

PRODUCT MONOGRAPH

PrTEVETEN® PLUS

Eprosartan Mesylate / Hydrochlorothiazide Tablets

(600 mg eprosartan / 12.5 mg hydrochlorothiazide)

Angiotensin II Receptor (AT₁) Antagonist and Diuretic

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PHARMACOLOGICAL CLASSIFICATION

Angiotensin II Receptor (AT₁) Antagonist and Diuretic

ACTION AND CLINICAL PHARMACOLOGY

TEVETEN[®] PLUS (eprosartan mesylate and hydrochlorothiazide) combines the actions of eprosartan mesylate, an angiotensin II (AT₁) receptor antagonist, and that of a thiazide diuretic, hydrochlorothiazide.

Eprosartan

Eprosartan antagonizes angiotensin II by blocking the angiotensin type 1 (AT₁) 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 AT₁ receptor found in many tissues (e.g., vascular smooth muscle, adrenal gland). There is also an AT₂ receptor found in many tissues but it is not known to be associated with cardiovascular homeostasis. Eprosartan does not exhibit any partial agonist activity at the AT₁ receptor. Its affinity for the AT₁ receptor is 1,000 times greater than for the AT₂ receptor. *In vitro* binding studies indicate that eprosartan is a reversible, competitive inhibitor of the AT₁ receptor.

Eprosartan 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.

Hydrochlorothiazide

Hydrochlorothiazide is a diuretic and antihypertensive which interferes with the renal tubular mechanisms of electrolyte reabsorption. It increases excretion of sodium and chloride in approximately equivalent amounts. Natriuresis may be accompanied by some loss of potassium and bicarbonate. While this compound is predominantly a saluretic agent, *in vitro* studies have shown that it has a carbonic anhydrase inhibitory action which seems to be relatively specific for the renal tubular mechanism. It does not appear to be concentrated in erythrocytes or the brain in sufficient amounts to influence the activity of carbonic anhydrase in those tissues.

Hydrochlorothiazide is useful in the treatment of hypertension. It may be used alone or as an adjunct to other antihypertensive drugs. Hydrochlorothiazide does not affect normal blood pressure.

Pharmacokinetics

Eprosartan

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. Plasma concentrations of eprosartan increase in a slightly less than dose-proportional manner over the 100 to 800 mg dose-range. The terminal elimination half-life of eprosartan following oral administration is 5 to 9 hours. Eprosartan does not significantly accumulate with chronic use.

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.

Eprosartan exhibited a population mean oral clearance (CL/F) for an average 60-year-old patient of 48.5 L/h. The mean steady-state volume of distribution (V_{ss}/F) was 308 liters in patients of all ages.

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/h for every year increase.

Eprosartan is not metabolized by the cytochrome P450 system. 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. No active metabolites were detected following oral and intravenous dosing with eprosartan in human subjects. Eprosartan was the only drug-related compound found in the plasma and feces. Following administration of i.v. 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.

Renal Insufficiency: Following administration of eprosartan 200 mg b.i.d. for 7 days, patients with mild renal impairment (creatinine clearance 60 to 80 mL/min) showed mean eprosartan C_{max} and AUC values similar to subjects with normal renal function. Compared to patients with normal renal function, mean AUC and C_{max} values were approximately 30% higher in patients with moderate renal impairment (creatinine clearance 30 to 59 mL/min) and 50% higher in patients with severe renal impairment (creatinine clearance 5 to 29 mL/min). 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 (see DOSAGE AND ADMINISTRATION, Eprosartan Monotherapy). Hemodialysis resulted in very limited effects on clearance ($CL_{HD} < 1L/h$) and was essentially not dialyzed.

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).

Geriatric: 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 two-fold, compared to healthy young men (aged 20 to 39 years) who received the same dose. The extent of plasma protein binding was not influenced by age.

Gender: There 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 for eprosartan were not influenced by race.

Hydrochlorothiazide

Hydrochlorothiazide is not metabolized but is eliminated rapidly by the kidney. The plasma half-life is 5.6-14.8 hours when the plasma levels can be followed for at least 24 hours. At least 61% of the oral dose is eliminated unchanged within 24 hours. Hydrochlorothiazide crosses the placental but not the blood-brain barrier and is excreted in breast milk.

Eprosartan and Hydrochlorothiazide

Concomitant administration of eprosartan and hydrochlorothiazide has no clinically significant effect on the pharmacokinetics of either drug.

Pharmacodynamics

Eprosartan

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 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 eprosartan was similar in men and women, but was somewhat smaller in patients over 65 years.

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 AT₁ receptor blockers, have generally been found to be less effective in low-renin hypertensives (frequently blacks).

Hydrochlorothiazide

Onset of diuretic action following oral administration occurs in 2 hours and the peak action in about 4 hours. Diuretic activity lasts about 6 to 12 hours.

Eprosartan and Hydrochlorothiazide

The components of TEVETEN[®] PLUS have been shown to have an additive effect on blood pressure reduction, reducing blood pressure to a greater degree than either component alone.

The antihypertensive effect of TEVETEN[®] PLUS is sustained over a 24 hour period. In clinical studies of one year's duration, the antihypertensive effect was maintained with continued therapy. Despite the significant decrease in blood pressure, administration of TEVETEN[®] PLUS had no clinically significant effect on heart rate.

INDICATIONS AND CLINICAL USE

TEVETEN[®] PLUS (eprosartan mesylate and hydrochlorothiazide) is indicated for the treatment of mild to moderate essential hypertension in patients for whom combination therapy is appropriate.

TEVETEN[®] PLUS is not indicated for initial therapy (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

TEVETEN[®] PLUS (eprosartan mesylate and hydrochlorothiazide) is contraindicated in patients who are hypersensitive to any component of this product. It is also contraindicated in pregnancy and in nursing women (see WARNINGS). Because of the hydrochlorothiazide component, it is also contraindicated in patients with anuria, or severe renal impairment, and in patients who are hypersensitive to thiazides or other sulfonamide-derived drugs.

WARNINGS

Serious Warnings and Precautions

When used in pregnancy, angiotensin receptor (AT₁) blockers (ARBs) can cause injury or even death of the developing fetus. When pregnancy is detected, TEVETEN[®] PLUS should be discontinued as soon as possible (see CONTRAINDICATIONS and WARNINGS, Pregnant Women).

Pregnant Women

Drugs that act directly on the renin-angiotensin-aldosterone-system (RAAS) can cause fetal and neonatal morbidity and death when administered to pregnant women. When pregnancy is detected, TEVETEN[®] PLUS (eprosartan mesylate and hydrochlorothiazide) should be discontinued as soon as possible (see CONTRAINDICATIONS).

The use of ARBs is not recommended during pregnancy. Epidemiological evidence regarding the risk of teratogenicity following exposure to angiotensin converting enzyme inhibitors (another class of therapeutic products interfering with the RAAS) during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Given the current evidence available on the risk with ARBs, similar risks may exist for this class of drugs. Patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with angiotensin II antagonists should be stopped immediately, and, if appropriate, alternative therapy should be started.

The use of ARBs during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalemia).

Infants with a history of *in utero* exposure to ARBs 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 a means of reversing hypotension and/or substituting for impaired renal function; however, limited experience with those procedures has not been associated with significant clinical benefit.

Eprosartan is not removed from plasma by dialysis.

Thiazides cross the placental barrier and appear in cord blood. The routine use of diuretics in otherwise healthy pregnant women is not recommended and exposes mother and fetus to unnecessary hazard including fetal or neonatal jaundice, thrombocytopenia and possibly other adverse experiences which have occurred in the adult. Diuretics do not prevent development of toxemia of pregnancy and there is no satisfactory evidence that they are useful in the treatment of toxemia.

Animal Data: Eprosartan 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 twice daily. 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 twice daily).

Nursing Women

It is not known whether eprosartan is excreted in human milk but significant levels have been found in the milk of lactating rats. Thiazides appear in human milk. Because many drugs are excreted in human milk and because of their potential for affecting the nursing infant adversely, if the initiation of treatment with

eprosartan and hydrochlorothiazide is regarded necessary, nursing should be discontinued first. Nursing women should not be treated with TEVETEN[®] PLUS (see CONTRAINDICATIONS).

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, therapy should be started 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.

Azotemia

Azotemia may be precipitated or increased by hydrochlorothiazide. Cumulative effects of the drug may develop in patients with impaired renal function. If increasing azotemia and oliguria occur during treatment of severe progressive renal disease the diuretic should be discontinued.

Hypersensitivity Reactions

Hypersensitivity reactions to hydrochlorothiazide may occur in patients with or without a history of allergy or bronchial asthma.

Thiazide diuretics have been reported to cause exacerbation or activation of systemic lupus erythematosus.

PRECAUTIONS

Patients with Renal Impairment

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).

Thiazides should be used with caution in patients with renal disease. Because of the hydrochlorothiazide component, TEVETEN[®] PLUS (eprosartan mesylate and hydrochlorothiazide) is not recommended in patients with severe renal impairment (creatinine clearance <30 mL/min) (see DOSAGE AND ADMINISTRATION).

Patients with Liver Impairment

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

Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma (see DOSING AND ADMINISTRATION).

Metabolism

Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals.

All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance: hypokalemia, hyponatremia and hypochloremic alkalosis. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance, irrespective of cause, include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, confusion, seizures, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, arrhythmias, and gastrointestinal disturbances such as nausea and vomiting.

Hypokalemia may develop, especially with brisk diuresis, when severe cirrhosis is present, or after prolonged therapy.

Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia may cause cardiac arrhythmia and may also sensitize or exaggerate the response of the heart to the toxic effects of digitalis (e.g., increased ventricular irritability).

Although any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease), chloride replacement may be required in the treatment of metabolic alkalosis. Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy. Thiazides may decrease serum protein-bound iodine levels without signs of thyroid disturbance.

Thiazides have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia.

Thiazides may decrease urinary calcium excretion. Thiazides may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

The antihypertensive effects of hydrochlorothiazide may be enhanced in postsympathectomy patients.

Valvular Stenosis

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.

Use in Children

The safety and efficacy in children have not been established. Treatment of children is not recommended.

Use in the Elderly

No overall differences in safety were observed between elderly patients and younger patients, but appropriate caution should nevertheless be used when prescribing to the elderly, as increased vulnerability to drug effect is possible in this patient population.

Diabetes

In diabetic patients, dosage adjustment of insulin or oral hypoglycemic agents may be required. Hyperglycemia may occur with thiazide diuretics. Thus, latent diabetes mellitus may manifest during thiazide therapy.

Drug Interactions

Diuretics: 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 eprosartan. The possibility of symptomatic hypotension with the use of eprosartan can be minimized by discontinuing the diuretic prior to initiation of treatment (see WARNINGS – Hypotension, and DOSAGE AND ADMINISTRATION). No pharmacokinetic drug interaction of clinical significance has been identified with eprosartan and thiazide diuretics.

Agents Affecting Serum Potassium: Since eprosartan decreases the production of aldosterone, potassium-sparing diuretics (e.g., spironolactone, triamterene, amiloride), 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.

Concomitant thiazide diuretic use may attenuate any effect that eprosartan may have on serum potassium. Concomitant use of laxatives may increase the risk of hypokalemia.

Lithium Salts: Lithium generally should not be given with diuretics. As with other drugs which eliminate sodium, lithium clearance may be reduced leading to lithium toxicity. Therefore, serum lithium levels should be monitored carefully if lithium salts are to be administered.

Digoxin and Anti-Arrhythmic Drugs: By lowering serum potassium levels, hydrochlorothiazide can increase effects and side-effects of digoxin and anti-arrhythmic drugs. Hypokalemia resulting from thiazide therapy may increase the risk of quinidine-induced ventricular arrhythmias.

Alcohol, Barbiturates, or Narcotics: Potentiation of orthostatic hypotension may occur with diuretic therapy.

Antidiabetic Drugs (Oral Agents and Insulin): Insulin requirements in diabetic patients treated with diuretics may be increased, decreased or unchanged.

Nonsteroidal Anti-inflammatory Drugs: In some patients, the administration of a nonsteroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics. Therefore, when TEVETEN[®] PLUS and nonsteroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired antihypertensive effect of the diuretic is obtained.

Cholestyramine and Colestipol Resins: Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85% and 43%, respectively.

Pressor Amines (e.g. norepinephrine): In the presence of diuretics, possible decreased response to pressor amines may be seen but not sufficient to preclude their use.

Skeletal Muscle Relaxants, Non-Depolarizing (e.g. Tubocurarine-type): Thiazide diuretics may increase the effects of non-depolarizing (tubocurarine-type) skeletal muscle relaxants.

Corticosteroids, ACTH: Intensified electrolyte depletion, particularly hypokalemia, may occur when given concomitantly with diuretics.

Warfarin: Concomitant administration of eprosartan and warfarin had no effect on steady-state prothrombin time ratios (INR) in healthy volunteers.

Ranitidine: Eprosartan pharmacokinetics were not affected by concomitant administration of ranitidine.

Antifungals: Concomitant administration of ketoconazole or fluconazole (potent inhibitors of CYP 3A4 and 2C9, respectively) had no effect on steady state pharmacokinetics of eprosartan.

ADVERSE REACTIONS

The combination of eprosartan mesylate and hydrochlorothiazide contained in TEVETEN[®] PLUS (eprosartan mesylate and hydrochlorothiazide) has been evaluated for safety in 1518 patients treated for hypertension. In open studies, 890 patients were treated from 6 months to 2 years. Of these, 528 patients were treated for at least 6 months and 449 patients were treated for 1 year or longer at various doses of eprosartan and at least 12.5 mg hydrochlorothiazide daily.

In controlled clinical trials, 268 patients were treated with eprosartan 600 mg plus hydrochlorothiazide 12.5 mg and about 3% of these patients discontinued therapy due to clinical adverse experiences.

The following potentially serious adverse reactions have been reported rarely in controlled clinical trials: syncope, hypotension.

The following table is based on double-blind controlled trials in patients treated at doses of 600 mg eprosartan and 12.5mg hydrochlorothiazide. In double-blind controlled clinical trials, the following adverse events occurred amongst patients treated with combination therapy at an incidence of 1% or greater. Of the 268 patients who received such combination therapy during the double-blind treatment period in the controlled trials, 110 patients were reported to have adverse events.

Table1: Frequency of adverse events, 1 % during the double-blind treatment period by preferred term and treatment group regardless of causality: Controlled studies

	Eprosartan 600 mg/ Hydrochlorothiazide 12.5 mg (N=268) (%)	Eprosartan 600mg (N=275) (%)	Hydrochlorothiazide 12.5mg (N=117) (%)	Placebo (N=122) (%)
General				
Asthenia	1.1	1.1	0.9	0.8
Fatigue	1.9	1.8	0.9	0.8
Central and peripheral nervous				
Dizziness	4.1	1.8	1.7	1.6
Headache	3.4	3.6	3.4	9.0
Neuralgia	1.1	1.1	0.0	1.6
Paresthesia	1.1	0.7	0.0	0.8
Vertigo	1.5	0.0	0.0	1.6
Gastrointestinal				
Abdominal pain	1.5	0.4	0.9	0.8
Liver and biliary				
SGPT increase	1.1	0	0.9	0
Metabolic and nutritional				
Hyperglycemia	1.5	0.7	2.6	0.8
Musculoskeletal				
Arthrosis	1.9	0.4	0.0	0.8
Back Pain	2.6	2.5	1.7	3.3
Psychiatric				
Insomnia	1.9	0.7	1.7	0.0
Depression	1.1	0.4	0.0	0.0
Respiratory				
Bronchitis	1.5	0.7	1.7	0
Urinary				
Albuminuria	1.9	0.7	1.7	1.6
Cystitis	1.1	0.0	0.9	0.8
Hematuria	1.1	0.7	1.7	0.8
Pyuria	1.5	1.1	1.7	0.8
Urinary tract infection	1.1	0.4	1.7	0.8
White cell and reticuloendothelial				
Leucocytosis	1.5	0.7	0.9	0.8

The most commonly reported adverse events in the eprosartan 600 mg and hydrochlorothiazide 12.5 mg group were dizziness (4.1%) and headache (3.4%).

In addition to the above, the following adverse reactions have been reported rarely in post-marketing experience: hypotension, including postural hypotension, skin reactions (rash, pruritus, urticaria), anemia, thrombocytopenia, myalgia and taste disorders.

Angioedema (involving swelling of the face, lips and/or tongue) has been very rarely reported.

Laboratory testing has demonstrated occasional elevation of liver enzymes.

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

For adverse reactions pertinent to the individual components of TEVETEN[®] PLUS, please consult the Product Monographs for eprosartan mesylate and hydrochlorothiazide.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

No specific information is available on the treatment of overdose with TEVETEN[®] PLUS (eprosartan mesylate and hydrochlorothiazide). Treatment is symptomatic and supportive.

Eprosartan

Limited data are available in regard to overdose with eprosartan. The most likely manifestations of overdose would be hypotension and/or tachycardia. If symptomatic hypotension should occur, supportive treatment should be instituted. Eprosartan is not removed by hemodialysis.

Hydrochlorothiazide

The most common signs and symptoms observed are those caused by electrolyte depletion (hypokalemia, hyponatremia, hypochloremia) and dehydration resulting from excessive diuresis and may present as nausea and somnolence. If digitalis has also been administered, hypokalemia may accentuate cardiac arrhythmias. The degree to which hydrochlorothiazide is removed by hemodialysis has not been established.

DOSAGE AND ADMINISTRATION

Dosage must be individualized. The fixed combination is not for initial therapy. The dose of TEVETEN[®] PLUS (eprosartan mesylate and hydrochlorothiazide) should be determined by the titration of the individual components.

Once the patient has been stabilized on the individual components as described below, one tablet of TEVETEN[®] PLUS given once daily may be substituted if the doses on which the patient were stabilized are the same as those in the fixed combination (see INDICATIONS AND CLINICAL USE).

TEVETEN[®] PLUS 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.

Eprosartan Monotherapy

The recommended initial dose of eprosartan monotherapy 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 eprosartan alone, a thiazide diuretic may be administered concomitantly.

Dosage Adjustment in Elderly and in Patients with Severe Renal Impairment: A lower initial starting dose of 400 mg eprosartan monotherapy once daily should be considered. The usual regimen of therapy with TEVETEN[®] PLUS may generally be followed for patients with creatinine >30 mL/min. Because of the hydrochlorothiazide component, TEVETEN[®] PLUS is not recommended in patients with severe renal impairment (creatinine clearance <30 mL/min) (see PRECAUTIONS - Renal Impairment).

Patients with Hepatic Impairment: Since dosage adjustment of eprosartan is required in patients with liver impairment, and thiazide diuretics may precipitate hepatic coma, a fixed combination product such as TEVETEN[®] PLUS is not advisable (see PRECAUTIONS - Impaired Liver Function).

Patients Treated With Diuretics

In patients receiving diuretics, eprosartan 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 - Hypotension, and PRECAUTIONS - 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.

PHARMACEUTICAL INFORMATION

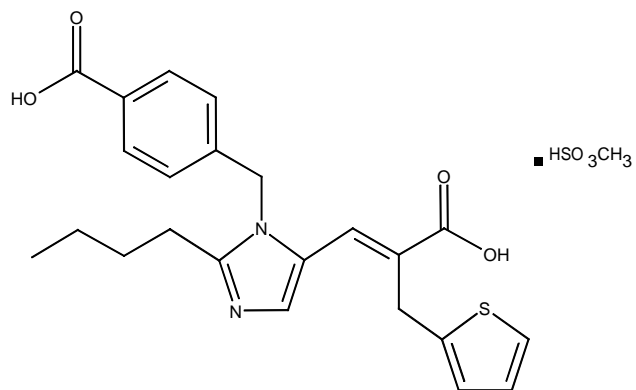
Drug Substances

Common Name: eprosartan mesylate

Chemical Names: 1) 2-thiophenepropanoic acid, -[[[2-butyl-1-[(4-carboxyphenyl) methyl] - 1H- imidazol-5-yl]methylene], (E)-monomethanesulfonate
2) (E)-2-Butyl-1-(p-carboxybenzyl)-alpha-2-thenylimidazole-5-acrylic acid, monomethanesulfonate.

Molecular Formula: $C_{23}H_{24}N_2O_4S \bullet CH_4O_3S$

Structural Formula:



Molecular Weight: 520.65

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

Physico-Chemical 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 pKa₁ = 4.11, pKa₂ = 5.68 and pKa₃ = 6.89.

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

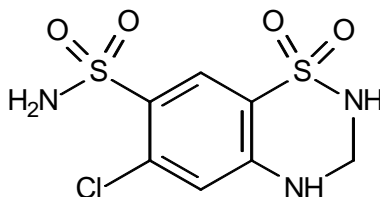
Common Name: Hydrochlorothiazide

Chemical Name: 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide

Molecular Formula: C₇H₈ClN₃O₄S₂

Molecular Weight: 297.74

Structural Formula: $C_7H_8ClN_3O_4S_2$



Description:

Hydrochlorothiazide is a white, or practically white, crystalline powder. It is slightly soluble in water, but freely soluble in sodium hydroxide solution.

Composition

TEVETEN[®] PLUS (600 mg eprosartan and 12.5 mg hydrochlorothiazide) is supplied as a film-coated, capsule-shaped, butterscotch-coloured tablet containing 600 mg eprosartan as eprosartan mesylate and 12.5 mg of hydrochlorothiazide as active ingredients.

TEVETEN[®] PLUS contains the following non-medicinal inactive ingredients: microcrystalline cellulose, lactose monohydrate, pregelatinized starch, crospovidone, magnesium stearate, polyvinyl alcohol, macrogol 3350, talc, titanium dioxide, iron oxide black, and iron oxide yellow.

Stability and Storage Recommendations

TEVETEN[®] PLUS (600 mg eprosartan and 12.5 mg hydrochlorothiazide) tablets should be stored between 15 and 25° C. Protect from moisture.

AVAILABILITY OF DOSAGE FORMS

TEVETEN[®] PLUS (600 mg eprosartan and 12.5 mg hydrochlorothiazide) is available as film-coated, capsule-shaped, butterscotch-coloured tablets debossed with 5147 on one side and no inscription on the other side.

TEVETEN[®] PLUS is available in blister packs of 28 tablets.

INFORMATION FOR THE CONSUMER

TEVETEN[®] PLUS (600 mg eprosartan as eprosartan mesylate and 12.5 mg hydrochlorothiazide) Tablets

Serious Warnings and Precautions

TEVETEN[®] PLUS should not be used during pregnancy. If you discover that you are pregnant while taking TEVETEN[®] PLUS, you should immediately discuss stopping this medication with your doctor.

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[®] PLUS read this leaflet before you give the first tablet.

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

You must follow the doctor's advice and take the tablets as instructed. If there is anything that you do not understand please ask your doctor or pharmacist.

Always keep medicines out of reach of children. Return any left-over medicines to the pharmacist.

What is TEVETEN[®] PLUS?

TEVETEN[®] PLUS is used for the treatment of high blood pressure. It contains the active ingredients eprosartan mesylate and hydrochlorothiazide. TEVETEN[®] PLUS also contains the following non-medicinal ingredients: microcrystalline cellulose, lactose monohydrate, pregelatinized starch, crospovidone, magnesium stearate, polyvinyl alcohol, macrogol 3350, talc, titanium dioxide, iron oxide black, and iron oxide yellow. If you are on a special diet, or if you are allergic to any substance (including thiazides or sulphamethoxazole based drugs), ask your doctor or pharmacist whether any of these ingredients may cause a problem. It is also important for your doctor and pharmacist to know what other medications, herbal products and other non-prescription medications that you are taking.

TEVETEN[®] PLUS is a combination of an angiotensin II antagonist (eprosartan mesylate) and a diuretic (hydrochlorothiazide).

Angiotensin II is a natural hormone produced by the body that functions by tightening the blood vessels, and thus increases blood pressure when it becomes too low. Eprosartan, contained in TEVETEN[®] PLUS, works by blocking the effect of angiotensin II, and as a result lowers blood pressure. Hydrochlorothiazide, a thiazide diuretic, works by making the kidneys pass more water and salt. Together, eprosartan and hydrochlorothiazide lower high blood pressure.

What is hypertension?

Hypertension is the medical term for 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 causes hypertension?

In most cases, the root cause of hypertension is not known, although there are several factors which increase the risk of developing the disease. The most common risk factors include family history, age, race, weight, drinking and smoking. Hypertension is a long-term condition, often without symptoms in the early stages of this condition.

Before taking TEVETEN[®] PLUS, you should tell your doctor:

- ✓ If you are taking other medicines, herbal remedies or nonprescription drugs. These include other medications for high blood pressure, arthritis medications, diabetic medications, etc.
- ✓ If you are pregnant, think you may be pregnant or thinking of becoming pregnant. Taking TEVETEN[®] PLUS during pregnancy can cause injury and even death to your baby. This medicine should not be used during pregnancy. If you become pregnant, or are planning to become pregnant while taking TEVETEN[®] PLUS, discuss stopping this medication with your doctor immediately.
- ✓ If you are breast feeding. It is known that the medicinal ingredients of TEVETEN[®] PLUS (eprosartan and hydrochlorothiazide) pass into breast milk. You should not take these tablets when breast feeding.
- ✓ If you have any heart, liver or kidney problems before you start taking your tablets.

- ✓ If you are taking potassium supplements or salt substitutes containing potassium consult your doctor.
- ✓ If you have diabetes you may need to initially watch your blood sugar more closely when using TEVETEN[®] PLUS.
- ✓ If you are on lithium you need to watch your lithium levels more closely.
- ✓ If you have experienced any bad, unusual symptoms, or allergic reaction to TEVETEN[®] PLUS, eprosartan or hydrochlorothiazide.

You should NOT take TEVETEN[®] PLUS if:

- ✓ You are allergic to any component of TEVETEN[®] PLUS (see **What is TEVETEN[®] PLUS?**). You may have allergic symptoms if you have ever reacted to thiazides or sulpha drugs in the past.
- ✓ You are pregnant. When used in pregnancy, drugs like TEVETEN[®] PLUS 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.
- ✓ You are breast feeding.
- ✓ You have kidney problems.

How to take TEVETEN[®] PLUS?

Usual dosage

Follow the doctor's instructions about how and when to take your medicine. The usual dose is one 600 mg/12.5 mg tablet once a day.

Please read the label carefully. If you have any questions about your medicine and how to take it, please ask your doctor or pharmacist.

TEVETEN[®] PLUS can be taken with or without food but it should be taken consistently with respect to food intake, and at the same time everyday.

Keep taking your medicine for as long as the doctor tells you. Generally the treatment for high blood pressure is lifelong. Well before your prescription is finished, it is important to follow-up with your doctor to get another one. Try not to run out of your medications. Continue to follow the doctor's instructions.

What happens if a dose is missed?

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.

If you take too many tablets:

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

Information on possible side-effects:

Like all medicines, TEVETEN[®] PLUS may cause unintended reactions, so-called side effects. Although most patients do not experience side effects when taking TEVETEN[®] PLUS, some patients may experience headache, dizziness, lightheadedness, rash, cough, aches in the joints or muscles, fatigue, weakness, tiredness, low blood pressure, or fainting. 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 a component of TEVETEN[®] PLUS 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 eprosartan. If you develop difficulty breathing or swallowing; or experience swelling of the face, lips and /or tongue, stop taking TEVETEN[®] PLUS and contact your doctor immediately.

How to store TEVETEN[®] PLUS?

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

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TOXICOLOGY

The acute 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 1 and 2).

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 1: Acute Toxicity of Eprosartan Alone

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 2: Chronic Toxicity of Eprosartan Alone

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 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 ($\leq 15\%$) 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 ($\leq 17\%$) 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 ($\leq 16\%$) 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.

The acute and subchronic toxicity of eprosartan and hydrochlorothiazide was evaluated in a series of single and repeat dose studies by oral administration for up to 3 months in mice and 3 months in dogs. The results of these studies are presented in Tables 3 and 4.

Table 3: Acute Toxicity of Eprosartan and Hydrochlorothiazide

Species	Route	Duration	Dose mg/kg/day	Major Findings
Dog, Beagle	oral	1 day	¹ (E/H)1000/0.3 (E/H)1000/1 (E/H)1000/3	Clinical Observations: - Emesis (18-34 min post dose) in 1 dog per group. - Emesis, within 24 hrs post dose, in 1 additional dog given high dose combination. - Soft/mucoid/yellow feces observed in 1 and 2 dogs given low and high dose combination. Body Weight: - No drug related effect Mortality: - No deaths.

¹(Eprosartan /Hydrochlorothiazide)

Table 4: Subchronic Toxicity of Eprosartan and Hydrochlorothiazide

Species	Route	Duration	Dosage (mg/kg/day)	Major Findings
mouse	oral (gavage)	90 days	(E/H) 0/0-control (E/H) 2000/0 (E/H) 0/62.5 (E/H) 300/9.375 (E/H) 2000/62.5	<p>Mortality: no drug-related deaths</p> <p>Clinical Observations: no drug-related clinical observations, changes in body weight, food consumption or ophthalmology.</p> <p>Organ Weights: Heart weight (absolute and relative to body weight) was significantly ($p < 0.05$) decreased for low-dose and high-dose combination females.</p> <p>Necropsy/Histology: Mild to moderate juxtaglomerular cell hyperplasia in male and female mice given the high-dose combination. Tubular de-/and regeneration was increased in male and female mice of the high-dose combination group and for males treated with 62.5 mg/kg/ day HCTZ alone.</p> <p>Conclusions: While low dose combination groups did not show signs of toxicity, in high dose combination group juxtaglomerular cell hyperplasia and renal tubular regeneration were observed.</p>
dog	oral (gavage)	30 days	(E/H) 0/0-control (E/H) 1000/0 (E/H) 0/31.25 (E/H) 100/3.125 (E/H) 1000/31.25	<p>Mortality: One female and one male dog of the high-dose combination group were sacrificed.</p> <p>Body Weight: Loss in BW in male and female in high-dose combination.</p> <p>Clinical observations: One male and one female in high-dose combination group showed emesis, bloody feces, and hypoactivity.</p> <p>-In surviving males and females of high-dose combination group increased emesis observed.</p> <p>-In low-dose combination group, or Eprosartan alone (1000mg/kg/day) increased emesis observed.</p> <p>Clinical Chemistry/Hematology/Urinalysis/Histology:</p> <p>-One female and one male dog of the high-dose combination group showed signs of hemoconcentration, increased serum urea, creatinine and potassium and decreased serum sodium.</p> <p>-Surviving males and females of the high-dose combination group showed increased emesis and chemistry and urinalysis changes.</p> <p>-Microscopic changes in the 3 of 7 survivors with increased creatinine included diffuse renal tubular degeneration and regeneration.</p> <p>Conclusions: -high dose combination (1000/31.25 mg/kg/day) caused nephrotoxicity progressing to renal failure, characterized by uremia and microscopic renal tubular degeneration and regeneration.</p>
dog	oral (gavage)	90 days	(E/H) 0/0 (E/H) 1000/0.3 (E/H) 1000/3.0	<p>Mortality: No drug related mortality.</p> <p>Clinical Observations: Drug related clinical signs (in both treatment groups) were limited to emesis and unformed (soft, mucoid or watery) or discolored (yellow) feces.</p> <p>Body Weight/Food Consumption /Electrocardiography/Ophthalmology/Tissue Weight/Necropsy/Histology: No drug related effects.</p> <p>Hematology/Clinical Chemistry/Urinalysis: No significant drug related effects.</p> <p>Conclusions: No significant toxicological effects associated with either the 1000/0.3 or 1000/3.0 mg/kg/day combination groups.</p>

Reproductive Toxicology

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 5).

Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed, via their diet, to doses of up to 100 and 4 mg/kg respectively, prior to mating and throughout gestation.

The combination (eprosartan and hydrochlorothiazide) given orally at doses up to 3/1 mg/kg/day (eprosartan and hydrochlorothiazide) did neither result in maternal nor fetal developmental toxicity effects.

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 >3 mg/kg/day and fetal mortality at doses >10 mg/kg/day, consistent with the unique sensitivity of pregnant and fetal rabbits to angiotensin converting enzyme inhibitors and angiotensin receptor (AT₁) antagonists given during mid- to late gestation (Table 5).

Table 5: Reproduction and Teratology of Eprosartan Alone

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

The teratogenic potential of eprosartan and hydrochlorothiazide was investigated in a series of studies. Eprosartan in combination with hydrochlorothiazide was orally administered (by gavage) to female New Zealand White rabbits. The results of these studies are presented in Table 6.

Table 6: Teratology of Eprosartan and Hydrochlorothiazide

Species	Route	Duration	Dosage (mg/kg/day)	Major Findings
rabbit	oral (gavage)	days 6-28 (gest) days 6-17 (gest) days 18-28 (gest) days 6-28 (gest)	¹ 0/0 30/10 10/3 10/3 3/1 1/0.3 0/3	Maternal toxicity (mortality, decreased food consumption and weight gain) but no developmental toxicity was evident at 30/10 mg/kg/day (eprosartan/HCTZ) when given on day 6 to 17 p.c. Maternal toxicity (body weight decreased and early delivery) and developmental toxicity (increased resorption rate) were evident at 10/3 mg/kg/day when given at late pregnancy (days 18 to 28).
rabbit	oral (gavage)	days 6-17 (gest)	0/0 0/10 10/3 30/0 30/10	Maternal toxicity but no developmental toxicity was evident at 30/0, 10/3 or 30/10 mg/kg/day (eprosartan/HCTZ) when given on days 6 - 17 of pregnancy. Maternal toxicity was greater in rabbits given 30/10 mg/kg/day compared to rabbits given 30/0 or 0/10 mg/kg/day.
rabbit	oral (gavage)	days 18-28 (gest)	0/0 0/3 3/1 10/0 10/3	Maternal toxicity (body weight loss, abortion and/or early delivery) and developmental toxicity (increased fetal mortality) were evident at 10 mg/kg/day of eprosartan alone and for the 10/3 mg/kg/day (eprosartan/HCTZ) combination. HCTZ produced no maternal or developmental toxicity and did not enhance the toxicity effects of eprosartan.

¹Eprosartan/HCTZ

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 7).

Table 7: Genotoxic Potential: Eprosartan

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

Similarly, *in vitro* and *in vivo* eprosartan and hydrochlorothiazide showed no evidence of mutagenicity in microbial assays (Ames mutagenicity assay of Salmonella typhimurium and Escherichia coli strains), in human lymphocytes and in a mouse micronucleus test (Table 8).

Table 8: Genotoxic Potential: Eprosartan and Hydrochlorothiazide

Test	System	Conc./Dose	Results
Mutagenicity	Salmonella typhimurium and Escherichia coli	312.5 - 5000 µg/plate (with and without S9)	Negative
Micronucleus	Mouse (CD-1) bone marrow cells	2000 mg/kg/day	Negative
Chromosome aberration	Human lymphocytes	860.2-1831 µg/mL (without S9) 1529-2635 µg/mL (with S9)	Negative

The 600/12.5 mixture of eprosartan and hydrochlorothiazide did not induce gene mutations (*in vitro*) and chromosomal aberrations (*in vitro* and *in vivo*) at non-toxic concentration/dose range.

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 9).

Table 9: Carcinogenicity of Eprosartan Alone

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).

Two-year feeding studies in mice and rats conducted under the auspices of the National Toxicology Program (NTP) uncovered no evidence of a carcinogenic potential of hydrochlorothiazide in female mice (at doses of up to approximately 600 mg/kg/day) or in male and female rats (at doses of up to approximately 100 mg/kg/day). The NTP, however, found equivocal evidence for hepatic carcinogenicity in male mice.

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