

**PRESCRIBING INFORMATION**

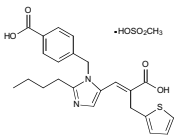
**USE IN PREGNANCY**

**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, TEVETEN<sup>®</sup> should be discontinued as soon as possible. See WARNINGS: Fetal/Neonatal Morbidity and Mortality.

**DESCRIPTION**

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

Its empirical formula is C<sub>22</sub>H<sub>24</sub>N<sub>2</sub>O<sub>4</sub>S•CH<sub>4</sub>O<sub>3</sub>S and molecular weight is 520.625. Its structural formula is:



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

TEVETEN<sup>®</sup> is available as aqueous film-coated tablets containing eprosartan mesylate equivalent to 400 mg or 600 mg eprosartan zwitterion (pink, oval, non-scored tablets or white, non-scored, capsule-shaped tablets, respectively).

**Inactive Ingredients**

The 400 mg tablet contains the following: croscarmellose sodium, hypromellose, iron oxide red, iron oxide yellow, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, pregelatinized starch, and titanium dioxide. The 600 mg tablet contains crospovidone, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, pregelatinized starch, and titanium dioxide.

**CLINICAL PHARMACOLOGY**

**Mechanism of Action**

Angiotensin II (formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzyme [kininase II]), a potent vasoconstrictor, is the principal pressor agent of the renin-angiotensin system. Angiotensin II also stimulates aldosterone synthesis and secretion by the adrenal cortex, cardiac contraction, renal resorption of sodium, activity of the sympathetic nervous system, and smooth muscle cell growth. Eprosartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT<sub>1</sub> receptor found in many tissues (e.g., vascular smooth muscle, adrenal gland). There is also an AT<sub>2</sub> receptor found in many tissues but it is not known to be associated with cardiovascular homeostasis. Eprosartan does not exhibit any partial agonist activity at the AT<sub>1</sub> receptor. Its affinity for the AT<sub>1</sub> receptor is 1,000 times greater than for the AT<sub>2</sub> receptor. *In vitro* binding studies indicate that eprosartan is a reversible, competitive inhibitor of the AT<sub>1</sub> receptor.

Blockade of the AT<sub>1</sub> receptor removes the negative feedback of angiotensin II on renin secretion, but the resulting increased plasma renin activity and circulating angiotensin II do not overcome the effect of eprosartan on blood pressure.

TEVETEN<sup>®</sup> does not inhibit kininase II, the enzyme that converts angiotensin I to angiotensin II and degrades bradykinin; whether this has clinical relevance is not known. It does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

**Pharmacokinetics**

**General**

Absolute bioavailability following a single 300 mg oral dose of eprosartan is approximately 13%. Eprosartan plasma concentrations peak at 1 to 2 hours after an oral dose in the fasted state. Administering eprosartan with food delays absorption, and causes variable changes (<25% in C<sub>max</sub> and AUC values which do not appear clinically important. Plasma concentrations of eprosartan increase in a slightly less than dose-proportional manner over the 100 mg to 800 mg dose range. The mean terminal elimination half-life of eprosartan following multiple oral doses of 600 mg was approximately 20 hours. Eprosartan does not significantly accumulate with chronic use.

**Metabolism and Excretion**

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

**Distribution**

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

The pooled population pharmacokinetic analysis from two Phase 3 trials of 299 men and 172 women with mild to moderate hypertension (aged 20 to 93 years) showed that eprosartan exhibited a population mean oral clearance (CL/F) for an average 60-year-old patient of 48.5 L/hr. The population mean steady-state volume of distribution (V<sub>ss</sub>/F) was 308 L.

Eprosartan pharmacokinetics were not influenced by weight, race, gender or severity of hypertension at baseline. Oral clearance was shown to be a linear function of age with CL/F decreasing 0.62 L/hr for every year increase.

**Special Populations**

**Pediatric**

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

**Geriatric**

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

**Gender**

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

**Race**

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

**Renal Insufficiency**

Following administration of 600 mg once daily, there was a 70-90% increase in AUC, and a 30-50% increase in C<sub>max</sub> in moderate or severe renal impairment. The unbound eprosartan fractions increased by 35% and 59% in patients with moderate and severe renal impairment, respectively. No initial dosing adjustment is generally necessary in patients with moderate or severe renal impairment, with maximum dose not exceeding 600 mg daily. Eprosartan was poorly removed by hemodialysis (CL<sub>HD</sub><1 L/hr) (see DOSAGE AND ADMINISTRATION).

**Hepatic Insufficiency**

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

**Drug Interactions**

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

**Pharmacodynamics and Clinical Effects**

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

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

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

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

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

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

**Clinical Trials**

The safety and efficacy of TEVETEN<sup>®</sup> have been evaluated in controlled clinical trials worldwide that enrolled predominantly hypertensive patients with sitting DBP ranging from 95 mmHg to <115 mmHg.

There is also some experience with use of eprosartan together with other anti-hypertensive drugs in more severe hypertension. The antihypertensive effects of TEVETEN<sup>®</sup> were demonstrated principally in five placebo-controlled trials (4 to 13 weeks' duration) including dosages of 400 mg to 1200 mg given once daily (two studies), 25 mg to 400 mg twice daily (two studies), and one study comparing total daily doses of 400 mg to 800 mg given once daily or twice daily. The five studies included 1,111 patients randomized to eprosartan and 395 patients randomized to placebo. The studies showed dose-related antihypertensive responses.

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

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

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

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

**INDICATIONS AND USAGE**

TEVETEN<sup>®</sup> is indicated for the treatment of hypertension. It may be used alone or in combination with other anti-hypertensives such as diuretics and calcium channel blockers.

**CONTRAINDICATIONS**

TEVETEN<sup>®</sup> 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<sup>®</sup> should be discontinued as soon as possible.

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

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

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

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

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

Eprosartan mesylate has been shown to produce maternal and fetal toxicities (maternal and fetal mortality, low maternal body weight and food consumption, resorptions, abortions and litter

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

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

In patients with an activated renin-angiotensin system, such as volume- and/or salt-depleted patients (e.g., those being treated with diuretics), symptomatic hypotension may occur. These conditions should be corrected prior to administration of TEVETEN<sup>®</sup>, or the treatment should start under close medical supervision. If hypotension occurs, the patient should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty once the blood pressure has stabilized.

#### PRECAUTIONS

##### Risk of Renal Impairment

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

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

##### Information for Patients

###### Pregnancy

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

###### Drug Interactions

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

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

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

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

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

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

##### Pregnancy

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

##### Nursing Mothers

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

##### Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

##### Geriatric Use

Of the total number of patients receiving TEVETEN<sup>®</sup> in clinical studies, 29% (681 of 2,334) were 65 years and over, while 5%

(124 of 2,334) were 75 years and over. Based on the pooled data from randomized trials, the decrease in diastolic blood pressure and systolic blood pressure with TEVETEN<sup>®</sup> was slightly less in patients  $\geq 65$  years of age compared to younger patients. In a study of only patients over the age of 65, TEVETEN<sup>®</sup> at 200 mg twice daily (and increased optionally up to 300 mg twice daily) decreased diastolic blood pressure on average by 3 mmHg (placebo corrected). Adverse experiences were similar in younger and older patients.

#### ADVERSE REACTIONS

TEVETEN<sup>®</sup> has been evaluated for safety in more than 3,300 healthy volunteers and patients worldwide, including more than 1,460 patients treated for more than 6 months, and more than 980 patients treated for 1 year or longer. TEVETEN<sup>®</sup> 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 patients treated with TEVETEN<sup>®</sup> discontinued therapy due to clinical adverse experiences, compared to 6.5% of 352 patients given placebo.

##### Adverse Events Occurring at an Incidence of 1% or More Among Eprosartan-treated Patients

The following table lists adverse events that occurred at an incidence of 1% or more among eprosartan-treated patients who participated in placebo-controlled trials of 8 to 13 weeks' duration, using doses of 25 mg to 400 mg twice daily, and 400 mg to 1200 mg once daily. The overall incidence of adverse events reported with TEVETEN<sup>®</sup> (54.4%) was similar to placebo (52.8%).

| Table 1. Adverse Events Reported by $\geq 1\%$ of Patients Receiving TEVETEN <sup>®</sup> (eprosartan mesylate) and Were More Frequent on Eprosartan than Placebo |                        |                   |
|---|------------------------|-------------------|
| Event   | Eprosartan (n=1,202) % | Placebo (n=352) % |
| <b>Body as a Whole</b>  |                        |                   |
| Infection viral   | 2                      | 1                 |
| Injury  | 2                      | 1                 |
| Fatigue   | 2                      | 1                 |
| <b>Gastrointestinal</b>   |                        |                   |
| Abdominal pain  | 2                      | 1                 |
| <b>Metabolic and Nutritional</b>  |                        |                   |
| Hypertriglyceridemia  | 1                      | 0                 |
| <b>Musculoskeletal</b>  |                        |                   |
| Arthralgia  | 2                      | 1                 |
| <b>Nervous System</b>   |                        |                   |
| Depression  | 1                      | 0                 |
| <b>Respiratory</b>  |                        |                   |
| Upper respiratory tract infection   | 8                      | 5                 |
| Rhinitis  | 4                      | 3                 |
| Pharyngitis   | 4                      | 3                 |
| Coughing  | 4                      | 3                 |
| <b>Urogenital</b>   |                        |                   |
| Urinary tract infection   | 1                      | 0                 |

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

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

Rare cases of rhabdomyolysis have been reported in patients receiving angiotensin II receptor blockers.

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

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

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

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

**Hematologic:** anemia, purpura;

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

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

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

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

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

**Respiratory:** asthma, epistaxis;

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

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

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

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

#### Laboratory Test Findings

In placebo-controlled studies, clinically important changes in standard laboratory parameters were rarely associated with administration of TEVETEN<sup>®</sup>. Patients were rarely withdrawn from TEVETEN<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> or placebo in controlled clinical trials. An elevated ALAT of  $>3.5 \times$  ULN occurred in 0.1% of patients taking TEVETEN<sup>®</sup> (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<sup>®</sup> (one patient) and in no patient given placebo in controlled clinical trials. Two patients were withdrawn from clinical trials for anemia.

##### Leukopenia

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

##### Neutropenia

A neutrophil count of  $\leq 1.5 \times 10^3/\text{mm}^3$  occurred in 1.3% of patients taking TEVETEN<sup>®</sup> and in 1.4% of patients given placebo in controlled clinical trials. No patient was withdrawn from any clinical trial for neutropenia.

##### Thrombocytopenia

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

##### Serum Potassium

A potassium value of  $\geq 5.6$  mmol/L occurred in 0.9% of patients taking TEVETEN<sup>®</sup> and 0.3% of patients given placebo in controlled clinical trials. One patient was withdrawn from clinical trials for hyperkalemia and three for hypokalemia.

#### OVERDOSAGE

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

#### DOSAGE AND ADMINISTRATION

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

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

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

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

No initial dosing adjustment is generally necessary for elderly or hepatically impaired patients or those with renal impairment. No initial dosing adjustment is generally necessary in patients with moderate and severe renal impairment, with maximum dose not exceeding 600 mg daily.

TEVETEN<sup>®</sup> may be taken with or without food.

##### HOW SUPPLIED

TEVETEN<sup>®</sup> is available as aqueous film-coated tablets as follows:

400 mg pink, non-scored, oval tablets, debossed with "SOLVAY" on one side and "5044" on the other.

NDC 64455-130-01 (bottles of 100)

600 mg white, non-scored, capsule-shaped tablets, debossed with "SOLVAY" on one side and "5046" on the other.

NDC 64455-131-01 (bottles of 100)

##### STORAGE

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

R<sub>x</sub> only

Manufactured by:

Solvay Pharmaceuticals, BV

Olst, The Netherlands

Tablets made in The Netherlands.

Marketed by:

**BIOVAIL**

Pharmaceuticals, Inc.

Biovail Pharmaceuticals, Inc.

Bridgewater, NJ, 08807, USA