PRODUCT MONOGRAPH

Pr TEVETEN®

Eprosartan Mesylate Tablets

(containing 400 mg and 600 mg eprosartan)

Angiotensin II receptor (AT_1) antagonist

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(containing 400 mg and 600 mg eprosartan)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Tablet / 400 mg and 600 mg	None. *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

TEVETEN (eprosartan mesylate) is indicated for the treatment of mild to moderate essential hypertension.

TEVETEN may be used alone or concomitantly with thiazide diuretics.

The safety and efficacy of concurrent treatment with TEVETEN and angiotensin converting enzyme inhibitors have not been established.

Geriatrics
In elderly patients with essential hypertension eprosartan taken once daily for 12 weeks in doses of 600-800 mg is well-tolerated and effective treatment. At study endpoint there were clinically significant and useful reductions in sitting SBP and DBP compared to baseline in both treatments. However, appropriate caution should nevertheless be used when prescribing to the elderly, as increased vulnerability to drug effect is possible in this patient population (see ACTION AND CLINICAL PHARMACOLOGY – Special Populations and Conditions: Geriatrics, and DOSAGE AND ADMINISTRATION).

Pediatrics
The safety and effectiveness in pediatric patients have not been established.

CONTRAINDICATIONS

Patients who are hypersensitive to TEVETEN (eprosartan mesylate) or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.

WARNINGS AND PRECAUTIONS

USE IN PREGNANCY
When used in pregnancy during the second and third trimesters, Angiotensin II receptor (AT_1) Antagonists can cause injury or even death to the developing fetus. When pregnancy is detected, TEVETEN should be discontinued as soon as possible (see WARNINGS AND PRECAUTIONS – Special Populations).

Cardiovascular

There is concern on theoretical grounds that patients with aortic stenosis might be at particular risk of decreased coronary perfusion when treated with vasodilators because they do not develop as much afterload reduction.

Hypotension:

Occasionally, symptomatic hypotension has occurred after administration of eprosartan, in some cases after the first dose. It is more likely to occur in patients who are volume-depleted by diuretic therapy, dietary salt restriction, dialysis, diarrhea, or vomiting. In those patients, because of the potential fall in blood pressure, these conditions should be corrected prior to starting therapy and under close medical supervision. Similar considerations apply to patients with ischemic heart or cerebrovascular disease, in whom an excessive fall in blood pressure could result in myocardial infarction or cerebrovascular accident.

Hepatic/Biliary/Pancreatic

Based on pharmacokinetic data which demonstrate increased plasma concentrations of eprosartan in hepatically impaired patients after administration of TEVETEN (eprosartan mesylate), a lower initial dose should be considered for patients with hepatic impairment or a history of hepatic impairment (see DOSAGE AND ADMINISTRATION).

Renal

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function have been seen in susceptible individuals. In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, such as patients with bilateral renal artery stenosis, unilateral renal artery stenosis to a solitary kidney, or severe congestive heart failure, treatment with agents that inhibit this system has been associated with oliguria, progressive azotemia, and rarely, acute renal failure and/or death. In susceptible patients, concomitant diuretic use may further increase risk.

Use of eprosartan should include appropriate assessment of renal function (see DOSAGE AND ADMINISTRATION).

Special Populations

Pregnant Women:

Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. When pregnancy is detected, TEVETEN 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 an angiotensin II receptor antagonist will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intra-amniotic environment.

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

Infants with histories of *in utero* exposure to an angiotensin II receptor antagonist should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function. Eprosartan is not removed from plasma by dialysis.

Animal Data: 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.).

Nursing Women:
It is not known whether eprosartan is excreted in human milk, however eprosartan is excreted in animal milk. Because many drugs are excreted in human milk and because of their potential for affecting the nursing infant adversely, 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.

Pediatrics
The safety and effectiveness in pediatric patients have not been established.

Geriatrics
In elderly patients with essential hypertension eprosartan taken once daily for 12 weeks in doses of 600-800 mg is well-tolerated and effective treatment. At study endpoint there were clinically significant and useful reductions in sitting SBP and DBP compared to baseline in both treatments. However, appropriate caution should nevertheless be used when prescribing to the elderly, as increased vulnerability to drug effect is possible in this patient population. (See ACTION AND CLINICAL PHARMACOLOGY – Special Populations and Conditions: Geriatrics, and DOSAGE AND ADMINISTRATION – Recommended Dose and Dosage Adjustment – Use in the Elderly).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

TEVETEN (eprosartan mesylate) has been evaluated for safety in more than 3,300 healthy volunteers and patients, including more than 1,460 patients treated for more than 6 months, and more than 980 patients treated for 1 year or longer.

Adverse experiences were similar in patients regardless of age, gender, or race.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

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

Adverse Events Occurring at an Incidence of 1% or More Among Eprosartan-Treated Patients:

The following table lists adverse events that occurred at an incidence of 1% or more among eprosartan-treated patients who participated in placebo-controlled trials of 8 to 13 weeks duration, using od and bid dosing. The overall incidence of adverse events reported with TEVETEN (54.4%) was similar to placebo (52.8%). The following potentially serious adverse reactions have been reported rarely with eprosartan: syncope, hypotension.

Table 1. Most Common* On-Therapy Adverse Experiences for Patients In Placebo-Controlled, Hypertension Studies

	Number of Patients with Adverse Experiences			
	Eprosartan (n=1202)		Placebo (n=352)	
	N	%	N	%
Central and Peripheral Nervous System				
Headache	121	10.1	38	10.8
Dizziness	35	2.9	13	3.7
Musculoskeletal System				
Myalgia	48	4.0	14	4.0
Arthralgia	22	1.8	4	1.1
Back pain	16	1.3	4	1.1
Respiratory System				
Upper respiratory tract infection	95	7.9	19	5.4
Rhinitis	48	4.0	10	2.8
Pharyngitis	44	3.7	9	2.6
Coughing	42	3.5	9	2.6
Sinusitis	38	3.2	12	3.4
Dyspnea	15	1.2	2	0.6
Bronchitis	13	1.1	8	2.3
Gastrointestinal System				
Diarrhea	30	2.5	9	2.6
Abdominal pain	18	1.5	3	0.9
Dyspepsia	16	1.3	6	1.7
Body as a Whole, General				
Viral infection	29	2.4	5	1.4
Injury	29	2.4	4	1.1
Chest pain	25	2.1	7	2.0
Fatigue	18	1.5	4	1.1
Pain	14	1.2	4	1.1
Dependent edema	13	1.1	8	2.3
Urinary System				
Urinary tract infection	16	1.3	1	0.3
Metabolic and Nutritional				
Hypertriglyceridemia	15	1.2	0	0.0
Heart Rate and Rhythm				
Palpitation	14	1.2	3	0.9
Psychiatric				
Depression	12	1.0	0	0.0
TOTAL**	654	54.4	186	52.8

* Includes adverse experiences reported for ≥1.0% of patients who received oral eprosartan monotherapy.

** Total patients with at least one adverse experience. Patients with multiple adverse experiences are counted only once.

Less Common Clinical Trial Adverse Drug Reactions (<1%)

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 regardless of drug relationship are listed below.

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

Cardiovascular**:** angina pectoris, bradycardia, nonspecific ST-T changes, T-wave inversion, extrasystoles, atrial fibrillation, hypotension, tachycardia, peripheral ischemia;

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

Hematologic: anemia, purpura;

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

Musculoskeletal: arthritis, aggravated arthritis, arthrosis, leg cramps, skeletal pain, tendonitis;

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.

Abnormal Hematologic and Clinical Chemistry Findings

In placebo-controlled studies, clinically important changes in standard laboratory parameters were rarely associated with administration of TEVETEN.

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

trials for elevations in serum creatinine and BUN, and three additional patients were withdrawn for increases in serum creatinine.

Liver Function Tests: Minor elevations of ALAT, ASAT, and alkaline phosphatase occurred for comparable percentages of patients taking TEVETEN (eprosartan mesylate) or placebo in controlled clinical trials. An elevated ALAT of >3.5 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 $\leq 3.0 \times 10^3/mm^3$ occurred in 0.3% of patients taking TEVETEN and in 0.3% of patients given placebo in controlled clinical trials. One patient was withdrawn from clinical trials for leukopenia.

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

Thrombocytopenia: A platelet count of $\leq 100 \times 10^9 L$ 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 ≥5.6 mmol/L occurred in 0.9% of patients taking TEVETEN and 0.3% of patients given placebo in controlled clinical trials. One patient was withdrawn from clinical trials for hyperkalemia and three for hypokalemia.

Post-Market Adverse Drug Reactions

The following adverse reactions have been identified during post-marketing use of TEVETEN:

- Headaches, dizziness, and asthenia have been rarely reported.
- Hypotension, including postural hypotension, has been very rarely reported.
- Skin reactions (rash, pruritus, urticartia) have been very rarely reported.
- Angioedema (involving swelling of the face, lips and/or tongue) has been very rarely reported.

Cases of muscle pain, muscle weakness, myositis and rhabdomyolysis have been reported in patients receiving angiotensin II receptor blockers.

DRUG INTERACTIONS

Drug-Drug Interactions

Table 2. Established or Potential Drug-Drug Interactions

Proper Name	Ref.	Effect	Clinical comment
Diuretics	T	Patients on diuretics, and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction in blood pressure after initiation of therapy with TEVETEN (eprosartan mesylate).	No drug interaction of clinical significance has been identified with thiazide diuretics. The possibility of symptomatic hypotension with the use of TEVETEN can be minimized by discontinuing the diuretic prior to initiation of treatment (see WARNINGS AND PRECAUTIONS – Cardiovascular: Hypotension, and DOSAGE AND ADMINISTRATION).
Agents Increasing Serum Potassium	T	Eprosartan decreases the production of aldosterone.	Potassium-sparing diuretics or potassium supplements should be given only for documented hypokalemia and with frequent monitoring of serum potassium. Potassium-containing salt substitutes should also be used with caution.
Lithium Salts	T	As with other drugs which eliminate sodium, lithium clearance may be reduced.	Serum lithium levels should be monitored carefully if lithium salts are to be administered.
Digoxin	CT	No effect on single oral-dose digoxin pharmacokinetics.	Concomitant administration of eprosartan and digoxin had no effect on single oral-dose digoxin pharmacokinetics.
Warfarin	CT	No effect on steady-state prothrombin time ratios (INR) in healthy volunteers.	Concomitant administration of eprosartan and warfarin had no effect on steady-state prothrombin time ratios (INR) in healthy volunteers.
Ranitidine	CT	No effect on eprosartan pharmacokinetics.	Concomitant administration of ranitidine has no effect on eprosartan pharmacokinetics.

Proper Name	Ref.	Effect	Clinical comment
Antifungals (ketoconazole and fluconazole)	CT	No effect on steady state pharmacokinetics of eprosartan.	Concomitant administration of ketoconazole or fluconazole had no effect on steady state pharmacokinetics of eprosartan.
Glyburide	CT	Does not affect 24-hour mean plasma glucose concentrations in diabetic patients.	Concomitant administration of eprosartan and glyburide in diabetic patients did not affect 24-hour mean plasma glucose concentrations.

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

DOSAGE AND ADMINISTRATION

Dosing Considerations

The dosage of TEVETEN (eprosartan mesylate) must be individualized.

Initiation of therapy requires consideration of recent antihypertensive drug treatment, the extent of blood pressure elevation, salt restriction, and other pertinent clinical factors (see WARNINGS AND PRECAUTIONS – Cardiovascular: Hypotension). The dosage of antihypertensive agents used with TEVETEN may need to be adjusted.

TEVETEN may be taken with or without food, but it should be taken consistently with respect to food intake and at the same time every day.

Recommended Dose and Dosage Adjustment

Monotherapy

The recommended initial dose of TEVETEN is 600 mg once daily.

Achievement of maximum blood pressure reduction in most patients may take 2 – 3 weeks after initiation of therapy.

In patients whose blood pressure is not adequately controlled, the dose may be increased to 800 mg once daily. In some patients treated once daily, the antihypertensive effect may diminish toward the end of the dosing interval. If satisfactory control is not being maintained for 24 hours, twice daily administration with the same total daily dosage should be considered. If blood pressure is not adequately controlled with TEVETEN alone, a thiazide diuretic may be administered concomitantly.

Concomitant Diuretic Therapy
In patients receiving diuretics, TEVETEN therapy should be initiated with caution, since these patients may be volume-depleted and thus more likely to experience hypotension following initiation of additional anti-hypertensive therapy. Whenever possible, all diuretics should be discontinued two to three days prior to the administration of TEVETEN to reduce the likelihood of hypotension (see WARNINGS AND PRECAUTIONS: Cardiovascular: Hypotension, and DRUG INTERACTIONS: Drug-Drug Interactions). If this is not possible because of the patient's condition, TEVETEN should be administered with caution and the blood pressure monitored closely. Thereafter, the dosage should be adjusted according to the individual response of the patient.

Use in the Elderly
A lower starting dose of 400 mg once daily should be considered. (See ACTION AND CLINICAL PHARMACOLOGY – Special Populations and Conditions: Geriatrics, and WARNINGS AND PRECAUTIONS – Special Populations: Geriatrics).

Use in Patients with Impaired Renal Function
A lower starting dose of 400 mg once daily should be considered in patients with severe renal impairment. Patients with moderate to severe renal impairment (creatinine clearance <60 mL/min) requiring 600 mg once daily to control their blood pressure should be monitored carefully and 600 mg once daily should be the maximum dose in these patients. (See ACTION AND CLINICAL PHARMACOLOGY – Special Populations and Conditions: Renal Insufficiency, and WARNINGS AND PRECAUTIONS - Renal).

Use in Patients with Impaired Hepatic Function
The starting dose of 400 mg once daily should be considered for patients with impaired hepatic function.

Use in Children
The safety and efficacy of TEVETEN have not been established in children.

Missed Dose
If a dose is forgotten, the missed dose should be taken as soon as possible. The next dose should be taken at the normal time. Two doses should not be taken within six hours of each other.

Administration
TEVETEN is formulated as an aqueous film-coated tablet. It may be taken with or without food, but it should be taken consistently with respect to food intake and at the same time every day.

OVERDOSAGE

Limited data are available in regard to overdosage with TEVETEN (eprosartan mesylate). The most likely manifestations of overdosage would be hypotension and/or tachycardia. If symptomatic hypotension should occur, supportive treatment should be instituted. Eprosartan was poorly removed by hemodialysis (CL_{HD}<1L/hr).

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

TEVETEN (eprosartan mesylate) antagonizes angiotensin II by blocking the angiotensin type 1 (AT_1) receptor. Angiotensin II is a potent vasoconstrictor, the primary vasoactive hormone of the renin-angiotensin system and an important component in the pathophysiology of hypertension. It also stimulates aldosterone secretion by the adrenal cortex. Eprosartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT_1 receptor found in many tissues (e.g., vascular smooth muscle, adrenal gland). There is also an AT_2 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_1 receptor. Its affinity for the AT_1 receptor is 1,000 times greater than for the AT_2 receptor. *In vitro* binding studies indicate that eprosartan is a reversible, competitive inhibitor of the AT_1 receptor.

TEVETEN does not inhibit angiotensin converting enzyme (ACE), also known as kininase II, the enzyme that converts angiotensin I to angiotensin II and degrades bradykinin, nor does it bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

Pharmacodynamics

Eprosartan inhibits the pharmacologic effects of angiotensin II infusions in healthy adult men. Single oral doses of eprosartan from 10 mg to 400 mg have been shown to inhibit the vasopressor, renal vasoconstrictive and aldosterone secretory effects of infused angiotensin II with complete inhibition evident at doses of 350 mg and above. Eprosartan inhibits the pressor effects of angiotensin II infusions. A single oral dose of 350 mg of eprosartan inhibits pressor effects by approximately 100% at peak, with approximately 30% inhibition persisting for 24 hours. 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 can be maintained with once- or twice-daily dosing over a 24-hour period. Attenuation of the effect towards the end of

the 24 hour dosing period may occur in some patients with once daily dosing. Discontinuing treatment with eprosartan does not lead to a rebound increase in blood pressure.

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

The antihypertensive effect of TEVETEN was similar in men and women, but was somewhat smaller in patients over 65.

Although data available to date indicate a similar pharmacodynamic effect of eprosartan in black and white hypertensive patients, this should be viewed with caution since antihypertensive drugs that affect the renin-angiotensin system, such as ACE inhibitors and angiotensin II AT_1 receptor blockers, have generally been found to be less effective in low-renin hypertensives (frequently blacks).

Pharmacokinetics

Table 3. Summary of pharmacokinetic parameter estimates (arithmetic mean ±S.D.) for eprosartan after single doses of eprosartan in healthy male volunteers (n=17)

Dose mean	**Cmax** (ng/mL)	**$t_{1/2}$ (h)**	**$AUC_{(0-t)}$** (ng.h/mL)	**Cl** (mL/min)	**Vdss** (L)
Eprosartan 300mg oral (fasted)	1612±720	4.52±3.05	5657±2694	ND	ND
Eprosartan 300mg oral (fed)	1205±484	7.25±4.61	4807±1907	ND	ND
Eprosartan 20mg i.v	2246±255	2.07±0.63	2631±576	131.8±36.2	12.6±2.6

Cmax: peak plasma concentration
$t_{1/2}$: elimination half-life
$AUC_{(0-t)}$: area under plasma concentration time curve
Cl: Clearance
Vdss: Volume of distributionND: Not determined

Eprosartan pharmacokinetics was not influenced by weight, race, gender or severity of hypertension at baseline.

Absorption: Eprosartan plasma concentrations peak at 1 to 2 hours after an oral dose in the fasted state. Absolute bioavailability following a single 300 mg oral dose of eprosartan is approximately 13%. Administering eprosartan with food delays absorption, and causes variable changes (25%) in C_{max} 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 to 800 mg dose-range. Eprosartan does not significantly accumulate with chronic use.

Distribution: Plasma protein binding of eprosartan is high (approximately 98%) and constant over the concentration range achieved with therapeutic doses. After intravenous dosing, the eprosartan volume of distribution is about 13 liters and total plasma clearance is about 8 L/h. The mean steady-state volume of distribution (Vss/F) was 308 liters in patients of all ages.

Metabolism: Eprosartan is not metabolized by the cytochrome P_{450} system. No active metabolites were detected following oral and intravenous dosing with eprosartan in human subjects.

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. Eprosartan was the only drug-related compound found in the plasma and feces. Following administration of intravenous eprosartan, about 61% of the material is recovered in the feces and about 37% in the urine. Following an oral dose of 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. The terminal elimination half-life of eprosartan following oral administration is 5 to 9 hours. Eprosartan exhibited a population mean oral clearance (CL/F) for an average 60-year-old patient of 48.5 L/h. Oral clearance was shown to be a linear function of age with CL/F decreasing 0.62 L/h for every year increase.

Special Populations and Conditions

Pediatrics: The safety and effectiveness in pediatric patients have not been established.

Geriatrics: Following single oral dose administration of eprosartan to healthy elderly men (aged 68 to 78 years), both AUC and C_{max} eprosartan values increased, on average by approximately 2-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 were no differences in the pharmacokinetics and plasma protein binding between men and women following administration of a single oral dose 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.

Hepatic Insufficiency: Geometric mean eprosartan AUC values increased approximately 40% in a study of mild to moderate hepatically impaired men vs. healthy men who each received a single 100 mg oral dose of eprosartan. The extent of eprosartan plasma protein binding was not influenced by hepatic dysfunction (see DOSAGE AND ADMINISTRATION).

Renal Insufficiency: Following administration of eprosartan 200 mg b.i.d. for 7 days, patients with mild renal impairment (CLcr 60 to 80 mL/min) showed mean eprosartan C_{max} and AUC values similar to subjects with normal renal function. Following treatment once daily of 600 mg for seven days, the AUC (0-24 hours) values were two-fold increased in patients with moderate (Clcr 30 to 59 mL/min) or severe renal impairment (Clcr 5 to 29 mL/min) from that in the patients with normal renal function. The C_{max} values were also 30-50% higher in patients with moderate or severe renal impairment than in patients with normal renal function. The unbound

eprosartan fraction was not influenced by mild to moderate renal impairment but increased approximately 2-fold in a few patients with severe renal impairment. Eprosartan was poorly removed by hemodialysis (CL_{HD}<1L/hr) (see DOSAGE AND ADMINISTRATION).

STORAGE AND STABILITY

TEVETEN (eprosartan mesylate) tablets should be stored at controlled room temperature, between 15 to 25°C. Protect from moisture.

SPECIAL HANDLING INSTRUCTIONS

None.

DOSAGE FORMS, COMPOSITION AND PACKAGING

TEVETEN (eprosartan mesylate) is available as aqueous film-coated tablets containing eprosartan mesylate equivalent to 400 mg and 600 mg eprosartan as follows:

400 mg pink, oval tablets debossed with SOLVAY on one side and 5044 on the other side;

600 mg white, capsule shaped tablet debossed with SOLVAY on one side and 5046 on the other side.

Composition:

400 mg Tablets: Eprosartan mesylate, equivalent to 400 mg eprosartan, is the active ingredient. Inactive ingredients include: croscarmellose sodium, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, pregelatinized starch, titanium dioxide.

600 mg Tablets: Eprosartan mesylate, equivalent to 600 mg eprosartan, is the active ingredient. Inactive ingredients include: crospovidone, hypromellose, 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.

Packaging:

TEVETEN 400 mg is available in blister packs of 28 tablets and HDPE bottles in pack sizes of 30, 60, 100, and 180 tablets.

TEVETEN 600 mg is available in blister packs of 28 tablets and HDPE bottles in pack sizes of 30, 90, and 100 tablets.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

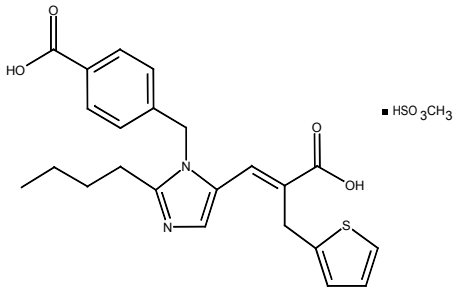
Proper name: Eprosartan mesylate

Chemical name: monomethane sulfonate of (E)-2-Butyl-1-(p-carboxybenzyl)-α-2-thienylmethylimidazole-5-acrylic acid

Molecular formula: $C_{23}H_{24}N_2O_4S \cdot CH_4O_3S$;

Molecular weight: 520.625

Structural formula:



Description: White to off-white free-flowing crystalline powder

Physicochemical properties: Freely soluble in ethanol, and melts between 248° and 250°C.

Solubility Profile: A saturated aqueous solution of eprosartan had a pH of 2 after 30 minutes. Higher pH values were obtained by the addition of sodium hydroxide solution.

pH	Solubility (g/L)
~1*	0.61
2	0.084
3	0.014
4	0.007
5	0.009
6	0.24
7	0.91
7.5	>20

*0.1 M HCL

The solubility in ethanol at room temperature is >100 mg/mL.

pKa Value: The apparent pKa values of eprosartan were determined to be $pKa_1 = 4.11$, $pKa_2 = 5.68$ and $pKa_3 = 6.89$.

Distribution Coefficients: The octanol/water (pH 7.4 phosphate buffer) distribution coefficient was determined to be 0.047 (log D=-1.43).

CLINICAL TRIALS

Study demographics and trial design

Table 4. Summary of patient demographics for clinical trials in Hypertension

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean Age (Range)	Gender (M/F)
013	Double blind, Placebo Controlled, Randomized, Optional Dose Titration	eprosartan 400 to 800mg od 200 to 400mg bid oral for 13 weeks	157	56.8 (27-82)	90/67
		placebo oral for 13 weeks	86	57.8 (24-83)	46/40
049	Double blind, Placebo Controlled, Randomized, Dose Ranging	eprosartan 400mg od 600mg od 800mg od 1200mg od oral for 8 weeks	290	55.7 (21-84)	176/114
		placebo oral for 8 weeks	74	55.9 (27-80)	44/30
076	Double blind, Active Controlled, Randomized	eprosartan 600mg od oral for 4 weeks	30	59.4±1.6	23/7
		losartan 50mg od oral for 4 weeks	30	58.7±2.1	24/6
124	Double blind, Placebo Controlled, Randomized	eprosartan 600mg od oral for 8 weeks	123	54.0±1.0	71/52
		placebo oral for 8 weeks	120	53.3±0.9	76/44

bid = twice daily dosing
od = once daily dosing

The data from four major studies (013, 049, 076 and 124) support the once daily use of eprosartan in the treatment of mild to moderate essential hypertension. The patients were 18 years of age or older and were predominantly Caucasian. Studies were conducted in all grades of hypertensive patients including mild to moderate hypertension (Sit DBP of 95 to 114 mmHg).

Table 5. - Results of studies 013, 049, 076 and 124 in Hypertension

Study #	Primary Endpoint	Least Squares Mean Changes (±SEM) of BP (mmHg) from Baseline at Study Endpoint for Eprosartan at specific dosages	Least Squares Mean Changes (±SEM) from Baseline at Study Endpoint for Placebo or active control	Treatment Difference statistical significance (95% CI); P-value
013	To compare the efficacy of eprosartan administered once and twice daily.	400mg od SitDBP -9.4	placebo Sit DBP -4.2	-5.0 (-7.7, 2.4); <0.0001*
		200mg bid Sit DBP -9.2		-5.2 (-7.8, -2.5);<0.0001* -0.1(-2.9, 2.6); 0.900 (od contrast with bid)
049	To determine the efficacy of eprosartan administered once daily.	400mg od SitDBP -5.1±0.9	placebo Sit DBP -3.3±1.0	-1.9 (-5.1, 1.3); 0.121
		600mg od SitDBP -6.2±0.9		-3.2 (-6.4, 0.0); 0.10*
		800mg od SitDBP -5.9±0.8		-2.7 (-5.9, 0.5); 0.028
		1200mg od SitDBP -7.6±0.9		-4.3 (-7.5, -1.1); 0.001*
076	To compare the effect of eprosartan to losartan on the excretion of uric acid.	600mg od SitDBP -12.4 SitSBP -12.7	50mg losartan SitDBP od -9.6 SitSBP od -10.9	2.8 (-1.7, 7.4); 0.220 1.8 (-4.9, 8.5); 0.587
124	To test the efficacy of eprosartan 600mg administered once daily.	600mg od SitDBP -7.6±0.8	SitDBP -1.5±0.8	-6.1 (-8.1, -4.1); <0.0001+
		SitSBP -6.6±1.3	SitDBP 0.9±1.3	-7.5 (-11.0, -4.1); <0.0001+

* Indicates significance at 0.05 using modified Bonferroni procedure.

+ Statistically significant at the 0.05 level.

Comparative Bioavailability Study

The bioequivalence of one eprosartan 600mg tablet and two of the previously marketed 300mg tablets, has been established in a bioavailability study. The single-dose study compared 2 x 300mg eprosartan tablets with 1 x 600mg eprosartan in fasting, healthy volunteers. The study was an open-label, randomized, three-period, period balanced, crossover study in healthy volunteers. During each treatment period, subjects received a single 600mg oral dose of eprosartan, administered as one of three different regimens: A) TEVETEN (eprosartan mesylate) 1x600mg; B) another eprosartan formulation, 1 x 600mg (data not shown); C) eprosartan 2 x 300mg, previous commercial formulation (Table 6). There was a minimum 7 day washout period between doses.

Table 6: Pharmacokinetic Comparison of TEVETEN (eprosartan) 1 x 600mg vs previous commercial formulation of eprosartan (2 x 300mg) From measured data Geometric Mean Arithmetic Mean (CV %)

Parameter	**TEVETEN (eprosartan)** 600mg Tablet	2 x 300mg eprosartan Tablet	**% Ratio of Geometric Means***	**Confidence Interval**
$AUC_{T\ (0\text{-}t)}$ (ng.h/mL)	8649 9728 (50.9)	8798 10098 (53.1)	99	(90,109)
$AUC(0\text{-}t^1)$ (ng.h/mL)	8608 9689(51.1)	8756 10065 (53.6)	99	(90,109)
C_{MAX} (ng.h/mL)	2271 2527(48.9)	2213 2462 (48.7)	103	(94, 114)
T_{MAX} (h)	1.60 (60.8)	1.92 (58.1)		

*represents the ratio of adjusted geometric means

$AUC_{T\ (0\text{-}t)}$: t is the time of the last quantifiable concentration

$AUC_{T\ (0\text{-}t^1)}$: t is the time of the last quantifiable concentration in common for all regimens for each subject

DETAILED PHARMACOLOGY

Human Pharmacology

Early Tolerance Studies

Oral and intravenous eprosartan was safe and well tolerated in healthy subjects when given single oral doses up to 800 mg, single intravenous doses up to 20 mg, and repetitive oral doses up to 300 mg twice daily for eight days. Oral eprosartan was safe and well tolerated in patients with essential hypertension at repetitive oral doses of up to 1200 mg once daily for one week and in patients with renal insufficiency at repetitive oral doses of 300 mg twice daily for 7 days. The most common adverse experiences following eprosartan dosing were headache, dizziness and fatigue. There appeared to be no gross differences in the frequency of adverse experiences following eprosartan dosing compared to placebo with the exception of headache which was reported more frequently following eprosartan dosing than following placebo dosing.

Inhibition of Angiotensin II Activity and the Renin-Angiotensin-Aldosterone System

Angiotensin II AT_1 receptor antagonism as the mechanism of action of eprosartan in humans has been confirmed. Single oral doses of eprosartan from 10 mg up to 400 mg have been shown to inhibit the vasopressor, renal vasoconstrictive and aldosterone secretory effects of infused angiotensin II with complete (100%) inhibition evident at doses of 350 mg and above. A dose-response relationship for these effects of eprosartan has been demonstrated. At 3 hours following single oral doses of 10, 30, 50, 70, 100, and 200 mg, eprosartan inhibited angiotensin Il-induced decreases in effective renal plasma flow (ERPF) by 39.1%, 49.9%, 33.0%, 56.0%, 71.0%, and 85.7%, respectively, relative to placebo. The effects of eprosartan on blood pressure and ERPF were mirrored by partial inhibition of the aldosterone secretory effects of angiotensin II. The results of two studies predicted that oral doses of eprosartan in the range of 200-400 mg would be effective anti-hypertensive doses in patients with essential hypertension. The absence of angiotensin II AT_1 agonist activity has also been confirmed. A single oral dose of eprosartan 350 mg administered in the absence of angiotensin II resulted in an increase in ERPF, which suggests that eprosartan has a renal vasodilatory effect in salt replete men. Eprosartan 350 mg had no vasopressor effect and did not stimulate aldosterone secretion.

Effects on Renal Hemodynamics and Function

The renal hemodynamic effects of eprosartan were evaluated in normal subjects, in patients with essential hypertension and in patients with renal insufficiency.

Eprosartan increased ERPF (effective renal plasma flow, as measured by the plasma clearance of para-aminohippurate) in salt replete as well as salt restricted normal subjects. A dose-related increase in ERPF of 25-30% compared to pre-dose values occurred in salt restricted normal subjects with a plateau of effect occurring between 200 mg and 400 mg. A single oral dose of eprosartan 400 mg increased ERPF to a greater extent than a single oral dose of losartan 50 mg, however this difference was not statistically significant. The renal hemodynamic effects of seven days of dosing with eprosartan 300 mg bid were superior to seven days of dosing with captoril 25 mg tid. Following eprosartan dosing, there was no reduction in GFR (glomerular filtration rate, as measured by plasma clearance of inulin) in normal subjects following single

doses or following repetitive dosing with 300 mg bid for 8 days.

Eprosartan maintained renal function in patients with essential hypertension and in patients with renal insufficiency. In a two-way crossover study, patients with essential hypertension received eprosartan 300 mg bid or placebo for 28 days. There were no clinically or statistically significant differences in ERPF or GFR for up to four hours following dosing between regimens on either day 1 or day 28 of treatment. In a three-way crossover study, patients with varying degrees of renal insufficiency received eprosartan 300 mg bid, captopril 25 mg tid or placebo for 7 days. Neither single dose (day 1) nor repetitive dosing (day 7) with eprosartan or captopril had any significant effects on renal function (ERPF and GFR) compared to placebo despite the severity of renal functional impairment. Eprosartan may be safely administered to patients with essential hypertension and patients with varying degrees of renal insufficiency without resulting in a deterioration of renal function. But the maximum dose should not exceed 600mg/day (see WARNINGS AND PRECAUTIONS; see DOSAGE AND ADMINISTRATION – Use in Patients with Impaired Renal Function).

Effects on the Metabolic and Endocrine System - Sodium Excretion and Adrenal Effects
Sodium excretion. In salt-restricted normal men, a natriuretic effect was evident following dosing with single oral doses of eprosartan (10 mg up to 400 mg) when pre-dose 24 hour urine sodium excretion was compared to 24-hour post-dose urine sodium excretion. This natriuretic effect of eprosartan was statistically significant at all doses studied except for the 400 mg dose. There was no apparent dose response for natriuresis. In patients with essential hypertension who were maintained on ad lib sodium diets, there were no gross changes in 24 hour sodium or potassium excretion after 6 or 7 days of repetitive oral dosing of eprosartan compared to pre-dose values or to placebo for any of the treatment groups (doses up to 1200 mg uid for 7 days). In another study of patients with essential hypertension who were also maintained on ad lib sodium diets, there were no clinically or statistically significant differences in sodium excretion for up to four hours following dosing between eprosartan 300 mg bid and placebo on either day 1 or day 28 of treatment. In patients with renal insufficiency, neither single dose (day 1) nor repetitive dosing (day 7) with eprosartan 300 mg bid or captopril 25 mg bid had a significant acute effect on sodium excretion compared to placebo despite the severity of renal functional impairment. Eprosartan may be safely administered to patients with essential hypertension and to patients with varying degrees of renal insufficiency without resulting in sodium retention. However, a lower starting dose of 400 mg once daily should be considered in patients with severe renal impairment. The maximum dose of eprosartan should not exceed 600mg/day in patients with moderate to severe renal impairment (creatinine clearance <60 mL/min) (see WARNINGS AND PRECAUTIONS; see DOSAGE AND ADMINISTRATION – Use in Patients with Impaired Renal Function).

Adrenal effects. In normal subjects, the adrenal responses to placebo, eprosartan and captopril were consistent with the pharmacologic activities of these compounds. Eprosartan suppressed the aldosterone secretion caused by exogenous angiotensin II in a dose related fashion. In placebo-treated subjects, sodium restriction stimulated aldosterone secretion and plasma renin activity, and exogenous angiotensin II further stimulated aldosterone secretion and suppressed renin secretion via feedback inhibition. In the eprosartan/salt restricted regimens, eprosartan

dosing with 200 mg or 400 mg suppressed aldosterone secretion, stimulated renin secretion and blunted the effects of exogenous angiotensin II infusion to either stimulate aldosterone or to suppress renin. In marked contrast, dosing with captopril 25 mg under salt restricted conditions suppressed aldosterone secretion and stimulated renin secretion but had no effect on exogenous angiotensin II-induced stimulation of aldosterone secretion or suppression of renin secretion. A single oral dose of eprosartan 400 mg had similar effects as losartan 50 mg on aldosterone and plasma renin activity.

In patients with essential hypertension, plasma renin activity at trough (12-24 hours following dosing) was unchanged after one week of eprosartan therapy at doses up to 1200 mg once daily or after 28 days of 300 mg bid compared to pre-dose, baseline values on day 1. In another study of patients with essential hypertension, there was a trend for plasma renin activity at trough to increase in both the eprosartan and enalapril treated groups after 12 weeks of therapy compared to pre-dose, baseline values. After 12 weeks of therapy, angiotensin II concentrations tended to increase in the eprosartan-treated patients, most likely as a result of removal of feedback inhibition, but not in the enalapril-treated patients. Serum aldosterone concentrations remained unchanged after 12 weeks of therapy in both the eprosartan and enalapril groups. Of note, despite an increase in angiotensin II concentrations in the eprosartan-treated group, serum aldosterone concentrations were not increased following 12 weeks of therapy with eprosartan. These observations in normal subjects and in patients with essential hypertension are consistent with the pharmacologic activities of these compounds and with direct angiotensin II AT_1 receptor antagonism of eprosartan. In general, the adrenal effects of eprosartan were less marked in normal subjects and in hypertensive patients who were on ad lib sodium diets.

TOXICOLOGY

The toxicity of eprosartan was evaluated in a series of single and repeat dose studies by oral or intravenous administration for up to 3 months in mice, 6 months in rats and 1 year in dogs (Tables 7 and 8).

Eprosartan showed no significant toxicity at dosages up to 2000 mg/kg/day in mice or 1000 mg/kg/day in rats and dogs.

Table 7. Acute Toxicity

Species	Route	Duration	Dose (mg/kg/day)	Major Findings
Rat (Sprague-Dawley)	Oral	Single dose	3, 10, 30, 100, 300, 600, 1000	No effects on survival, body weight, clinical observations, hematology, clinical chemistry or urinalysis.
Rat (Sprague-Dawley)	i.v.	Single dose	10, 30, 100, 300	No effects on survival, clinical observations, hematology, clinical chemistry or histopathology.
Dog (Beagle)	Oral	Single dose	30, 100, 300, 600, 1000	No effects on survival, body weight, clinical observations, hematology, clinical chemistry or histopathology.
Dog (Beagle)	i.v.	Single dose	100 and 300	Emesis at >100 mg/kg. Mild increases in serum transaminase and alkaline phosphatase activities in male and female at 300 mg/kg. Mild intra-hepatic cholangitis in males at >100 mg/kg. No effect on survival or body weight.

Table 8. Chronic Toxicity

Species	Route	Duration	Dose (mg/kg/day)	Major Findings
Mouse (CD-1)	Oral	10 days	300, 1000, 3000	No effects on survival, clinical observations, body weight, or clinical chemistry.
Mouse (CD-1)	Oral	3 months	100, 300, 1000, 2000	Transient (wk 1-2) body weight weight loss and decreased food consumption at doses > 1000 mg/kg. No effects on survival, clinical observations, hematology, clinical chemistry, organ weights or histopathology.
Rat (Sprague-Dawley)	Oral	7 days	100, 300, 1000, 3000	No effects on survival, clinical observations, body weight, hematology, clinical chemistry, or histopathology.
Rat (Sprague-Dawley)	Oral	1 month	30, 100, 1000	No effects on survival, clinical observations, body weight, food consumption, ophthalmology, hematology, clinical chemistry, urinalysis, organ weights or histopathology.
Rat (Sprague-Dawley)	Oral	1 month (impurity evaluation)	100, 1000	No effects on survival, clinical observations, body weight, food consumption, ophthalmology, hematology, clinical chemistry, urinalysis, organ weights or histopathology.
Rat (Sprague-Dawley)	Oral	6 months	30, 100, 1000	No effects on survival, clinical observations, body weight, food consumption, ophthalmology, hematology, clinical chemistry, urinalysis, organ weights or histopathology, increased ALT and AST activities in a few at 100 and 1000 mg.
Rat (Sprague-Dawley)	i.v.	4 days	50, 150	No effects on survival, body weight, clinical observations, hematology, clinical chemistry or histopathology.
Rat - males (Sprague-Dawley)	i.v.	14 days	1, 10, 30	Minimal inflammatory cell infiltrates at injection site. No effects on survival, body weight, clinical observations, hematology, clinical chemistry, ophthalmology, organ weights or histopathology.
Rat - males (Sprague-Dawley)	i.v.	1 month	10, 50, 150	Mortality (50 mg/kg) and transient hypoactivity or convulsions at >50 mg/kg. No effects on body weight, food consumption, hematology, clinical chemistry, ophthalmology, organ weights or histopathology.
Dog (Beagle)	Oral	4 days	100, 1000	No effects on survival, body weight, clinical observations, hematology, clinical chemistry, organ weights or histopathology.
Dog - males (Beagle)	Oral	1 month	100, 300, 1000	Mild decrease (<15%) in erythrocyte parameters at 1000 mg/kg. No effects on survival, body weight, food consumption, electrocardiography, ophthalmology, hemostasis, clinical chemistry, urinalysis, organ weights or histopathology on day 29, 1.4 to 1.9 x increase in serum urea nitrogen in 1 of 3 dogs at 100 mg or 300 mg and in 2 of 3 dogs at 1000 mg.
Dog (Beagle)	Oral	6 months	30, 100, 1000	Mild decrease (<17%) in erythrocyte parameters in males (>100 mg/kg) and females (>30 mg/kg). No effects on survival, body weight, food consumption, electrocardiography, ophthalmology, hemostasis, clinical chemistry, urinalysis, organ weights or histopathology.
Dog (Beagle)	Oral	1 year	30, 100, 1000	Mild decrease (<16%) in erythrocyte parameters at 1000 mg/kg at weeks 13 and 26; no effect on erythrocyte parameters at week 52. No effects on survival, body weight, food consumption, electrocardiography, ophthalmology, hemostasis, clinical chemistry, urinalysis, organ weights or histopathology.
Male Dog (Beagle)	i.v.	14 days	1, 10, 30	Emesis at 30 mg/kg. No effects on survival, body weight, food consumption, electrocardiography, ophthalmology, hematology, hemostasis, clinical chemistry, urinalysis, organ weights or histopathology.

Reproduction

In general reproductive performance studies, eprosartan had no effects on mating, fertility or gonadal function in male or female rats given oral dosages up to 1000 mg/kg/day (Table 9).

Table 9. Reproduction and Teratology

Species	Route	Duration (Days*)	Dose (mg/kg/day)	Major Findings
Segment 1				
Male Rat (Sprague-Dawley)	Oral	105 days	30, 100, 1000	No effects on body weight, clinical signs, mating, fertility, reproductive organ weights or gonadal function (spermatogenesis).
Female Rat (Sprague-Dawley)	Oral	14ac - 21pc	0.3, 3, 30, 100, 300, 1000	No effects on body weight, food consumption, clinical observations, mating, fertility, gonadal function, pregnancy, parturition or lactation. No effect on offspring viability, growth and development.
Segment 2				
Rat (Sprague-Dawley)	Oral	6 - 17pc	30, 100, 1000	No maternal or developmental effects.
Rabbit New Zealand White	Oral	6 - 18pc 6 - 28pc	100, 500, 1000 1, 10, 30, 60	Maternal toxicity, but no fetal toxicity, at 100 mg/kg when dosed 6-18pc. Maternal toxicity (mortality, decreased body weight and food consumption and abortions) and fetal mortality at >10 mg/kg when dosed 6-28pc.
Rabbit New Zealand White	Oral	6 - 28pc	0.3, 3, 30	Maternal decreased food consumption (>3 mg/kg) or increased mortality, decreased body weight gain, adverse clinical signs and abortions at 30 mg/kg. Fetal mortality at 30 mg/kg.
Rabbit New Zealand White	Oral	6 - 18pc	10, 30	Maternal toxicity (decreased food consumption and body weight gain at >10 mg/kg) and lethality (30 mg/kg). No fetal developmental toxicity at 10 or 30 mg/kg.
Segment 3				
Rat (Sprague-Dawley)	Oral	6pc - 21pp	30, 100, 1000	No effects on pregnancy, parturition or lactation. No effect on survival, growth, or postnatal development of offspring.
Rat (Sprague-Dawley)	i.v.	15pc - 20pp	10, 50, 150	No effects on pregnancy, parturition or lactation. No effects on survival, growth or postnatal development of offspring.

* ac = ante coitum; pc = post coitum; pp = post partum

Teratology

Eprosartan had no effects on pregnancy, parturition or lactation in female rats and did not affect fetal development, survival, growth or postnatal development of offspring when given orally at dosages up to 1000 mg/kg/day or intravenously at dosages up to 150 mg/kg/day. When given to pregnant rabbits, eprosartan produced maternal toxicity at doses $\geq$3 mg/kg/day and fetal mortality at doses $\geq$10 mg/kg/day, consistent with the unique sensitivity of pregnant and fetal rabbits to angiotensin converting enzyme inhibitors and angiotensin receptor (AT_1) antagonists given during mid- to late gestation (Table 9).

Genotoxicity

In vitro and *in vivo* Eprosartan showed no evidence of mutagenicity or clastogenicity in a microbial assay (*Salmonella typhimurium* and *Escherichia coli*), in L5178Y mouse lymphoma cells, in human lymphocytes and in a mouse micronucleus test (Table 10).

Table 10. Genotoxicity

Test	System	ug/mL or plate	Results
Mutagenicity	*Salmonella typhimurium* and *Escherichia coli*	50 - 5000 (with and without S9)	Negative
Mutagenicity and chromosome damage	L5178Y Mouse lymphoma cell	198 - 2750 (with S9) 198 - 3250 (without S9)	Negative
Mutagenicity and chromosome damage	L5178Y Mouse lymphoma cells	400 - 1250 (with S9) 400 - 900 (without S9)	Negative
Micronucleus	Mouse (CD-1) bone marrow cells	1250, 2500	Negative
Chromosome aberration	Human lymphocytes	1000 - 2000 (with S9) 100 - 2500 (without S9)	Negative; slight polyploidy at cytotoxic concentrations

Carcinogenicity

Eprosartan was not carcinogenic in rats or mice dosed for up to 2 years at 600 mg/kg/day and 2,000 mg/kg/day, respectively; the systemic exposure (AUCs) at these doses was approximately similar to or 3 times greater, respectively, than exposure achieved in humans given the maximum recommended human dose (800 mg) (Table 11).

Table 11. Carcinogenicity

Species	Route	Duration	Dose (mg/kg/day)	Major Findings
Mouse (CD-1)	Oral	2 years	100, 1000, 2000	No carcinogenic effect. Decreased survival rate at 2000 mg; decreased mean body weights at 2000 mg (6-13%) and at 1000 mg (3- 9%); increased number of mice with lung congestion at 2000 mg.
Rat (Sprague-Dawley)	Oral	2 years	30, 100, 600	No carcinogenic effect. Increase in non-neoplastic lung lesions in males at equal to or greater than 30 mg (for edema and hemorrhage) and at 600 mg (necrosis).

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PART III: CONSUMER INFORMATION

[Pr]TEVETEN®
(eprosartan mesylate tablets)

This leaflet is part III of a three-part "Product Monograph" published when TEVETEN was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about TEVETEN. Contact your doctor or pharmacist if you have any questions about the drug.

Please read this leaflet before you start to take your medicine. Keep this leaflet until you have finished all your tablets. You may want to read it again. If you are helping someone else to take **TEVETEN** read this leaflet before you give the first tablet.

ABOUT THIS MEDICATION

What the medication is used for:
TEVETEN is used for the treatment of high blood pressure

High blood pressure increases the workload of the heart and arteries. If this condition continues for a long time, damage to the blood vessels of the brain, heart, and kidneys can occur, and may eventually result in a stroke, heart failure or kidney failure. High blood pressure also increases the risk of heart attacks. Reducing your blood pressure decreases your risk of developing these illnesses.

What it does:
TEVETEN belongs to a group of drugs known as angiotensin II antagonists, which help to control high blood pressure. Angiotensin II, a natural hormone produced by the body, helps to keep blood pressure normal. One function of angiotensin II is to increase blood pressure, usually when it becomes too low. TEVETEN works by blocking the effect of angiotensin II, and as a result blood pressure is lowered.

When it should not be used:
You should not take TEVETEN if:

- ✓ If you are allergic to TEVETEN or any components of this formulation (see "What the important nonmedicinal ingredients are").
- ✓ If you are pregnant. When used in pregnancy during the second and third trimesters, drugs like TEVETEN can cause fetal injury or death. Therefore, it is very important that you notify your doctor immediately if you are pregnant or plan to become pregnant.
- ✓ If you have previously taken TEVETEN and become unwell, you should tell the doctor.
- ✓ If you have recently taken or are taking any other medicines, tell the doctor before you start taking TEVETEN.

What the medicinal ingredient is:
Eprosartan mesylate

What the important nonmedicinal ingredients are:
croscarmellose sodium (only in the 400 mg tablet), crospovidone (only in the 600 mg tablet), hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, pregelatinized starch, titanium dioxide,iron oxide red, iron oxide yellow, and polysorbate 80.

What dosage forms it comes in:
Tablets, 400 mg and 600 mg strengths.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

TEVETEN should not be used during pregnancy. If you discover that you are pregnant while taking TEVETEN, please discuss stopping this medication with your physician.

BEFORE you use TEVETEN talk to your doctor or pharmacist if:

- you are taking other medicines to control blood pressure.
- you are pregnant or think you may be pregnant. If you become pregnant, notify your doctor immediately.
- you are breast feeding. It is known that TEVETEN does pass into animal milk. You should not take these tablets when breast feeding unless the doctor tells you to.
- you have any heart, liver or kidney problems, tell your doctor before you start taking your tablets

INTERACTIONS WITH THIS MEDICATION

Be sure to tell your doctor about all other prescription and non-prescription medicines you are taking, in particular:

- diuretics (water pills)
- potassium-sparing diuretics
- potassium supplements
- lithium salts

PROPER USE OF THIS MEDICATION

Usual dose:
Follow the doctor's instructions about how and when to take your medicine. The doctor will decide how many tablets you need to take each day and for how long.
If you have any questions about your medicine and how to take it, please ask your doctor or pharmacist.

Remember this medicine is for the person named by the doctor. **Never** give it to others.

TEVETEN can be taken with or without food, but it should be taken consistently with respect to food intake and at the same time every day. TEVETEN should be swallowed with water.

Keep taking your medicine for as long as the doctor tells you. It may be necessary for the doctor to increase or decrease the dose. Your tablets may look different (colour/shape) if the dose is changed. Continue to follow the doctor's instructions.

Overdose:
If you have taken more tablets than the recommended dose, tell a doctor immediately. Show the doctor your pack of tablets.

Missed Dose:
If you forget to take a tablet, take it as soon as you remember. Take your next dose at the normal time. Do not take two doses within 6 hours of each other.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, TEVETEN may cause unintended reactions, so-called side effects. Although most patients do not experience side effects when taking TEVETEN, some patients may experience headache, dizziness, lightheadedness, cough, aches in the joints or muscles, fatigue, weakness, or tiredness. If you develop any unusual discomfort, tell the doctor as soon as possible.

Side effects such as myalgia (muscle pain), myasthenia (muscle weakness), myositis (muscle inflammation) and rhabdomyolysis (a muscle-wasting disease), in rare cases leading to kidney failure, have been reported with the use of angiotensin receptor blockers, the class of drugs to which TEVETEN belongs. You should contact your physician promptly if you experience muscle pain that you cannot explain, muscle tenderness or weakness, or when you notice dark/brown urine.

Allergic reactions have been reported very rarely with TEVETEN. If you develop difficulty breathing or swallowing; or experience swelling of the face, lips and/or tongue, stop taking TEVETEN and seek medical attention immediately.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
very rare	allergic reactions			✓
	dark/brown urine		✓	
	muscle inflammation		✓	
	muscle pain		✓	
	muscle weakness		✓	

This is not a complete list of side effects. For any unexpected effects while taking TEVETEN , contact your doctor or pharmacist.

HOW TO STORE IT

The expiry date of this medicine is printed on the label. Keep your tablets in their original pack at 15 - 25°C. Protect from moisture.

Store all medicines out of reach of children – preferably in a locked cupboard. Please return any left over medicine to the pharmacist.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

Toll-free telephone: 866-234-2345
Toll-free fax: 866-678-6789
By email: cadrmp@hc-sc.gc.ca

By regular mail:
National AR Centre
Marketed Health Products Safety and Effectiveness Information Division
Marketed Health Products Directorate
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:
http://www.solvaypharma.ca
or by contacting the sponsor, Solvay Pharma Inc., at:
1-800-268-4276

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