TEVETEN

EPROSARTAN MESILATE

1. NAME OF THE MEDICINE

Eprosartan mesilate

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Teveten tablets contain eprosartan mesilate equivalent to either 400 mg or 600 mg eprosartan as the active ingredient.

Teveten (eprosartan mesilate) is a non-biphenyl nontetrazole angiotensin II receptor (AT1) 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.

Eprosartan mesilate 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.

Excipient with known effect:

The tablets also contain lactose monohydrate.

For the full list of excipients, see Section **6.1 List of excipients**.

3. PHARMACEUTICAL FORM

Teveten 400 mg tablets are light to moderately pink, oval, film coated tablets marked with "5044" on one side.

Teveten 600 mg tablets are white, capsule-shaped, film-coated tablets marked with "5046" on one side.

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS

Teveten is indicated for the treatment of essential hypertension.

4.2. DOSE AND METHOD OF ADMINISTRATION

The usual starting dose of Teveten is 600 mg once-daily. 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 600 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 600 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 600 mg once-daily, if further response is required.

4.3. CONTRAINDICATIONS

Teveten is contraindicated in:

- Patients with known hypersensitivity to any component of the product.
- Pregnancy and lactation. (see Section **4.6 Fertility, pregnancy and lactation**)
- Haemodynamically significant bilateral renovascular disease or severe stenosis of a solitary functioning kidney.
- The concomitant use of Teveten with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR <60ml/min/1.73m2).

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Patients at 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. There is no experience in patients with recent kidney transplantation.

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-inflammatory 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.

Patients should be adequately hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy, and periodically thereafter.

Dual blockade of the renin-angiotensin-aldosterone (RAAS)

There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended (see Section **4.5 Interactions with other medicines and other forms of interactions** and **5 Pharmacological properties**).

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. ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

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 Section **4.2 Dose and method of administration**).

Hyperkalaemia

During treatment with other medicinal products which affect the renin-angiotensin-aldosterone system 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 other medicinal products which may increase the potassium level (e.g. heparin) may lead to an increase in serum potassium and should therefore be co-administered cautiously with eprosartan.

Primary Hyperaldosteronism

Treatment with eprosartan is not recommended in patients with primary hyperaldosteronism.

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.

Other

As observed for angiotensin converting enzyme inhibitors, eprosartan and the other angiotensin II receptor blockers may be less effective in lowering blood pressure in people of indigenous African origin than in people of other racial origin, possibly because of higher prevalence of low-renin states in the indigenous African hypertensive population.

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

Use in 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 Sections **5.2 Pharmacokinetic properties** and **4.2 Dose and method of administration**)

Use in renal impairment

There is limited experience with Teveten in patients with renal impairment. 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. 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 Section **5.2 Pharmacokinetic properties** and **4.2 Dose and method of administration**).

When eprosartan is used in patients with renal impairment, renal function should be assessed before starting treatment with eprosartan and at intervals during therapy. If worsening of renal function is observed during therapy, treatment with eprosartan should be reassessed.

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 should be considered in these patients.

Paediatric use

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

Effects on laboratory tests

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.

4.5. INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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

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 (e.g. hydrochlorothiazide); or sustained-release calcium channel blockers (e.g. 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.

Clinical trial data has shown that dual blockade of the renin-angiotensin-aldosterone-system (RAAS) through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is associated with higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent.

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.

Since in placebo-controlled clinical studies elevated serum potassium concentration were observed, and based on experience with the use of other drugs that affect the renin-angiotensin-aldosterone system, concomitant use of K-sparing diuretics, K-supplements, salt substitutes containing potassium or other drugs that may increase serum potassium levels (e.g. heparin) may lead to increase in serum potassium (see Section **5.1 Pharmacodynamic properties**).

As with ACE inhibitors, concomitant use of angiotensin II receptor blockers and NSAIDs may lead to an increased risk of worsening renal function, including possible acute renal failure, and an increase in serum potassium, especially in patients with pre-existing poor 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 of renal function after initiation of concomitant therapy, and periodically thereafter.

Concomitant use of losartan with the NSAID indometacin led to a decrease in efficacy of the angiotensin II receptor blocker; a class effect cannot be excluded.

4.6. FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

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 Section **4.3 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 Section **4.3 Contraindications**). Eprosartan is excreted in the milk of lactating rats, however there is no information on excretion of the drug in human breast milk.

4.7. EFFECTS ON 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.

4.8. ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

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 mesilate) in Six Placebo-Controlled Clinical Studies

Event	Frequency	
Event	**Eprosartan (%) (n=1202)**	**Placebo (%) (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

Post-marketing data

In addition to those adverse events reported during clinical trials, the following side effects have been reported spontaneously during post marketing 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.

Unknown: Impaired renal function including renal failure in patients at risk (e.g. renal artery stenosis), arthralgia

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at https://www.tga.gov.au/reporting-problems.

4.9. OVERDOSE

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.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES

Mechanism of action

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) e.g. cough.

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).

5.2. PHARMACOKINETIC PROPERTIES

Absorption

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.

Distribution

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.

Metabolism

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

Excretion

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

Other

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 Sections **4.2 Dose and method of administration** and **4.4 Special warnings and precautions for use**).

In patients with hepatic impairment, AUC (but not Cmax) values of eprosartan are on average increased approximately 40% (see Sections **4.2 Special warnings and precautions for use** and **4.4 Dose and method of administration**)

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 Sections **4.2 Dose and method of administration** and **4.4 Special warnings and precautions for use**).

5.3. PRECLINICAL SAFETY DATA

Genotoxicity

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

Carcinogenicity

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.

6. PHARMACEUTICAL PROPERTIES

6.1. LIST OF EXCIPIENTS

The tablets also contain lactose monohydrate, microcrystalline cellulose, pregelatinised maize starch, magnesium stearate, croscarmellose sodium (400 mg only), Opadry YS-1-14643-A (400 mg only), crospovidone (600 mg only) and Opadry OY-S-9603 (600 mg only).

6.2. INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3. SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging

6.4. SPECIAL PRECAUTIONS FOR STORAGE

Teveten tablets should be stored below 25°C.

6.5. NATURE AND CONTENTS OF CONTAINER

Teveten 400 mg tablets are available in PVC/PCTFE (Aclar)/Aluminium blister packs containing 14*, 28 or 56* tablets.

Teveten 600 mg tablets are available in PVC/PCTFE (Aclar)/Aluminium or PVC/PVDC /Aluminium blister packs containing 7 (starter pack), 14*, 28 or 56* tablets.

*Not marketed in Australia.

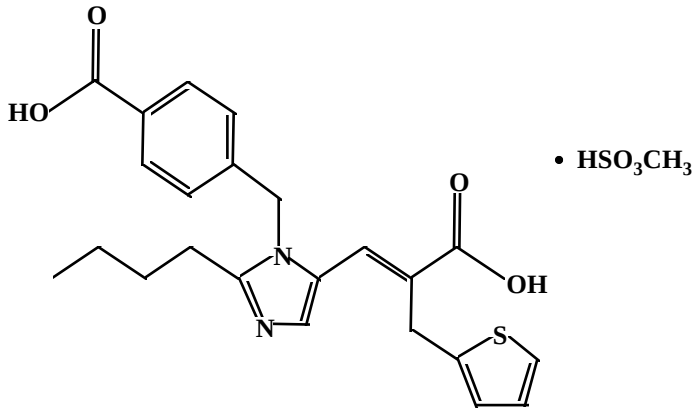
6.6. SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7. PHYSICOCHEMICAL PROPERTIES

Chemical structure:

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



• HSO_3CH_3

CAS#:

144143-96-4

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8. SPONSOR

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9. DATE OF FIRST APPROVAL

22nd May 2001

10. DATE OF REVISION

06 June 2018

Summary table of changes -Version 8	
Section changed	**Summary of new information**
Section 4.4	Additional information relating to renal impairment, primary hyperaldosteronism, aortic and mitral valve stenosis/hypertrophic cardiomyopathy and people of indigenous African origin.
Section 4.5:	Additional information relating to concomitant NSAID use
Section 4.8	Editorial restructure of post marketing section, addition of post marketing event: arthralgia
Entire document	Minor editorial changes including: 1. Movement of text within sections to improve readability 2. Reformatted according to Approved form for product information in relation to medicine under subsection 7D (1) of the Therapeutic Goods Act 1989