhibitors should be anticipated.

### Information for Patients

**Pregnancy:** Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to drugs that act on the renin-angiotensin system, and they should also be told that these consequences do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

### Drug Interactions

No clinically significant pharmacokinetic interactions were observed when valsartan was coadministered with amlodipine, atenolol, cimetidine, digoxin, furosemide, glyburide, hydrochlorothiazide, or indomethacin. The valsartan-atenolol combination was more antihypertensive than either component, but it



## Diovan™ valsartan

did not lower the heart rate more than atenolol alone.

Coadministration of valsartan and warfarin did not change the pharmacokinetics of valsartan or the time-course of the anticoagulant properties of warfarin.

**CYP 450 Interactions:** The enzyme(s) responsible for valsartan metabolism have not been identified but do not seem to be CYP 450 isozymes. The inhibitory or induction potential of valsartan on CYP 450 is also unknown.

### Carcinogenesis, Mutagenesis, Impairment of Fertility

There was no evidence of carcinogenicity when valsartan was administered in the diet to mice and rats for up to 2 years at doses up to 160 and 200 mg/kg/day, respectively. These doses in mice and rats are about 2.6 and 6 times, respectively, the maximum recommended human dose on a mg/m<sup>2</sup> basis. (Calculations assume an oral dose of 320 mg/day and a 60-kg patient.)

Mutagenicity assays did not reveal any valsartan-related effects at either the gene or chromosome level. These assays included bacterial mutagenicity tests with *Salmonella* (Ames) and *E coli*; a gene mutation test with Chinese hamster V79 cells; a cytogenetic test with Chinese hamster ovary cells; and a rat micronucleus test.

Valsartan had no adverse effects on the reproductive performance of male or female rats at oral doses up to 200 mg/kg/day. This dose is 6 times the maximum recommended human dose on a mg/m<sup>2</sup> basis. (Calculations assume an oral dose of 320 mg/day and a 60-kg patient.)

**Pregnancy Categories C (first trimester) and D (second and third trimesters)**

See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

### Nursing Mothers

It is not known whether valsartan is excreted in human milk, but valsartan was excreted in the milk of lactating rats. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

### Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

### Geriatric Use

In the controlled clinical trials of valsartan, 1214 (36.2%) of patients treated with valsartan were ≥ 65 years and 265 (7.9%) were ≥ 75 years. No overall difference in the efficacy or safety of valsartan was observed in this patient population, but greater sensitivity of some older individuals cannot be ruled out.

### ADVERSE REACTIONS

Diovan has been evaluated for safety in more than 4000 patients, including over 400 treated for over 6 months, and more than 160 for over 1 year. Adverse experiences have generally been mild and transient in nature and have only infrequently required discontinuation of therapy. The overall incidence of adverse experiences with Diovan was similar to placebo.

The overall frequency of adverse experiences was neither dose-related nor related to gender, age, race, or regimen. Discontinuation of therapy due to side effects was required in 2.3% of valsartan patients and 2.0% of placebo patients. The most common reasons for discontinuation of therapy with Diovan were headache and dizziness.

The adverse experiences that occurred in placebo-controlled clinical trials in at least 1% of patients treated with Diovan and at a higher incidence in valsartan (n=2316) than placebo (n=888) patients included viral infection (3% vs. 2%), fatigue (2% vs. 1%), and abdominal pain (2% vs. 1%).

Headache, dizziness, upper respiratory infection, cough, diarrhea, rhinitis, sinusitis, nausea, pharyngitis, edema, and arthralgia occurred at a more than 1% rate but at about the same incidence in placebo and valsartan patients.

In trials in which valsartan was compared to an ACE inhibitor with or without placebo, the incidence of dry cough was significantly greater in the ACE-inhibitor group (7.9%) than in the groups who received valsartan (2.6%) or placebo (1.5%). In a 129-patient trial limited to patients who had had dry cough when they had previously received ACE inhibitors, the incidences of cough in patients

who received valsartan, HCTZ, or lisinopril were 20%, 19%, and 69% respectively (p<0.001).

Dose-related orthostatic effects were seen in less than 1% of patients. An increase in the incidence of dizziness was observed in patients treated with Diovan 320 mg (8%) compared to 10 to 160 mg (2% to 4%).

Diovan has been used concomitantly with hydrochlorothiazide without evidence of clinically important adverse interactions.

Other adverse experiences that occurred in controlled clinical trials of patients treated with Diovan (> 0.2% of valsartan patients) are listed below. It cannot be determined whether these events were causally related to Diovan.

**Body as a Whole:** Allergic reaction and asthenia

**Cardiovascular:** Palpitations

**Dermatologic:** Pruritus and rash

**Digestive:** Constipation, dry mouth, dyspepsia, and flatulence

**Musculoskeletal:** Back pain, muscle cramps, and myalgia

**Neurologic and Psychiatric:** Anxiety, insomnia, paresthesia, and somnolence

**Respiratory:** Dyspnea

**Special Senses:** Vertigo

**Urogenital:** Impotence

Other reported events seen less frequently in clinical trials included chest pain, syncope, anorexia, vomiting, and angioedema.

### Clinical Laboratory Test Findings

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

**Creatinine:** Minor elevations in creatinine occurred in 0.6% of patients taking Diovan and 0.6% given placebo in controlled clinical trials.

**Hemoglobin and Hematocrit:** Greater than 20% decreases in hemoglobin and hematocrit were observed in 0.4% and 0.8%, respectively, of Diovan patients, compared with 0.1% and 0.1% in placebo-treated patients. One valsartan patient discontinued treatment for microcytic anemia.

**Liver function tests:** Occasional elevations (greater than 150%) of liver chemistries occurred in Diovan-treated patients. Three patients (< 0.1%) treated with valsartan discontinued treatment for elevated liver chemistries.

**Neutropenia:** Neutropenia was observed in 1.9% of patients treated with Diovan and 0.8% of patients treated with placebo.

**Serum Potassium:** Greater than 20% increases in serum potassium were observed in 4.4% of Diovan-treated patients compared to 2.9% of placebo-treated patients. No patient treated with valsartan discontinued therapy for hyperkalemia.

### OVERDOSAGE

Limited data are available related to overdosage in humans. The most likely manifestations of overdosage would be hypotension and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted.

Valsartan is not removed from the plasma by hemodialysis.

Valsartan was without grossly observable adverse effects at single oral doses up to 2000 mg/kg in rats and up to 1000 mg/kg in marmosets, except for salivation and diarrhea in the rat and vomiting in the marmoset at the highest dose (60 and 37 times, respectively, the maximum recommended human dose on a mg/m<sup>2</sup> basis). (Calculations assume an oral dose of 320 mg/day and a 60-kg patient.)

### DOSAGE AND ADMINISTRATION

The recommended starting dose of Diovan is 80 mg once daily when used as monotherapy in patients who are not volume-depleted. Diovan may be used over a dose range of 80 mg to 320 mg daily, administered once-a-day.

The antihypertensive effect is substantially present within 2 weeks and maximal reduction is generally attained after 4 weeks. If additional antihypertensive effect is required, the dosage may be increased to 160 mg or 320 mg or a diuretic may be added. Addition of a diuretic has a greater effect than dose increases beyond 80 mg.

No initial dosage adjustment is required for elderly patients, for patients with mild or moderate renal impairment, or for patients with mild or moderate liver

insufficiency. Care should be exercised with dosing of Diovan in patients with hepatic or severe renal impairment.

Diovan may be administered with other antihypertensive agents.

Diovan may be administered with or without food.

#### HOW SUPPLIED

Diovan is available as capsules containing valsartan 80 mg or 160 mg. Both strengths are packaged in bottles of 100 capsules and 4000 capsules and unit dose blister packages. Capsules are imprinted as follows:

80 mg Capsule - Light grey/light pink opaque, imprinted CG FZF

Bottles of 100 .....NDC 0083-4000-01

Bottles of 4000 .....NDC 0083-4000-41

Unit Dose (blister pack) .....NDC 0083-4000-61

Box of 100 (strips of 10)

160 mg Capsule - Dark grey/light pink opaque, imprinted CG GOG

Bottles of 100 .....NDC 0083-4001-01

Bottles of 4000 .....NDC 0083-4001-41

Unit Dose (blister pack) .....NDC 0083-4001-61

Box of 100 (strips of 10)

Store below 30°C (86°F). Protect from moisture. Dispense in tight container (USP).

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