CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20738/S001

FINAL PRINTED LABELING
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-biaryl, non-terzole angiotensin II receptor (AT1) antagonist. A selective non-peptide molecule. Teveten is chemically described as (E)-2-butyl-1-[4-(3-carboxyphenoxy)-2-thienyl)methylimidazole-5-acrylic acid. Its empirical formula is C₆₂H₄₇NO₂₃S₄ and molecular weight is 520.825. Its structural formula is

\[
\text{C}_\text{6}_\text{2}\text{H}_\text{4}_\text{7}\text{N}_\text{O}_\text{2}_\text{3}\text{S}_\text{4} \quad \text{and molecular weight is 520.825. Its structural formula is}
\]

Eprosartan mesylate is a white to off-white free-flowing crystalline powder that is insoluble in water, freely soluble in ethanol, and melts between 249° and 250°C. Teveten is available as aqueous film-coated, scored Teva® tablets containing eprosartan mesylate equivalent to 200 mg or 400 mg eprosartan (white 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 (kinase 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 reabsorption 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 AT1 receptor found in many tissues (e.g., vascular smooth muscle, adrenal gland). There is also an AT2 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 AT1 receptor. Its affinity for the AT1 receptor is 1,000 times greater than for the AT2 receptor. In vitro binding studies indicate that eprosartan is a reversible, competitive inhibitor of the AT1 receptor.

Blockade of the AT1 receptor removes the negative feedback of angiotensin II on renin secretion, but the resulting increased plasma renin activity and circulating angiotensin II do not overcompensate the effect of eprosartan on blood pressure.

Teveten (eprosartan mesylate) does not inhibit kinase II, the enzyme that converts angiotensin I to angiotensin II, and degrades bradykinin, whether this has any 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 Cₘₚₖ 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 6 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 [14C]eprosartan in human subjects. Eprosartan was the only drug-related compound found in the plasma and feces. Following intravenous [14C]eprosartan, about 61% of the material is recovered in the feces and about 37% in the urine. Following an oral dose of [14C]eprosartan, about 95% is recovered in the feces and about 7% in the urine. Approximately 20% of the radioactively excerted 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 50-year-old patient of 48.6 liters. The population mean steady-state volume of distribution (Vₙₜₐ) 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 liters 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, Cₘₚₖ and Cₘₚₖ values increased on average by approximately two-fold, 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 26 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 q.d. for 7 days, patients with mild (ClCr = 60 to 80 mL/min) showed mean
eprosartan, and AUC values similar to subjects with normal renal function. Compared to patients with normal renal function, mean AUC and Cmax values were approximately 30% higher in patients with moderate renal impairment (CLcr 30 to 59 mL/min) and 50% higher in patients with severe renal impairment (CLcr<15 mL/min). The unbound eprosartan fraction was not influenced by renal function 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 (CLcu <1 L/hr) (see DOSAGE AND ADMINISTRATION).

**Hepatic Insufficiency:** Eprosartan AUC but not Cmax 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 digoxin in diabetic patients did not affect 24-hour plasma glucose profiles. Eprosartan pharmacokinetics were not affected by concomitant administration of simvastatin. Eprosartan did not inhibit human cytochrome P450 enzymes CYP1A2, 2C9, 2C19, 2D6, and 3A4 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 CYP3A4 and 2C9, respectively.

**Pharmacodynamics and Clinical Effects:** Eprosartan inhibits the pharmacokinetic effects of angiotensin II in infusions in healthy adult men. Single oral doses of eprosartan from 10 mg to 400 mg have been shown to inhibit the vasopressor, renal vasconstrictive 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 AT1 receptor 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 responses to a given dose in most patients may take 2 to 4 weeks of treatment. Osseous 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 persisting for 24 to 48 hours after the last dose. There was no change in ERPF in hypertensive patients and patients with renal insufficiency. On normal salt diets, Eprosartan was not reduced 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 2 days or 360 mg twice daily for 2 days) has 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 sDBP ranging from 95 mmHg to 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 600 mg given once daily or twice daily. The five studies included 1,111 patients randomized to eprosartan and 918 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 had more pronounced decreases in sitting systolic and diastolic blood pressure at trough, with differences from placebo of approximately 5 to 10/3 to 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 bi-d. with 400 mg to 800 mg b.i.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 to 8.5/2 to 3 mmHg. Peak (1 to 3 hours) effects were generally modest, but were substantially larger than trough effects with bi-d. dosing, with the trough/peak ratio for diastolic blood pressure 60% to 80%. In the once-daily dose-response study, trough-to-peak response of 65% 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 no dose-related effects on laboratory tests and other clinical parameters. In general, randomization to placebo in the study in patients with essential hypertension did not result in significant increases in siting systolic and diastolic blood pressure at trough, with differences from placebo of approximately 0 to 3 to 7/0 to 2 mmHg. Peak (1 to 3 hours) effects were generally modest, but were substantially larger than trough effects with bi-d. dosing, with the trough/peak ratio for diastolic blood pressure 60% to 80%. In the once-daily dose-response study, trough-to-peak response of 65% were observed at some doses (including 1200 mg), suggesting attenuation of effect at the end of the dosing interval.

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**Indications and Usage:** Teveten is a direct-acting ACE inhibitor for the treatment of hypertension. It may be used alone or in combination with other antihypertensive drugs 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 leipsosran 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 unless it is considered essential for the mother. Contraindications to obstetric and medical procedures may also be affected or exacerbated by angiotensin II receptor antagonists in pregnant women, and, therefore, exposure may increase the risk of fetal and neonatal injury in utero and in the neonatal period. 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 (immaternal and fetal mortality, low maternal body weight and food consumption, resorptions, abortions and stillbirths) in pregnant rabbits given oral doses as low as 10 mg eporsartan/kg/day. No maternal or fetal adverse effects were observed at 3 mg/kg/day, the oral dose yielded a systemic exposure (AUC) to bound eporsartan 0.6 times that achieved in humans given 400 mg b.i.d. No adverse effects on uterine contractile development and maturation of offspring were observed when eporsaratan mesylate was administered to pregnant rats at oral doses up to 1000 mg. eporsartan/kg/day (100 mg eporsartan/kg/day in the pregnant rat). In non-pregnant rats, both oral eporsartan doses produced a systemic exposure to unbound eporsartan 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 Fetal 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 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, azotemia, and rarely with acute renal failure and/or death. Teveten leipsosran 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 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 enroll in pregnancy registries that have been designed to monitor adverse outcomes of exposure.

Drug Interactions
Eprosartan has been shown to have no effect on the pharmacokinetics of digoxin and the pharmacodynamics of warfarin and glyburide. Thus, no dose adjustment is necessary during concurrent use with these agents. Because eporsartan is 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 shown to have no effect on eporsartan pharmacokinetics. Ranitidine has also shown to have no effect on eporsartan pharmacokinetics.

Eprosartan (up to 400 mg b.i.d. or 600 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 concurrently with sustained-release calcium-channel blockers (tiazide-releasemefenidipine) 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 at doses of 600 mg and 2000 mg eporsartan/kg/day, respectively, for up to 2 years. In male and female rats, the systemic exposure (AUC) to unbound eporsartan 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 eporsartan was approximately 25 times the exposure achieved in humans given 400 mg b.i.d.

Eprosartan mesylate was not mutagenic in vitro or in 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 polyposidy with metabolic activation and equivocal for polyposidy without metabolic activation.

Eprosartan mesylate had no adverse effects on the normative 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 bid.

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, 21% (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 elderly patients over the age of 65, Teveten 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 2,300 healthy volunteers and patients worldwide, including more than 1,400 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 treated with placebo.

Table 1. Adverse Events Reported by ≥2% of Patients Receiving Teveten (eprosartan mesylate) and Were More Frequent on Eprosartan than Placebo

<table>
<thead>
<tr>
<th>Event</th>
<th>Eprosartan (n=1202)</th>
<th>Placebo (n=352)</th>
<th>%</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body as a Whole</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Infection site</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>1</td>
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<tr>
<td>Injury</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Fatigue</td>
<td>7</td>
<td></td>
<td>7</td>
<td></td>
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<tr>
<td>Gastrointestinal</td>
<td></td>
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<td></td>
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<tr>
<td>Abdominal pain</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>1</td>
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<tr>
<td>Metabolic and</td>
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<tr>
<td>Nutritional</td>
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<tr>
<td>Hypertension/edema</td>
<td>3</td>
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<tr>
<td>Musculoskeletal</td>
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<tr>
<td>Arthralgia</td>
<td>1</td>
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<tr>
<td>Nervous System</td>
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<tr>
<td>Depression</td>
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<tr>
<td>Respiratory</td>
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<tr>
<td>Upper respiratory</td>
<td>5</td>
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<tr>
<td>tract infection</td>
<td>5</td>
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<td>5</td>
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<tr>
<td>Rhinitis</td>
<td>3</td>
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<tr>
<td>Pharyngitis</td>
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<tr>
<td>Coughing</td>
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<tr>
<td>Urogenital</td>
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<tr>
<td>Urinary tract infection</td>
<td>1</td>
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</tr>
</tbody>
</table>

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, muscle aches, influenza-like symptoms, bronchitis, asthenia, insomnia, depression, 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 these events were causally related to eprosartan.

Body: Alcohol intolerance, asthenia, subcostal chest pain, peripheral edema, fatigue, fever, hot flashes, influenza-like symptoms, malaise, rigors, pain, rash, cardiovascular: angina pectoris, bradycardia, abnormal ECG, specific abnormal ECG, extrasystoles, atrial fibrillation, hypotension, back pain, palpitations.

Gastrointestinal: anorexia, constipation, dry mouth, dyspepsia, flatulence, gastritis, gastroenteritis, gingivitis, glossitis, peptic ulcer, toothache, vomiting.

Hematologic: anemia, purpura.

Liver and Biliary: increased SGOT, increased SGPT.

Metabolic and Nutritional: increased creatine phosphokinase, diabetes mellitus, glycosuria, goiter, hypercholesterolemia, hyperglycemia, hyperkalemia, hypokalemia, hyperuricemia.

Musculoskeletal: arthritis, aggravated arthritis, arthralgia, skeletal pain, tendinitis, back pain.


Respiratory: Rhinitis, asthmatic, apnea.

Skin and Appendages: eczema, furunculosis, purpura, rash, maculopapular rash, increased sweating.

Special Senses: conjunctivitis, abnormal vision, keratitis, tinnitus.

Urinary: albuminuria, cystitis, hematuria, medication, polyuria, renal calculi, renal 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 x 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 ≤ 3.0 x 10^9/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 ≤ 1.5 x 10^9/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 ≤ 100 x 10^9/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 ≥ 6.0 mmol/L occurred in 0.9% of patients taking Tevoten 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 5000 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 Tevoten is 800 mg once daily when used as monotherapy in patients who are not volume-depleted (see WARNINGS; Hypotension in Volume-and/or Saline-Dependent Patients). Tevoten can be administered once or twice daily with total daily doses ranging from 400 mg to 1600 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.

Tevoten 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 hepatologically impaired patients or those with renal impairment.

Tevoten may be taken with or without food.

HOW SUPPLIED
Tevoten (eprosartan mesylate) is available as aqueous film-coated, scored Tablets as follows:
- 200 mg white, oval tablets debossed with 5B 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 80'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 80's intended for institutional use only
- NDC 0007-5044-25 (bottles of 500)

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

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Trends in U.S.A.
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ATACAND™ (Candesartan Cilexetil) Tablets

**DESCRIPTION**

ATACAND (candesartan cilexetil), a prodrug, is hydrolyzed to candesartan during absorption from the gastrointestinal tract. Candesartan, candesartan C-12, and gluteic acid are the major metabolites. The pharmacokinetics of candesartan are linear over the dose range of 4 mg to 32 mg. The area under the curve (AUC) for 32 mg is approximately three times higher than that for 4 mg. The terminal elimination half-life of candesartan is approximately 11 hours. The drug is highly bound to plasma proteins. The volume of distribution is approximately 294 liters. The renal clearance of candesartan is approximately 19 liters/hour.

**Pharmacokinetics**

**General**

Candesartan cilexetil is rapidly and completely bioactivated by liver hydroxylases during absorption from the gastrointestinal tract to candesartan, a selective AT1 subtype angiotensin II receptor antagonist. Candesartan is widely distributed in the body and is eliminated primarily by the kidneys. The elimination half-life of candesartan is approximately 10 hours. The area under the curve (AUC) for 32 mg is approximately three times higher than that for 4 mg. The terminal elimination half-life of candesartan is approximately 11 hours. The drug is highly bound to plasma proteins. The volume of distribution is approximately 294 liters. The renal clearance of candesartan is approximately 19 liters/hour.

**Metabolism and Excretion**

Candesartan is metabolized by the liver and is excreted in the urine. The renal clearance of candesartan is approximately 19 liters/hour. The drug is highly bound to plasma proteins. The volume of distribution is approximately 294 liters. The renal clearance of candesartan is approximately 19 liters/hour.

**Distribution**

The volume of distribution of candesartan is 5.1 L/kg. Candesartan is highly bound to plasma proteins (>99%) and does not penetrate red blood cells. The protein binding is constant across therapeutic concentrations and is not affected by age, sex, or renal function.

**Special Populations**

**Pediatric**

The pharmacokinetics of candesartan in pediatric patients have not been studied. In adult patients, the dosage regimen is 16 mg once daily.

**Geriatric and Gender**

The pharmacokinetics of candesartan are not significantly different between geriatric and gender populations. The dosage regimen is 16 mg once daily.

**Renal Insufficiency**

In patients with renal impairment, the clearance of candesartan is reduced. The dosage regimen is 16 mg once daily.

**Hepatic Insufficiency**

The clearance of candesartan in patients with hepatic insufficiency is reduced. The dosage regimen is 16 mg once daily.

**Drug Interactions**

**Precautions**

Drug interactions may occur with concomitant use of candesartan with other medications that are renally cleared or metabolized by the cytochrome P450 system.

**Contraindications**

Candesartan is contraindicated in patients who are allergic to any component of this product.

**Warnings**

**Reproductive Toxicity**

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 renal dysfunction and hydrops fetalis. Candesartan has been shown to cause fetal renal dysfunction and hydrops fetalis when administered to rabbits during organogenesis.
ATACAND™ Candesartan Cilexetil Tablets

Plasma concentrations of angiotensin II, 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 normotensive dependent type II diabetes mellitus and hypertension, there was no change in the level of HbA1c.

Clinical Trials

The antihypertensive effects of ATACAND were examined in a placebo-controlled trial of 6 to 12 weeks duration, primarily by 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 in add-on to hydrochlorothiazide and amiloride. These studies included a total of 2350 patients randomized to one of several doses of candesartan cilexetil and 107 to placebo. Except for a study in diabetics, all studies showed significant effects, generally dose related, of 2-3 mg or more. In the 24 hour systolic and diastolic pressures compared to placebo, with doses of 8-32 mg giving effects of approximately 15/10 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 effect was maintained over 24 hours, with trough to peaks ratios of blood pressure being reduced daily over 30%. 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 lower population). This has been generally true for angiotensin II antagonists and ACE inhibitors.

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

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

ATACAND 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 pregnant women 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 hydrops fetalis, neonatal death, spontaneous abortion, 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 lung hypoplasia, craniofacial deformations, 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.

This adverse effect does not appear to have resulted from intravenous drug exposure that has been limited to the first trimester. Mothers whose uterine and fetal tissues are exposed to an angiotensin II receptor antagonist only during the first trimester should be informed. Nonetheless, when pregnant women become pregnant, physicians should have the patient discontinue the use of ATACAND as soon as possible.

Rarely (probably less often than 1 in every thousand pregnant women) no alternative to a drug acting on the renin-angiotensin system will be found. In these cases, the mother should be apprised of the potential hazards to their fetus and the need for close maternal and fetal examination should be performed to assess the intra-amniotic environment.

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

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**ATACAND™ (Candesartan Cilexetil) Tablets**

9119600

**ATACAND™ (Candesartan Cilexetil) Tablets**

300 mg/kg/day (23 times the maximum daily human dose of 32 mg on a body surface area basis).

**Hypertension in Volume- and Salt-Depressed Patients**

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

**PRECAUTIONS**

**Impaired Renal Function:**
As a consequence of inhibiting the renin-angiotensin-aldosterone system, severe reductions in renal function have been anticipated in susceptible individuals treated with ATACAND. In patients with impaired renal function who are volume-depleted, symptoms of hypertension may be accentuated. In these patients, monitoring BP and stopping ATACAND if BP becomes too high, are essential precautions.

**Drug Interactions**
No significant drug interactions have been reported in studies of candesartan cilexetil given with other drugs such as beta-blockers, diuretics, digoxin, warfarin, hydrochlorothiazide, and oral contraceptives in healthy volunteers. Because of the antiangiotensin II receptor antagonist action of ATACAND, the concomitant use with drugs like ACE inhibitors, angiotensin receptor blockers (ARBs), aldosterone antagonists, beta-blockers, calcium channel blockers, nonsteroidal anti-inflammatory drugs (NSAIDs), and others that are renin-angiotensin-aldosterone system inhibitors is not recommended. In addition, the concomitant use of potassium-sparing diuretics, potassium supplements, or potassium-sparing diuretics with these drugs is not recommended.

**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. There were no increases in the number or type of tumors observed among the rats treated with the drug. The maximum tolerated doses of candesartan cilexetil provided systemic exposure (AUC) values which were lower than those in the comparable species. Treatment with candesartan cilexetil was associated with a dose-related increase in the number of tumors found in the kidneys of male and female rats. In addition, a subchronic study of up to 13 weeks showed no significant effect on the fertility of male or female rats. However, a study in which the drug was administered during the whole period of gestation revealed a decrease in the number of live born offspring.
ATACAND™ (Candesartan Cilexetil) Tablets

Bacteriuria 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 controlled heart failure trial that was withdrawn for hyperkalemia (serum potassium > 7.8 mEq/L). This patient was also receiving spironolactone.

Lack of data are available in regard to overdosage in humans. In one uncontrolled case of an intentional overdose, a 13-year-old female patient (body mass index of 31.5 kg/m²) ingested an estimated 180 mg of candesartan cilexetil, in conjunction with multiple other pharmaceutical agents (ibuprofen, naproxen sodium, diphenhydramine hydrochloride and codeine). 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 syncope; 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 deplete.

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 anti-hypertensive 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.

HOW SUPPLIED

No. 3732 — Tablets ATACAND, 4 mg, are white to off-white, circular/biconvex shaped, non film-coated tablets, coated ACP on one side and 004 on the other. They are supplied as follows:

NDC 81113-004-31 unit of use bottles of 30
NDC 81113-004-84 unit of use bottles of 90
NDC 81113-004-28 unit dose packages of 100
NDC 81113-004-82 bottles of 1000.

No. 3760 — Tablets ATACAND, 8 mg, are light pink, circular/biconvex shaped, non film-coated tablets, coated ACP on one side and 008 on the other. They are supplied as follows:

NDC 81113-008-31 unit of use bottles of 30
NDC 81113-008-84 unit of use bottles of 90
NDC 81113-008-28 unit dose packages of 100
NDC 81113-008-82 bottles of 1000.

No. 3761 — Tablets ATACAND, 16 mg, are pink, circular/biconvex shaped, non film-coated tablets, coated ACP on one side and 016 on the other. They are supplied as follows:

NDC 81113-016-31 unit of use bottles of 30
NDC 81113-016-84 unit of use bottles of 90
NDC 81113-016-28 unit dose packages of 100
NDC 81113-016-82 bottles of 1000.

No. 3763 — Tablets ATACAND, 32 mg, are pink, circular/biconvex shaped, non film-coated tablets, coated ACP on one side and 032 on the other. They are supplied as follows:

NDC 81113-032-31 unit of use bottles of 30
NDC 81113-032-84 unit of use bottles of 90
NDC 81113-032-28 unit dose packages of 100
NDC 81113-032-82 bottles of 1000.
AVAPRO® (Irbesartan) Tablets

DESCRIPTION
Irbesartan is an angiotensin II receptor (AT, subtype) blocker. Irbesartan is a non-peptide compound, chemically described as N-{[1-(5-methyl-1H-tetrazol-5-yl)-1,1-diphenyl]-4-(methylamino)-3-piperidinyl}-2H-benzimidazol-2-yl} acetamide. Its molecular formula is C{eq}_{38}\text{H}_{40}\text{N}_{2}\text{O}_{3}\text{, and the structural formula is:}

\[
\text{C}_{38}\text{H}_{40}\text{N}_{2}\text{O}_{3}
\]

Irbesartan is a white to off-white crystalline powder with a molecular weight of 428.58. It is a nonpolar compound with a partition coefficient (octanol/water) of 11.1 at pH 7.4. Irbesartan is slightly soluble in alcohol and methylene chloride and practically insoluble in water.

AVAPRO is available for oral administration in scored tablets containing 75 mg, 150 mg, or 300 mg of irbesartan. The inactive ingredients include: lactose, microcrystalline cellulose, pregelatinized starch, croscarmellose sodium, colloidal 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 blocking the AT, angiotensin II receptor.

Irbesartan is an AT, receptor in many tissues, but it is not involved in cardiovascular homeostasis.

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

Blockade of the AT, receptor removes the negative feedback of angiotensin II on renin secretion, but the resulting decreased 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 bioconversion 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 1-2 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 I-14C-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 5%). The remaining oxidative metabolites do not add appreciably to irbesartan's pharmacological activity.

Irbesartan and its metabolites are excreted by both biliary and renal routes. Following either oral or intravenous administration of I-14C-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 isozymes indicated irbesartan was oxidized primarily by 2C8; metabolism by 3A4 was negligible. Irbesartan was neither metabolized by nor did it substantially induce or inhibit, isozymes commonly associated with drug metabolism (1A1, 1A2, 2A6, 2C8, 2D6, 3A4). There was no induction or inhibition of 3A4.

Distribution
Irbesartan is 90% bound to serum proteins (primarily albumin and α1-acid glycoprotein) with negligible binding to cellular components of blood. The average volume of distribution is in the range of 157±2 l. Irbesartan accumulates.

Studies in animal brain barrier and pit.

Special Populations
Pediatric: Irbesartan is not recommended for use in children.

Gender: No gender differences in plasma drug levels or pharmacokinetic parameters were detected in healthy volunteers or patients.

Hepatic Insufficiency: No adequate data are available at this time.

Renal Insufficiency:

In patients with impaired renal function, irbesartan is not recommended for use in patients with severe renal impairment (creatinine clearance ≤15 mL/min).

In patients with mild to moderate renal insufficiency, irbesartan is not recommended for use in patients with severe renal impairment (creatinine clearance ≤15 mL/min).

Dosage and Administration
Irbesartan is not recommended for use in patients with severe renal impairment (creatinine clearance ≤15 mL/min).

In patients with mild to moderate renal insufficiency, irbesartan is not recommended for use in patients with severe renal impairment (creatinine clearance ≤15 mL/min).

CAUTION: FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION

AVAPRO® (Irbesartan) Tablets

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.

*Registered trademark of Sanofi

Figure 1. Placebo vs. AVAPRO 300 mg
volume of distribution is 53-63 liters. Total plasma and renal clearances are in the range of 157-476 and 3.2-8.5 mL/min, respectively. With repetitive dosing, irbesartan accumulates to no clinically relevant extent.

Studies in animals indicate that radiolabeled irbesartan weekly 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.

**Genetic**: In elderly subjects (age 65-80 years), irbesartan elimination half-life was not significantly altered, but AUC and Cmax 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 Cmax 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-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 (50%) and 40% at 300 mg and 400 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 plasma 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) placebo-controlled, 6-8 week trials in patients with baseline diastolic blood pressures of 95-110 mmHg. Doses of 150 mg and 300 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 (1-400 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.

**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 Mortality 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, uric acid, reversible or irreversible renal failure, and death. Oligninazolam has also been reported, presumably resulting from decreased fetal renal function. Oligninazolam in this setting has been associated with fetal limb contractures, craniofacial deformations, 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 during the first trimester should be so informed. Nonetheless, when patients become pregnant while on irbesartan or placebo-controlled trials, physicians should have the patient discontinue the use of AVAPRO as soon as possible.

Rarer (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 alternative treatment and examinations should be performed to assess the intraamnionic environment.

If oligninazolam 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 oligninazolam may not appear until several hours 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, hydrourter and/or absence of renal papilla were observed in fetuses at doses ≥250 mg/kg/day (approximately equivalent to the maximum recommended human dose (MRHD), 300 mg/day, on a body surface area basis). Subcutaneous edema was observed in fetuses at doses ≥180 mg/kg/day (about 4 times the MRHD on a body surface area basis). As these anomalies were not observed in rats in which irbesartan exposure (oral doses of 50, 150 and 450 mg/kg/day) was limited to gestation days 6-15, they appear to reflect late gestational effects of the drug. In pregnant rabbits, oral doses of 50 mg/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.
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 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 nilfipine.

In vitro studies show significant inhibition of the formation of oxidized ibersartan metabolites with the known cytochrome CYP 2C8 substrates/inhibitors sulphenazole, talbutamide and nilfipine. However, in clinical studies the consequences of concomitant ibersartan on the pharmacodynamics of warfarin were negligible. Based on in vitro data, no interaction would be expected with drugs whose metabolism is dependent upon cytochrome P450 isoenzymes 1A1, 1A2, 2A6, 2B6, 2C9, 2D6, 3A4.

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence of carcinogenicity was observed when ibersartan 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 ibersartan (AUC0-24h, bound plus unbound) for about 3.5 and 11 times, respectively, the average systemic exposure in humans receiving the maximum recommended dose (MMD) of 300 mg ibersartan/day, whereas 1000 mg/kg/day (administered to females only) provided an average systemic exposure about 21 times that reported for humans at the MMD. For male and female mice, 1000 mg/kg/day provided an exposure to ibersartan about 3 and 5 times, respectively, the average human exposure at 300 mg/day.

Ibersartan was not mutagenic in a battery of tests (Ames bacterial test, rat hepatocyte DNA repair test, V79 mammalian-cell forward gene-mutation assay). Ibersartan was negative in several tests for induction of chromosomal aberrations (in vitro-human lymphocyte assay, in vivo-mouse micronucleus study).

Ibersartan had no adverse effects on fertility or mating of male or female rats at oral doses ≤550 mg/kg/day, the highest dose permitted a systemic exposure to ibersartan (AUC0-24h, bound plus unbound) about 5 times that found in humans receiving the maximum recommended dose of 300 mg/day.

Pregnancy

Pregnancy Category C (first trimester) and D (second and third trimester).

See WARNINGS: Fetal/Neonatal Morbidity and Mortality.

Nursing Mothers

It is not known whether ibersartan is excreted in human milk, but ibersartan or some metabolite of ibersartan 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 (ibersartan) in controlled clinical studies, 911 patients (16.5%) were 65 years and over, and while 150 patients (2.9%) were 75 years and over. No overall differences in effectiveness or safety were observed between these younger and older patients, but greater sensitivity to some side effects of 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 1363 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 particularly in the mild and transient with no relationship to the dose of AVAPRO.

In placebo-controlled clinical trials, discontinuation of therapy due to a clinical adverse event was required in 3.3 percent of patients treated with AVAPRO, whereas 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=1655) and at a higher incidence versus placebo (n=541) included diarrhea (3% vs. 2%), dizziness/heartburn (2% vs. 1%), muscle/skeletal 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 ibersartan, but were less than or equal to the incidence in placebo-treated patients (0.2%). Dizziness, syncope, and vertigo were reported with equal or less frequency in patients receiving ibersartan compared with placebo.

Body as a whole: fever, temperature升高, upper respiratory infection.

Cardiovascular: flushing, hypotension, cardiovascular collapse, myocardial infarction, angina pectoris, arrhythmia/conduction disorder, cardio-respiratory arrest, heart failure, hypotensive crisis.

Musculoskeletal: arthralgia, dermatitis, eosinophilia, erythema face, urticaria.

Endocrine/Metabolic: Electrolyte imbalances: sexual dysfunction, libido change, gout.

Gastrointestinal: constipation, oral lesion, gastroesophageal reflux, abdominal distention.

Musculoskeletal/Connective Tissue: extremity edema, muscle cramps, arthritis, muscle ache, muscularkeletal chest pain, joint stiffness, bursitis, muscle weakness.

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

Renal/Gouturinary: abnormal urination, prostate disorder.

Respiratory: epistaxis, tracheobronchitis, congestion, pulmonary congestion, dyspnea, wheezing.

Special Sensitivity: 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/mm3) occurred at similar frequencies among patients receiving AVAPRO (0.3%) and placebo-treated patients (0.5%).

OVERDOSE

No data are available in regard to overdose in humans. However, daily doses of 500 mg for 8 weeks were well-tolerated. The most likely manifestations of overdose are expected to be hypotension and tachycardia; bradycardia might also occur from overdose. Ibersartan is not removed by hemodialysis.

To obtain up-to-date information about the treatment of overdose, 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 overdose, 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/m² basis, respectively.

DOSEAGE 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:

<table>
<thead>
<tr>
<th></th>
<th>75 mg</th>
<th>150 mg</th>
<th>300 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Debossing</td>
<td>2771</td>
<td>2772</td>
<td>2773</td>
</tr>
<tr>
<td>Bottle of 30</td>
<td>0087-2771-31</td>
<td>0087-2772-31</td>
<td>0087-2773-31</td>
</tr>
<tr>
<td>Bottle of 90</td>
<td>0087-2771-32</td>
<td>0087-2772-32</td>
<td>0087-2773-32</td>
</tr>
<tr>
<td>Bottle of 500</td>
<td>0087-2771-15</td>
<td>0087-2772-15</td>
<td>0087-2773-15</td>
</tr>
<tr>
<td>Blister of 100</td>
<td>0087-2771-35</td>
<td>0087-2772-35</td>
<td>0087-2773-35</td>
</tr>
</tbody>
</table>

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

Issued October 1997

P0617-00
Diovan™

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 AT1 receptor subtype. Valsartan is chemically described as N1(1-cyclopentyl)-N2(1H-1,2,3-benzotriazol-5-yl)-1H-1,2,5-benzotriazine-4-sulfonamide. Its empirical formula is C29H26N5O6. Its molecular weight is 485.5, and its structural formula is

![Structural formula of valsartan](image)

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, crospovidone, gelatin, iron oxide, 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 AT1 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 AT2 receptor found in many tissues, but AT2 is not known to be associated with cardiovascular homeostasis. Valsartan has much greater affinity (about 20,000-fold) for the AT2 receptor than for the AT1 receptor. The primary metabolite of valsartan is essentially inactive with an affinity for the AT1 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.

Blockage 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 (Cmax) by about 50%. AUC and Cmax values of valsartan increase approximately linearly with increasing dose over the clinical dosage 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 urine (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 enzymes.

Following intravenous administration, plasma clearance of valsartan is about 2 L/h and its renal clearance is 0.82 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.

Gender: 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) 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 of angiotensin II 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 consequently 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 in two placebo-controlled, 4- to 12-week trials in patients with mild to moderate hypertension. In the first study, a 300-mg dose of valsartan was the most effective dose. Valsartan is effective at a single daily dose of 160 mg, and the antihypertensive response may be maximized in 1 to 2 weeks. In patients with baseline diastolic blood pressure of 95 to 115, the studies allowed comparison of once-daily and twice-daily regimens of 160 mg/day; comparison of peak and trough effects; comparison of Diovan with other antihypertensive agents (ACE inhibitors, beta blockers, calcium channel blockers, and diuretics); and comparison of the effects of valsartan with those of other antihypertensive agents.

Diovan is contraindicated in patients with severe hepatic impairment. Diovan is given with caution in patients with renal insufficiency. Valsartan is not removed from the plasma by hemodialysis. Diovan is given with caution in patients with renal insufficiency. Valsartan is not removed from the plasma by hemodialysis. Diovan is given with caution in patients with renal insufficiency. Valsartan is not removed from the plasma by hemodialysis. Diovan is given with caution in patients with renal insufficiency. Valsartan is not removed from the plasma by hemodialysis. Diovan is given with caution in patients with renal insufficiency. Valsartan is not removed from the plasma by hemodialysis.
The effect of vasodilator therapy on blood pressure was confirmed in a randomized, double-blind, placebo-controlled trial. Vasodilators were administered to hypertensive patients and compared to placebo. The results showed a significant decrease in systolic and diastolic blood pressure with vasodilator therapy, indicating that vasodilator therapy is an effective treatment for hypertension.

In an observational study involving hypertensive patients, the use of angiotensin-converting enzyme (ACE) inhibitors was compared to placebo. The study found that ACE inhibitors significantly reduced blood pressure compared to placebo, with a greater reduction in systolic and diastolic blood pressure observed in the ACE inhibitor group. This study supports the use of ACE inhibitors in the management of hypertension.

In a randomized controlled trial, patients with hypertension were randomly assigned to receive either a beta-blocker or a diuretic. The results showed that both treatments were effective in reducing blood pressure, but there were no significant differences between the two groups. This suggests that beta-blockers and diuretics are equally effective in managing hypertension.

A meta-analysis of randomized controlled trials was conducted to evaluate the long-term effects of antihypertensive therapy. The results showed a significant reduction in the risk of cardiovascular events and all-cause mortality in patients treated with antihypertensive drugs compared to placebo. This meta-analysis supports the use of antihypertensive therapy in the prevention of cardiovascular disease.

In a prospective cohort study, the incidence of hypertension was compared between patients treated with and without antihypertensive therapy. The results showed a significantly lower incidence of hypertension in patients treated with antihypertensive drugs compared to those without treatment. This study highlights the importance of antihypertensive therapy in reducing the risk of hypertension.

In conclusion, the results of these studies demonstrate the effectiveness of various antihypertensive therapies in the management of hypertension. Further research is needed to identify the most effective and individualized treatment options for patients with hypertension.
did not lower the heart rate more than atenolol alone.

Co-administration 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. Do not be CYP 450 isoenzymes. The inhibitory or induction potential of valsartan on CYP 450 is also unknown.

Cardiogenic Hypertension, Myocardial Infarction, Impairment of Fertility

There was no evidence of cardiogenicity when valsartan was administered in the diet to mice and rats for up to 2.5 years at doses up to 160 and 200 mg/kg/day, respectively. These doses in mice and rats are about 2.5 and 6 times, respectively, the maximum recommended human dose on a mg/m² 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 chromosomal 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/m² basis. (Calculations assume an oral dose of 320 mg/day and a 60-kg patient.)

Pregnancy Category 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 (38.2%) of patients treated with valsartan were ≥65 years and 268 (7.5%) were ≥75 years. No overall differences 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

Diabetes 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 valsartan was similar to placebo.

The overall frequency of adverse experiences with higher dose-related reactions was greater for patients treated with valsartan, and at higher incidence in valsartan (≥4%) than placebo (≥2%): patients included viral infection (2% vs. 2%), fatigue (2% vs. 2%), and abdominal pain (2% vs. 2%).

Headache, dizziness, upper respiratory infection, cough, diarrhea, pharyngitis, edema, and arthralgia occurred at a more than 1% rate but at about the same incidence in placebo and valsartan patients. In trials 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 (2.5%) or placebo (1.5%). In a 12-week 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 85% respectively (n=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 Diroxan 320 mg (2%) compared to 10 to 160 mg (2% to 4%).

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

Other adverse experiences occurred in controlled clinical trials of patients treated with Droxan (≥0.2% of valsartan patients) are listed below. It cannot be determined if these adverse experiences were caused specifically by treatment with Droxan.

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

Urinary: Impotence

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

Clinical Laboratory Test Findings

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

Creatinine: Minor elevations in creatinine occurred in 0.5% of patients taking Droxan and 0.8% given placebo in controlled clinical trials. Hemoglobin and Hematocrit: Greater than 20% decreases in hemoglobin and hematocrit were observed in 0.4% and 0.9%, respectively, of Droxan 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 chemistry occurred in Droxan-treated patients. Three patients (0.1%) had liver chemistry Droxan, and Droxan discontinued treatment for elevated liver chemistry.

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

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

OVERDOSAGE

Limited data are available related to overdose in humans. The most likely manifestations of overdose 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 not 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/m² basis). (Calculations assume an oral dose of 320 mg/day and a 60-kg patient.)

DOSEAGE AND ADMINISTRATION

The recommended starting dose of Droxan is 80 mg once daily when used as monotherapy in patients who are not volume-depleted. Droxan may be used over a dose range of 80 mg to 320 mg daily, administered once-a-day. The antimicrobial effect is substantially present within 2 weeks and maximal reduction is generally attained after 4 weeks. If additional antimicrobial 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 gray/light pink opaque, Imprinted CG FZF
   Bottles of 100 .......................................................... NDC 0063-4000-01
   Bottles of 4000 ......................................................... NDC 0063-4000-41
   Unit Dose (blister pack) ........................................... NDC 0063-4000-61
   Box of 100 (strips of 10)

160 mg Capsule - Dark gray/light pink opaque, Imprinted CG GOG
   Bottles of 100 .......................................................... NDC 0063-4001-01
   Bottles of 4000 ......................................................... NDC 0063-4001-41
   Unit Dose (blister pack) ........................................... NDC 0063-4001-61
   Box of 100 (strips of 10)

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

666751                        C97-5  (Rev. 4/97)

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Pharmaceuticals Division
Summit, New Jersey 07901