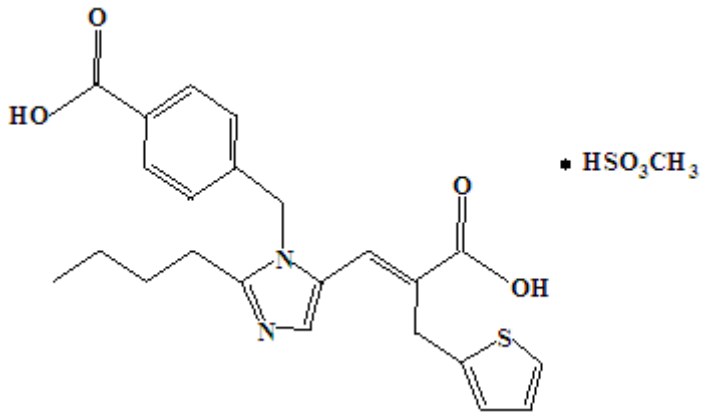
Teveten

Eprosartan mesylate tablets 400mg & 600mg

DESCRIPTION

Teveten (eprosartan mesylate) is a non-biphenyl nontetrazole angiotensin II receptor (AT_1) antagonist. It is chemically described as the monomethanesulphonate of (*E*)-α-[[2-butyl-1-[(4-carboxyphenyl)methyl]-1H-imidazol-5-yl]methylene]-2-thiophenepropanoic acid.

It has a molecular weight (MW) of 520.6 and may be represented structurally as:



Eprosartan mesylate (CAS 0144143-96-4) is a white to off-white powder with a melting point range of 248°C to 250°C and at room temperature has a solubility of 0.91 mg/mL in water at a pH of 7.

Teveten tablets contain eprosartan mesylate equivalent to either 400 mg or 600 mg eprosartan as the active ingredient. The tablets also contain lactose, cellulose- microcrystalline, starch- pregelatinised maize, magnesium stearate, titanium dioxide, hypromellose , macrogol 400 and polysorbate 80 as excipients. Each tablet strength also contains various other ingredients as follows:

400 mg: croscarmellose sodium, iron oxide yellow (CI 77492) and iron oxide red (CI 77491).

600 mg: crospovidone.

PHARMACOLOGY

Eprosartan is a potent angiotensin II receptor antagonist, which selectively binds to the AT_1 receptor. Angiotensin II is a potent vasoconstrictor, and the

primary active hormone of the renin-angiotensin-aldosterone system, playing a major part in the pathophysiology of hypertension. Angiotensin II binds to AT_1 receptors in many tissues (e.g. smooth vascular musculature, kidney suprarenals and heart) and produces biological effects such as vasoconstriction, sodium retention and release of aldosterone.

Eprosartan blocks the binding of angiotensin II to the AT_1 receptors, which prevents vasoconstriction, thus lowering blood pressure and aldosterone secretion. In hypertensive patients, comparable blood pressure control is achieved when eprosartan is administered once or twice daily. Blood pressure control is maintained in a consistent and smooth manner over a 24-hour period with no first dose postural hypotension. Discontinuation of treatment with eprosartan does not lead to a rebound increase in blood pressure.

In patients with hypertension, eprosartan does not produce a change in heart rate.

In hypertensive patients eprosartan does not affect fasting triglycerides, total cholesterol, or LDL (low density lipoprotein) cholesterol levels. In addition eprosartan has no effect on fasting blood sugar levels.

Eprosartan does not compromise renal autoregulatory mechanisms. In normal adult males eprosartan has been shown to increase mean effective renal plasma flow. Eprosartan does not reduce glomerular filtration rate in normal males, in patients with hypertension or in patients with varying degrees of renal insufficiency. Eprosartan has a natriuretic effect in normal subjects on a salt restricted diet. Eprosartan may be safely administered to hypertensive patients with varying degrees of renal insufficiency without causing sodium retention or a deterioration of renal function.

Eprosartan does not significantly affect urinary uric acid excretion.

Eprosartan does not potentiate effects related to bradykinin (ACE, mediated) eg cough.

Pharmacokinetics

The absolute bioavailability of eprosartan following a single 300 mg oral dose is approximately 13%. In the fasted state, eprosartan plasma concentrations peak 1 to 2 hours following an oral dose. Concurrent administration with food delays eprosartan absorption, resulting in variable changes of <25% in Cmax and AUC, which are not considered to be of clinical consequence. Plasma concentrations are dose proportional from 100 mg to 200 mg, but less than proportional for 400 mg and 800 mg doses. Eprosartan does not significantly accumulate with chronic use.

Eprosartan is highly bound to plasma proteins (approximately 98%), and binding has been demonstrated to be constant over the range of therapeutic concentrations. The extent of plasma protein binding is not influenced by gender, age, hepatic dysfunction or mild-moderate renal impairment, but has

been shown to decrease in a small number of patients with severe renal impairment.

The volume of distribution of eprosartan is approximately 0.22 L/kg and the total plasma clearance is approximately 2.2 mL/min/kg.

Biliary and renal excretion contributes to the elimination of eprosartan. The terminal elimination half-life of eprosartan is 5 to 9 hours.

There are no active metabolites following oral and intravenous dosing with [^{14}C] eprosartan in human subjects. Eprosartan was the only drug-related compound found in the plasma and faeces. Following intravenous [^{14}C] eprosartan, about 61% is recovered in the faeces and about 37% in the urine. Following an oral dose of [^{14}C] eprosartan, about 90% is recovered in the faeces 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.

There was no difference in the pharmacokinetics in men and women following a single oral dose of eprosartan.

In the elderly, AUC and Cmax values of eprosartan are on average increased, approximately 2 fold, compared with young subjects (see Precautions and Dosage and Administration).

In patients with hepatic impairment, AUC (but not Cmax) values of eprosartan are on average increased approximately 40% (see Precautions and Dosage and Administration sections).

In patients with moderate renal impairment (creatinine clearance 30-59 mL/min), AUC and Cmax values are approximately 30% higher than in subjects with normal renal function. In severe renal impairment (creatinine clearance 5-29 mL/min), AUC and Cmax values are approximately 50% higher than normal (see Precautions and Dosage and Administration sections).

Clinical Trials

The safety and efficacy of eprosartan have been demonstrated in more than 2400 hypertensive patients enrolled in a variety of clinical trials worldwide. Clinical trials included mild to moderate hypertensive patients (sitting DBP ≥ 95 mmHg and < 115 mmHg) and severe hypertensive patients (sitting DBP ≥ 115 mmHg and ≤ 125 mmHg).

Doses up to 1200 mg per day for 8 weeks, have been shown in clinical trials to be effective with no apparent dose relationship in the incidence of adverse experiences reported.

The antihypertensive effects of eprosartan were demonstrated in five placebo-controlled trials (8 to 13 weeks duration) using 400 mg to 1200 mg given once-daily as monotherapy and two placebo-controlled trials (8 to 13 weeks

duration) using dosages of 25 to 400 mg twice daily. These studies included 1472 patients randomised to receive eprosartan and 605 patients randomised to receive placebo. At study endpoint, patients treated with eprosartan experienced significant decreases in sitting diastolic blood pressure at trough, with differences from placebo of -1.8 to -6.1 mmHg over the range of doses studied. Furthermore, at study endpoint, the decrease in sitting systolic blood pressure at trough resulted in differences from placebo of -0.8 to -10.3 mmHg over the range of doses studies.

In a placebo-controlled, dose-ranging study of eprosartan administered once-daily, both diastolic and systolic blood pressures decreased as the total daily dose increased from 400 to 1200 mg. In a placebo-controlled, dose-titration study additional blood pressure lowering effect of the drug was seen as the dose was increased from 400 mg to 800 mg daily.

An ambulatory blood pressure monitoring study using eprosartan 600 mg and 1200 mg demonstrated satisfactory once daily efficacy with good 24-hour control. The 0-24 hour and 20-24 hour ambulatory DBP seen with eprosartan 600 mg once daily was significantly lower than that observed for placebo. The trough-peak ratios were greater than 80%, confirming that a substantial proportion of the peak antihypertensive effect remained at the end of the dosing interval.

Three other studies, investigating eprosartan once-daily, also measured trough-peak ratios. Peak (1-3 hours) effects were uniformly, but moderately, larger than trough effects, with the trough to peak ratio for diastolic blood pressure being in the range of 61-90%. Similar trough to peak ratios were seen for once and twice daily dosing.

One study investigated the effect of eprosartan in 243 patients dosed either once or twice daily. Eprosartan 400 mg to 800 mg once-daily produced a placebo-corrected decrease in diastolic blood pressure (-5.2 mmHg) equivalent to eprosartan dosed 200 mg to 400 mg twice daily (-5.0 mmHg).

In long-term follow-up, open-labelled studies, blood pressure control was maintained up to 24 months.

In three clinical studies (n=791) comparing eprosartan with the Angiotensin Converting Enzyme (ACE) inhibitor enalapril, the blood pressure lowering effect of eprosartan was shown to be at least as great as that of enalapril. In one of the studies, in severe hypertensives, eprosartan showed a statistically significant greater decrease in sitting and standing systolic blood pressure than did enalapril.

Two of these studies also compared the incidence of cough, as ACE inhibitor-induced cough (a dry, persistent cough) can lead to discontinuation of ACE inhibitor therapy. In the first study, patients who previously had cough while taking an ACE inhibitor were treated with eprosartan, an ACE inhibitor (enalapril) or placebo for six weeks. The incidence of dry, persistent cough was 2.6% on eprosartan, 2.7% on placebo, and 25% on the ACE inhibitor. The incidence of this cough was significantly lower in the eprosartan group

(p=0.008) compared to the ACE inhibitor group and not significantly different from the placebo group. In the second study comparing the incidence of cough in 259 patients treated with eprosartan to 261 patients treated with the ACE inhibitor enalapril, the incidence of dry, persistent cough in eprosartan-treated patients (1.5%) was significantly lower (p=0.018) than that observed in patients treated with the ACE inhibitor (5.4%). In addition, analysis of overall data from six double blind clinical trials involving 1,554 patients showed the incidence of spontaneously reported cough in patients treated with eprosartan was similar to placebo (3.5% vs. 2.6%, respectively).

INDICATIONS

Teveten is indicated for the treatment of essential hypertension.

CONTRAINDICATIONS

Teveten is contraindicated in:

- Patients with known hypersensitivity to any component of the product.
- Pregnancy and lactation. (see 'PRECAUTIONS')
- Haemodynamically significant bilateral renovascular disease or severe stenosis of a solitary functioning kidney.

PRECAUTIONS

Risk of renal impairment: Patients whose renal function is dependent on the activity of the renin-angiotensin-aldosterone system (e.g. patients with severe cardiac insufficiency, bilateral renal artery stenosis, or renal artery stenosis of a solitary kidney) have developed oliguria and/or progressive azotaemia and rarely acute renal failure during therapy with ACE inhibitors. There is inadequate experience in patients with severe cardiac insufficiency or renal artery stenosis. Therefore it is possible that renal function may be impaired with eprosartan due to inhibition of the renin-angiotensin-aldosterone system. When eprosartan is used in patients with renal impairment, renal function should be assessed before starting treatment with eprosartan and at intervals during the course of therapy.

Combination use of angiotensin converting enzyme inhibitors or angiotensin receptor antagonists and anti-inflammatory drugs and thiazide diuretics.

The use of an ACE inhibiting drug (ACE inhibitor or angiotensin receptor antagonist) and an anti-inflamatory drug (NSAID or COX-2 inhibitor) and a thiazide diuretic at the same time increases the risk of renal impairment. This includes use in fixed combination products containing more than one class of drug. Combined use of these medications should be accompanied by

increased monitoring of serum creatinine, particularly at the institution of the treatment. The combination of drugs from these three classes should be used with caution particularly in elderly patients or those with pre-existing renal impairment.

There is limited experience with Teveten in patients with renal impairment. Based on pharmacokinetic data, which demonstrate increased plasma concentrations of eprosartan in renally impaired patients, a lower starting dose should be considered in these patients (see Pharmacokinetics, Dosage and Administration).

Hepatic impairment: There is limited experience with Teveten in patients with hepatic insufficiency. Based on pharmacokinetic data, which demonstrate increased plasma concentrations of eprosartan in hepatically impaired patients, a lower starting dose should be considered in these patients (see Pharmacokinetics, Dosage and Administration.)

Sodium/volume depletion: At the start of therapy, symptomatic hypotension may occur in patients with severe sodium depletion and/or volume depletion (e.g. diuretic therapy). Sodium and/or volume depletion should be corrected before commencing therapy or a reduced initial dose of eprosartan used (see Dosage and Administration).

Other conditions: Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Carcinogenesis, mutagenesis and impairment of fertility*:* Carcinogenicity has not been observed in rats or mice administered eprosartan orally by gavage for 2 years. The highest doses tested were 600 mg/kg/day in rats and 2000 mg/kg/day in mice. These doses provided systemic exposure to eprosartan, which in rats was less than, and in mice, about 3 times more than the exposure expected in human patients receiving the maximum daily dose of 800 mg, based on AUC.

Eprosartan was not genotoxic in a series of assays for gene mutations and chromosomal damage.

Administration of eprosartan to male or female rats during gametogenesis at oral doses up to 1000 mg/kg/day did not impair fertility or foetal development (approximately 0.7 times the human exposure at the maximum recommended clinical dose, based on AUC).

Use in pregnancy (Category D):

Unless continued eprosartan therapy is considered essential, 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 eprosartan should be stopped immediately and, if appropriate, alternative therapy should be started (see 'CONTRAINDICATIONS').

There is little experience with the use of eprosartan during pregnancy. It has been reported that drugs that act directly on the renin-angiotensin system can cause foetal and neonatal morbidity and death. Several dozen cases have been reported in the world literature in patients who were taking ACE-inhibitors.

When administered to women in the second or third trimesters of pregnancy, drugs that act directly on the renin-angiotensin system have been associated with foetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible renal failure and even death. Oligohydramnios has also been reported, presumably as a result of a decrease in foetal renal function. Oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation and hypoplastic lung development. Prematurity, intrauterine growth retardation and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug.

Intra-uterine exposure to the drug during the first trimester does not appear to result in these adverse events. However, mothers whose embryos and foetuses have been exposed to an angiotensin II receptor antagonist during the first trimester should be informed of the potential risks.

In rare cases, where no alternative treatment can be found, serial ultrasound examinations should be performed to assess the intra-amniotic environment. If oligohydramnios is observed, Teveten should be stopped immediately unless it is considered lifesaving for the patient. Patients and physicians should be aware that oligohydramnios might not appear until after the foetus has sustained irreversible injury.

Women of childbearing age should be warned of the potential hazards to their foetus and asked to report pregnancies to their physician as soon as possible.

Infants with a history of *in utero* exposure to an angiotensin II receptor antagonist should be closely observed for hypotension, oliguria and hyperkalaemia.

Eprosartan was not teratogenic in rats at oral doses of up to 1000 mg/kg/day (approximately 0.7 times the human exposure at the maximum recommended clinical dose, based on AUC). It was not teratogenic in rabbits at doses up to 30 mg/kg/day (the highest dose tolerated and approximately 9 times the human exposure at the maximum recommended clinical dose, based on AUC), but was maternotoxic from 3 mg/kg/day and caused increased foetal mortality from 10 mg/kg/day (less than human exposure at the maximum recommended clinical dose, based on AUC). The mechanism of the high toxicity in rabbits has not been investigated, but may be related to effects on the renin-angiotensin system in combination with higher exposure levels at low doses.

Use in lactation: Due to the potential for adverse effects in the nursing infant, breast feeding women should not be treated with Teveten (see 'CONTRAINDICATIONS')

Eprosartan is excreted in the milk of lactating rats, however there is no information on excretion of the drug in human breast milk.

Use in children: As the safety and efficacy in children have not been established, treatment of children is not recommended.

Interactions: Concomitant use of Teveten and other antihypertensives may result in enhanced blood pressure lowering effects.

No clinically significant drug interactions have been observed. Eprosartan has shown no effect on digoxin pharmacokinetics, or the pharmacodynamics of warfarin and glibenclamide. No evidence of clinically significant adverse interactions occurred with concomitant use of thiazide diuretics (eg hydrochlorothiazide); or sustained-release calcium channel blockers (eg sustained release nifedipine).

Ranitidine, ketoconazole and fluconazole have shown no effects on the pharmacokinetics of eprosartan.

In vitro human cytochrome P450 enzymes CYP1A, 2A6, 2C9/8, 2C19, 2D6, 2E, and 3A, associated with drug-metabolism, are not inhibited by eprosartan.

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors. The possibility of a similar effect after the use of eprosartan cannot be excluded and careful monitoring of serum lithium levels is recommended during concomitant use.

Effects on the ability to drive and use machines: Based on its pharmacodynamic properties, eprosartan is unlikely to affect the ability to drive or operate machinery. However, it should be taken into account that occasionally dizziness or weariness may occur during treatment of hypertension.

ADVERSE REACTIONS

Teveten has been evaluated for safety in more than 2,900 subjects worldwide, including more than 1000 patients treated for more than 6 months, and 394 patients treated for 1 year or longer. In general, Teveten was well tolerated at doses up to 1200 mg daily for up to 8 weeks. The overall incidence of adverse experiences reported with eprosartan was comparable to placebo. Most adverse events were of mild or moderate severity and did not require discontinuation of therapy.

In placebo-controlled clinical trials, 4.1% of patients treated with Teveten discontinued therapy due to clinical adverse experiences, compared to 6.5% discontinuations among placebo-treated patients.

Table 1 lists adverse events that occurred at an incidence of 1% or more among eprosartan-treated patients who participated in placebo-controlled

trials of 4 to 13 weeks duration, using doses of 25mg to 400mg twice daily, and 400mg to 1200mg once-daily.

Table 1. Adverse Events Reported by ≥ 1% of Patients Receiving Teveten (eprosartan mesylate) in Six Placebo-Controlled Clinical Studies

Placebo (%)

	Frequency	
Event	**Eprosartan (%)**	**Placebo (%)**
	(n=1202)	**(n=352)**
Body as a Whole		
Infection viral	2.4	1.4
Injury	2.4	1.1
Chest pain	2.1	2
Fatigue	1.5	1.1
Pain	1.2	1.1
Cardiovascular		
Palpitation	1.2	0.9
Gastrointestinal		
Abdominal pain	1.5	0.9
Diarrhoea	2.5	2.6
Dyspepsia	1.3	1.7
Metabolic and Nutritional		
Oedema dependent	1.1	2.3
Hypertriglyceridemia	1.2	0
Musculoskeletal		
Myalgia	4	4
Arthralgia	1.8	1.1
Back pain	1.3	1.1
Nervous system		
Headache	10.1	10.8
Dizziness	2.9	3.7
Depression	1.0	0
Respiratory		
Upper respiratory tract infection	7.9	5.4
Rhinitis	4	2.8
Pharyngitis	3.7	2.6

Coughing	3.5	2.6
Sinusitis	3.2	3.4
Dyspnoea	1.2	0.6
Bronchitis	1.1	2.3
Urogenital		
Urinary tract infection	1.3	0.3

Laboratory test finding: In controlled clinical trials, clinically important changes in standard laboratory parameters possibly associated with administration of Teveten were rarely observed and occurred at rates comparable to those seen with placebo.

No increased incidence of hyperkalaemia was observed in eprosartan-treated patients compared to placebo-treated patients. However, based on experience with other drugs that affect the renin-angiotensin system, regular monitoring of serum potassium is recommended in patients concomitantly treated with potassium sparing diuretics, potassium supplements or salt substitutes containing potassium.

Post-marketing data: In addition to those adverse events reported during clinical trials, the following side effects have been reported spontaneously during postmarketing use of eprosartan.

Common (1% ≤10%): Nausea, vomiting, unspecific gastro-intestinal complaints, asthenia.

Uncommon (0.1% ≤1%): Hypotension, including postural hypotension.

Rare (0.01% ≤0.1%): Anxiety, insomnia, nervousness, paraesthesia, somnolence, vertigo and allergic skin reactions (rash, pruritis, urticaria).

Very rare (0.001% ≤0.01%): As with other angiotensin II receptor antagonists, very rare cases of facial swelling and/or angioedema have been reported.

The following adverse events have been reported spontaneously during postmarketing use of eprosartan.

Renal and urinary disorders: Impaired renal function including renal failure in patients at risk (e.g. renal artery stenosis)

DOSAGE AND ADMINISTRATION

The usual starting dose of Teveten is 600 mg once-daily. The dose may be increased to 800 mg daily, if further response is required. Achievement of maximal blood pressure reduction in most patients may take 2 to 3 weeks of treatment.

The safety and efficacy of Teveten has been established in combination with hydrochlorothiazide or nifedipine.

Teveten may be taken with or without food.

Discontinuation of treatment does not lead to a rapid rebound increase in blood pressure.

Hepatic or renal impairment*:* A starting dose of 400 mg once-daily should be considered in patients with renal or hepatic impairment. The dose may be increased up to 800 mg once-daily, if further response is required.

Sodium/volume depletion: A starting dose of 400 mg once-daily should be considered in patients who are sodium and/or volume depleted. The dose may be increased up to 800 mg once-daily, if further response is required.

Use in the elderly: In clinical trials the efficacy and safety of eprosartan was not influenced by the age of the patient. However, based on pharmacokinetic data demonstrating a significant increase in plasma concentrations of eprosartan in elderly patients, a reduced starting dose of 400 mg once-daily should be considered in these patients. The dose may be increased up to 800 mg once-daily, if further response is required.

OVERDOSAGE

Limited data are available on overdosage in humans. Eprosartan was well tolerated after oral dosing (maximum unit dose taken to date in humans 1200 mg) with no mortality in rats and mice up to 3000 mg/kg and in dogs up to 1000 mg/kg. The most likely manifestation of overdosage would be hypotension. If symptomatic hypotension should occur, supportive treatment should be instituted.

Contact the National Poisons Centre on 0800 764 766 for management of overdose.

STORAGE

Teveten tablets should be stored in a dry place at or below 25°C.

PRESENTATION

400 mg: Light to moderately pink, oval, film coated tablet marked with "5044"; on one side and ";Solvay"; on the other side. Blister packs of 14 (starter pack), 28 and 56 tablets.

600 mg: White, capsule-shaped, film-coated tablet marked with "5046" on one side and "Solvay" on the other side. Blister packs of 7 (starter pack), 14, 28 and 56 tablets.

MEDICINE CLASSIFICATION

Prescription Only Medicine

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New Zealand

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Date of Preparation

14 July 2009