PRODUCT MONOGRAPH

PrTEVETEN®

Eprosartan Mesylate Tablets

(containing 400 mg and 600 mg eprosartan)

Angiotensin II receptor (AT_1) antagonist

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Date of Preparation:
December 22, 2014

Date of Previous Revision:
January 8, 2016

Date of Revision:
September 04, 2018

Submission Control No: 216410

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Oral	Tablet / 400 mg	croscarmellose sodium, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, pregelatinized starch, titanium dioxide
	Tablet / 600 mg	crospovidone, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, pregelatinized starch, titanium dioxide

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.

For information on the concurrent treatment of TEVETEN and angiotensin converting enzyme inhibitors, see WARNINGS AND PRECAUTIONS - Dual Blockade of the Renin-Angiotensin-Aldosterone System (RAAS); and DRUG INTERACTIONS.

Geriatrics

In elderly patients with essential hypertension eprosartan taken once daily for 12 weeks in doses of 600-800 mg is a 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

TEVETEN (eprosartan mesylate) is contraindicated in:

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see DOSAGE FORMS, COMPOSITION AND PACKAGING section of the product monograph.

- Pregnant women (see WARNINGS AND PRECAUTIONS, Special Populations, Pregnant Women).

- Nursing women (see WARNINGS AND PRECAUTIONS, Special Populations, Nursing Women).

- Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption (see WARNINGS AND PRECAUTIONS, Sensitivity/Resistance).

- Patients with hemodynamically significant bilateral renovascular disease or severe stenosis of a solitary functioning kidney (see WARNINGS AND PRECAUTIONS, Renal).

- Combination with angiotensin converting enzyme (ACE) inhibitors in patients with diabetic nephropathy (see WARNINGS AND PRECAUTIONS, Dual Blockade of the Renin-Angiotensin-Aldosterone System (RAAS)).

Concomitant use of angiotensin receptor antagonists (ARBs) –including TEVETEN- with aliskiren-containing drugs in patients with diabetes mellitus (type 1 or type 2) or moderate to severe renal impairment (GFR < 60 ml/min/1.73m^2) is contraindicated (see WARNINGS AND PRECAUTIONS, Dual Blockade of the Renin-Angiotensin-Aldosterone System (RAAS); WARNINGS AND PRECAUTIONS, Renal, Renal Impairment; and DRUG INTERACTIONS, Table 2).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

When used in pregnancy, angiotensin receptor (AT_1) blockers (ARBs) can cause injury or even death of the developing fetus. When pregnancy is detected, TEVETEN should be discontinued as soon as possible (see CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS – Special Populations).

General

As observed for angiotensin converting enzyme inhibitors, eprosartan and the other angiotensin antagonists are apparently less effective in lowering blood pressure in black people than in non-blacks, possibly because of higher prevalence of low-renin states in the black hypertensive population.

Cardiovascular

Aortic and Mitral Valve Stenosis / Hypertrophic Cardiomyopathy:

As with all vasodilators, eprosartan should be used with caution in patients with aortic and mitral valve stenosis or hypertrophic cardiomyopathy. There is concern on theoretical grounds that patients with aortic stenosis might be at particular risk of decreasegd 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.

Dual blockade of the renin-angiotensin-aldosterone system (raas)

There is evidence that co-administration of angiotensin receptor antagonists (ARBs), such as TEVETEN, or of angiotensin converting enzyme (ACE) inhibitors, with aliskiren increases the risk of hypotension, syncope, stroke, hyperkalemia and deterioration of renal function, including renal failure, in patients with diabetes mellitus (type 1 or type 2) and/or moderate to severe renal

impairment (GFR < 60 ml/min/1.73m^2). Therefore, the use of TEVETEN in combination with aliskiren-containing drugs is contraindicated in these patients (see CONTRAINDICATIONS).

Further, co-administration of ARBs, including TEVETEN, with other agents blocking the RAAS, such as ACE inhibitors or aliskiren-containing drugs, is generally not recommended in any patients, since such treatment has been associated with an increased incidence of severe hypotension, renal failure, and hyperkalemia (see DRUG INTERACTIONS).

If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure. The concomitant use of angiotensin II receptor blockers (ARBs) and ACE inhibitors in patients with diabetic nephropathy is contraindicated (see CONTRAINDICATIONS).

For additional information, see DRUG INTERACTIONS.

Endocrine and metabolism

Hyperkalemia:

During treatment with medicinal products which affect the renin-angiotensin-aldosterone system, including eprosartan, hyperkalaemia may occur, especially in the presence of renal impairment and/or heart failure. Adequate monitoring of serum potassium in patients at risk is recommended.

Based on experience with the use of other medicinal products which affect the renin-angiotensin-aldosterone system, concomitant use of eprosartan with potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium or any medicinal products that may increase potassium levels (e.g. heparin, NSAIDs) may lead to an increase in serum potassium. Therefore, co-administration with eprosartan should be done cautiously (see DRUG INTERACTIONS, Drug-Drug Interactions).

Primary Hyperaldosteronism:

It is not recommended to treat patients with primary hyperaldosteronism with eprosartan.

Hepatic/biliary/pancreatic

There is limited experience on the use of eprosartan in patients with hepatic impairment. Therefore, special care should be exercised in this patient population.

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).

Neurologic

Effects on Ability to Drive and Use Machines:

The effect of eprosartan on ability to drive and use machines has not been studied. When driving vehicles or operating machines, it should be taken into account that occasional dizziness or asthenia may occur during treatment of hypertension.

Renal

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.

The use of ARBs – including TEVETEN– with aliskiren-containing drugs is contraindicated in patients with moderate to severe renal impairment (GFR < 60 ml/min/1.73m^2). (See CONTRAINDICATIONS and DRUG INTERACTIONS, Table 2).

No dose adjustment is required in patients with mild to moderate renal insufficiency (creatinine clearance ≥ 30 mL/min). Caution is recommended for use in patients with creatinine clearance < 30 mL/min or in patients undergoing dialysis. Use of eprosartan should include appropriate assessment of renal function (see DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment, Use in Patients with Impaired Renal Function).

Renal Transplantation:

There is no experience in patients with recent kidney transplantation.

Sensitivity/resistance

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medication (see CONTRAINDICATIONS).

Special populations

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 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 risk 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, hyperkalaemia).

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.

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 but significant levels have been found in the milk of lactating rats. 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 is regarded necessary, nursing should be discontinued first. Nursing women should not be treated with TEVETEN (see CONTRAINDICATIONS).

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 a 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 > 3,300 healthy volunteers and patients, including > 1,460 patients treated for > 6 months, and > 980 patients treated for ≥ 1 year.

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% Among Eprosartan-Treated Patients:

The following table lists adverse events that occurred at an incidence of ≥ 1% 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.

In addition, asthenia has been seen commonly in clinical trials.

Less common clinical trial adverse drug events (< 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, 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 ≤ 3.0 x 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 ≤1.5 x 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 ≤ 100 x 10^9L 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
- Hypotension, including postural hypotension
- Skin reactions, including rash, pruritus, urticaria
- Angioedema involving swelling of the face, lips and/or tongue
- Arthralgia

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

Since there is currently inadequate therapeutic experience in patients with severe cardiac insufficiency or renal artery stenosis, it cannot be ruled out that renal function may be impaired (including renal failure in patients at risk e.g. renal artery stenosis) with eprosartan due to inhibition of the renin-angiotensin-aldosterone system.

DRUG INTERACTIONS

Overview

Eprosartan has been shown not to inhibit human cytochrome P450 enzymes CYP1A, 2A6, 2C9/8, 2C19, 2D6, 2E, and 3A *in vitro*.

Drug-Drug Interactions

Table 2. Established or Potential Drug-Drug Interactions

Proper Name	Ref.	Effect	Clinical comment
Other Antihypertensive Drugs (including Diuretics)	CT	Concomitant use with other antihypertensive drugs may potentiate the antihypertensive effect of eprosartan.	See WARNINGS AND PRECAUTIONS - Cardiovascular: Hypotension, and DOSAGE AND ADMINISTRATION.
Dual blockade of the Renin-Angiotensin-Aldosterone System (RAAS) with ARBs, ACEIs or aliskiren-containing drugs	CT	Dual Blockade of the Renin-Angiotensin-Aldosterone-System (RAAS) with ARBs, ACEIs or aliskiren-containing drugs is contraindicated in patients with diabetes and/or renal impairment, and is generally not recommended in other patients, since such treatment has been associated with a higher frequency of adverse events such as severe hypotension, decreased renal function (including acute renal failure), and hyperkalemia compared to the use of a single RAAS-acting agent.	See CONTRAINDICATIONS; and WARNINGS AND PRECAUTIONS, Dual Blockade of the Renin-Angiotensin-Aldosetrone System (RAAS).
Agents Increasing Serum Potassium	T, CT	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.

Table 2. Established or Potential Drug-Drug Interactions

Proper Name	Ref.	Effect	Clinical comment
			Since in placebo-controlled clinical studies significantly elevated serum potassium concentrations were observed, and based on experience with the use of drugs that affect the renin-angiotensin-aldosterone system, concomitant use of potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium or drugs that may increase serum potassium levels (e.g. heparin, NSAIDs) may lead to increase in serum potassium (see WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Hyperkalemia).
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. Toxicity and a reversible increase in serum lithium concentrations have been reported during concurrent therapy with lithium preparations and ACE inhibitors. The possibility of a similar effect after the use of eprosartan can not be excluded and careful monitoring of serum lithium levels is recommended during concomitant use.
Non-steroidal Anti-inflammatory Drugs (NSAIDs)	T	As with ACE inhibitors, concomitant use of Angiotensin II antagonists and NSAIDs may lead to an increased risk of worsening of renal function, including possible acute renal failure and an increase in serum potassium, especially in patients with poor pre-existing renal function.	The combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy, and periodically thereafter.
Indometacin	T	A decrease in efficacy of the angiotensin II receptor blocker.	Concomitant use of losartan with the NSAID indomethacin led to a decrease in efficacy of the angiotensin II receptor blocker, a class effect cannot be excluded.

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.

If blood pressure is not adequately controlled with TEVETEN alone, a thiazide diuretic may be administered concomitantly. See WARNINGS AND PRECAUTIONS, Dual Blockade of the Renin-Angiotensin-Aldosterone System (RAAS); and DRUG INTERACTIONS.

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

For management of a suspected drug overdose, contact your regional Poison Control Centre.

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 is 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) (see WARNINGS AND PRECAUTIONS, General).

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 300 mg oral (fasted)	1612 ± 720	4.52 ± 3.05	5657 ±2694	ND	ND
Eprosartan 300 mg oral (fed)	1205 ± 484	7.25 ± 4.61	4807±1907	ND	ND
Eprosartan 20 mg 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 distribution
ND: 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 - light to moderately pink, oval tablets inscripted with 5044 on one side and no inscription on the other side;

600 mg - white, capsule-shaped tablet imprinted with 5046 on one side and no inscription 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.

TEVETEN 600 mg is available in blister packs of 28 tablets.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

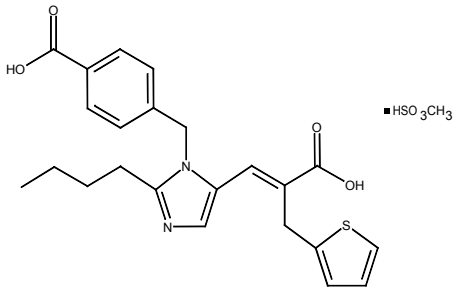
Proper name: Eprosartan mesylate

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 800 mg od 200 to 400 mg 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 400 mg od 600 mg od 800 mg od 1200 mg 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 600 mg od oral for 4 weeks	30	59.4 ± 1.6	23/7
		losartan 50 mg od oral for 4 weeks	30	58.7 ± 2.1	24/6
124	Double blind, Placebo Controlled, Randomized	eprosartan 600 mg 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.	400 mg od SitDBP - 9.4	placebo Sit DBP - 4.2	-5.0 (-7.7, 2.4); <0.0001*
		200 mg 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.	400 mg od SitDBP - 5.1 ± 0.9	placebo Sit DBP - 3.3 ± 1.0	-1.9 (-5.1, 1.3); 0.121
		600 mg od SitDBP - 6.2 ± 0.9		-3.2 (-6.4, 0.0); 0.10*
		800 mg od SitDBP - 5.9 ± 0.8		-2.7 (-5.9, 0.5); 0.028
		1200 mg 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.	600 mg od SitDBP -12.4 SitSBP -12.7	50 mg 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 600 mg administered once daily.	600 mg od SitDBP -7.6 ± 0.8	SitDBP -1.5 ± 0.8	-6.1 (-8.1, -4.1); <0.0001+
		SitSBP -6.6 ± 1.3	SitSBP 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 600 mg tablet and two of the previously marketed 300 mg tablets, has been established in a bioavailability study. The single-dose study compared 2 x 300 mg eprosartan tablets with 1 x 600 mg 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 600 mg oral dose of eprosartan, administered as one of three different regimens: A) TEVETEN (eprosartan mesylate) 1 x 600 mg; B) another eprosartan formulation, 1 x 600 mg (data not shown); C) eprosartan 2 x 300 mg, previous commercial formulation (Table 6). There was a minimum 7 day washout period between doses.

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

Parameter	TEVETEN (eprosartan) 600 mg Tablet	2 x 300 mg eprosartan Tablet	% Ratio of Geometric Means*	90% Confidence Interval
$AUC_{T\ (0\text{-}t)}$ (ng.h/mL)	8649 9728 (50.9)	8798 10098 (53.1)	99	(90,109)
$AUC_{T\ (0\text{-}t^1)}$ (ng.h/mL)	8608 9689(51.1)	8756 10065 (53.6)	99	(90,109)
C_{max} (ng/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

C_{max}: peak plasma concentration

T_{max}: time to peak plasma concentration

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 600 mg/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 600 mg/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.

Acute Toxicity

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.

Long-Term Toxicity

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 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 and Teratology

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 ≥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 (AT_1) antagonists given during mid- to late gestation (Table 9).

Mutagenicity and Carcinogenicity

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

PrTEVETEN®

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. Read this leaflet carefully before you start taking TEVETEN® and each time you get a refill. This leaflet is a summary and will not tell you everything about TEVETEN®. Talk to your doctor, nurse, or pharmacist about your medical condition and treatment and ask if there is any new information about TEVETEN®.

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® is an angiotensin receptor blocker (ARB). You can recognize an ARB because its medicinal ingredient ends in "-**SARTAN**".

This medicine does not cure your disease. It helps to control it. Therefore, it is important to continue taking TEVETEN® regularly even if you feel fine.

When it should not be used:

Do not take TEVETEN® if you:

- are allergic to eprosartan mesylate or to any non-medicinal ingredient in the formulation.
- have experienced an allergic reaction with swelling of the face, lips, tongue, throat or sudden difficulty breathing or swallowing, to any ARB. Be sure to tell your doctor, nurse, or pharmacist that this has happened to you.
- are pregnant or intend to become pregnant. Taking TEVETEN® during pregnancy can cause injury and even death to your baby.
- are breastfeeding. It is possible that TEVETEN® passes into breast milk.
- have previously taken TEVETEN® and became unwell. Be sure to tell your doctor, nurse, or pharmacist that this has happened to you.
- have diabetes or kidney disease and are already taking a blood pressure-lowering medicine that contains aliskiren (such as Rasilez®), or an angiotensin converting enzyme (ACE) inhibitor. You can recognize ACE inhibitors because the name of their medicinal ingredient ends in "-pril".

What the medicinal ingredient is:

Eprosartan mesylate

What the non-medicinal 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:

- 400 mg light to moderately pink, oval film-coated tablets
- 600 mg white, capsule-shaped film-coated tablets

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions - Pregnancy

TEVETEN® should not be used during pregnancy. If you discover that you are pregnant while taking TEVETEN®, stop the medication and contact your doctor, nurse, or pharmacist as soon as possible.

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

- have experienced an allergic reaction to any drug used to lower blood pressure.
- have narrowing of a heart valve, heart or blood vessel disease.
- have diabetes, liver or kidney disease.
- are dehydrated or suffer from excessive vomiting, diarrhea, or sweating.
- are taking a salt substitute that contains potassium, potassium supplements, or a potassium-sparing diuretic (a specific kind of "water pill" that makes your body keep potassium).
- are on a low-salt diet.
- are on dialysis.
- are less than 18 years old.
- you are taking other medicines to control blood pressure.
- are taking a medicine that contains aliskiren, such as Rasilez®, used to lower high blood pressure. The combination with TEVETEN® is not recommended.
- are taking an angiotensin converting enzyme inhibitor (ACEI). You can recognize ACEIs because their medicinal ingredient ends in '-**PRIL**'.

- you produce too much of a hormone called aldosterone.
- you have been told by your doctor that you have an intolerance to some sugars.

Driving and using machines: Before you perform tasks which may require special attention, wait until you know how you respond to TEVETEN®. Dizziness, lightheadedness, or fainting can especially occur after the first dose and when the dose is increased.

INTERACTIONS WITH THIS MEDICATION

As with most medicines, interactions with other drugs are possible. Tell your doctor, nurse, or pharmacist about all the medicines you take, including drugs prescribed by other doctors, vitamins, minerals, natural supplements, or alternative medicines.

The following may interact with TEVETEN®:

- agents increasing serum potassium, such as a salt substitute that contains potassium, potassium supplements, or a potassium-sparing diuretic (a specific kind of "water pill").
- blood pressure-lowering drugs, including diuretics ("water pills"), aliskiren-containing products (e.g. Rasilez®), or angiotensin converting enzyme inhibitors (ACEIs).
- lithium used to treat mood disorder.
- nonsteroidal anti-inflammatory drugs (NSAIDs), used to reduce pain and swelling. Examples include ibuprofen, naproxen, celecoxib, and indometacin.
- medicines that increase potassium levels, such as heparin.

PROPER USE OF THIS MEDICATION

Take TEVETEN® exactly as prescribed. It is recommended to take your dose at about the same time everyday.

Usual adult 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.

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 think you have taken too much TEVETEN® contact your doctor, nurse, pharmacist, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If you have forgotten to take your dose during the day, carry on with the next one at the usual time. Do not double dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Side effects may include:

- back or leg pain, muscle cramps
- headache
- diarrhea, vomiting
- rash
- drowsiness, insomnia
- dizziness
- lightheadedness
- cough
- rhinitis
- fatigue, weakness or tiredness
- joint pain (arthralgia).

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

Symptom / effect		Talk with your doctor, nurse, or pharmacist		Stop taking drug and seek immediate medical help
		Only if severe	In all cases	
Common	**Liver Disorder:** yellowing of the skin or eyes, dark urine, abdominal pain, nausea, vomiting, loss of appetite		√	
	Low Blood Pressure: dizziness, fainting, lightheadedness	√		
Uncommon	**Allergic Reaction:** rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			√

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

Symptom / effect		Talk with your doctor, nurse, or pharmacist		Stop taking drug and seek immediate
	Rhabdomyolysis: muscle pain that you cannot explain, muscle tenderness or weakness, dark brown urine		√	
	Kidney Disorder: change in frequency of urination, nausea, vomiting, swelling of extremities, fatigue		√	
	Decreased White Blood Cells: infections, fatigue, fever, aches, pains, and flu-like symptoms		√	

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

HOW TO STORE IT

Keep out of reach and sight of children.

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.

Please return any left over medicine to the pharmacist.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report on line at:**
https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 1908C
    Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at
https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

The most recent version of this document plus the full product monograph, prepared for health professionals can be found at:

www.mylan.ca
or by contacting the sponsor, BGP Pharma ULC, Etobicoke, Ontario, M8Z 2S6 at:
1-844-596-9526

This leaflet was prepared by BGP Pharma ULC.

Last revised: September 04, 2018
