AUSTRALIAN PRODUCT INFORMATION

TEVETEN® PLUS

Eprosartan mesilate and hydrochlorothiazide tablets

1 NAME OF THE MEDICINE

Eprosartan mesilate and hydrochlorothiazide

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

TEVETEN PLUS tablets contain eprosartan mesilate equivalent to eprosartan 600 mg and 12.5 mg hydrochlorothiazide as the active ingredients.

Excipients with known effect: lactose

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

Capsule shaped, butterscotch coloured, film-coated tablet, one side plain, the other side embossed 5147.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Treatment of hypertension. Treatment should not be initiated with this fixed dose combination.

4.2 DOSE AND METHOD OF ADMINISTRATION

TEVETEN PLUS should not be initiated as first line therapy.

TEVETEN PLUS may be used for patients whose blood pressure is not adequately controlled on either hydrochlorothiazide or eprosartan alone. Most of the antihypertensive effect with eprosartan is usually attained within four weeks of initiation of treatment. Therefore, TEVETEN PLUS should only be initiated after an adequate trial period of monotherapy with eprosartan or hydrochlorothiazide, preferably lasting 4 - 6 weeks.

The recommended dose of TEVETEN PLUS is one tablet daily.

TEVETEN PLUS can be taken with or without food.

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

Patients who are Salt or Volume Depleted or on Existing Diuretic Therapy

In patients who are salt or volume depleted, for example due to diuretic therapy, the condition should be corrected before starting TEVETEN PLUS. Patients on diuretic therapy should cease the diuretic 2-3 days before starting TEVETEN PLUS.

Elderly, Hepatically or Renally Impaired Patients

Initial dose adjustment is generally not required in the elderly, in patients with mild to moderate hepatic impairment or in patients with mild to moderate renal impairment (creatinine clearance ≥ 30 mL/min). TEVETEN PLUS is not recommended in patients with severe hepatic impairment or severe renal impairment (creatinine clearance < 30 mL/min).

4.3 CONTRAINDICATIONS

TEVETEN PLUS is contraindicated in:

- Patients with known hypersensitivity to any component of the product and sulfonamide derived drugs (e.g. thiazides)
- Pregnancy and lactation
- Severe hepatic impairment
- Cholestasis and biliary obstructive disorders
- Severe renal impairment (creatinine clearance < 30 mL/min)
- Haemodynamically significant bilateral renovascular disease or severe stenosis of a solitary functioning kidney
- Therapy resistant hypokalaemia or hypercalcaemia
- Refractory hyponatraemia
- Symptomatic hyperuricaemia/gout
- The concomitant use of TEVETEN PLUS 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

Renal function should be closely monitored in patients whose vascular tone and renal function depend predominantly 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 functioning kidney. Patients whose renal function is dependent on the activity of the renin-angiotensin-aldosterone system have developed oliguria and/or progressive azotaemia and rarely acute renal failure during therapy with ACE inhibitors. Therefore, the possibility of a similar effect with the use of an angiotensin II receptor antagonist cannot be excluded.

If worsening of renal function is observed during therapy, treatment with eprosartan + hydrochlorothiazide should be reassessed (see Section 4.3 CONTRAINDICATIONS). Renal function should be monitored closely because there is an increased risk for severe hypotension and renal insufficiency in these patients.

Dual Blockade of the Renin-angiotensin-aldosterone System (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 Sections 4.3 CONTRAINDICATIONS, 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.

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.

Hypersensitivity

Hypersensitivity reactions to hydrochlorothiazide are more likely in patients with a history of allergies including hypersensitivity to sulphonamide-derived substances.

Choroidal Effusion, Acute Myopia and Secondary Angle-Closure Glaucoma

Hydrochlorothiazide, a sulphonamide, can cause an idiosyncratic reaction, resulting in choroidal effusion with visual field defect, acute transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue hydrochlorothiazide as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulphonamide or penicillin allergy.

Sodium/Volume Depletion

At the start of therapy, symptomatic hypotension may occur in patients with severe sodium depletion and/or volume depletion (e.g. vigorous diuretic therapy and/or dietary salt restriction, vomiting, diarrhoea and haemodialysis). Sodium and/or volume depletion should be corrected before commencing therapy with TEVETEN PLUS.

Electrolyte Imbalance

Hydrochlorothiazide can cause fluid or electrolyte imbalance (hypokalaemia, hyponatraemia, hypercalcaemia, hypomagnesaemia, and hypochloraemic alkalosis). As for any patient receiving diuretic therapy, periodic determination of serum electrolytes should be considered.

Potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium or other medicinal products which may increase the potassium level (e.g. trimethoprim containing medicines) may lead to an increase in serum potassium and should be co-administered cautiously with eprosartan + hydrochlorothiazide (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Hypokalaemia is mainly associated with higher doses of thiazide diuretic monotherapy. Hyponatraemia and chloride deficit are usually mild and asymptomatic and usually do not require treatment. Calcium excretion may be decreased by thiazide diuretics, causing a slight elevation in serum calcium levels in the absence of a known disorder of calcium metabolism (e.g. hyperthyroidism). Thiazides should be discontinued before carrying out tests for parathyroid function.

Metabolic and Endocrine Effects

Hydrochlorothiazide may impair glucose tolerance, and this may require dosage adjustment of antidiabetic medication. Latent diabetes mellitus may become manifest during therapy with thiazide diuretics.

Minor metabolic or endocrine effects have been reported with low dose (12.5 mg) thiazide diuretics. Monitoring of laboratory parameters may be necessary in patients at risk of metabolic disturbances.

Aortic and Mitral Valve Stenosis, Obstructive Hypertrophic Cardiomyopathy

As with other vasodilators patients with aortic or mitral valve stenosis or obstructive hypertrophic cardiomyopathy should be treated with caution.

Primary Hyperaldosteronism

Patients with primary hyperaldosteronism do not react sufficiently on antihypertensives which act though inhibition of renin-angiotensin-aldosterone system. Therefore, treatment with TEVETEN PLUS is not recommended.

Non-melanoma Skin Cancer

An increased risk of non-melanoma skin cancer (NMSC) [e.g. basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)] with increasing cumulative dose of hydrochlorothiazide (HCTZ) exposure has been observed in two epidemiological studies based on the Danish National Cancer Registry (see Section 5.1 PHARMACODYNAMIC PROPERTIES – CLINICAL TRIALS). Photosensitizing actions of HCTZ could act as a possible mechanism for NMSC.

Patients taking HCTZ should be informed of the risk of NMSC and advised to regularly check their skin for any new lesions and promptly report any suspicious skin lesions. Possible preventive measures such as limited exposure to sunlight and UV rays and, in case of exposure, adequate protection should be advised to the patients in order to minimize the risk of skin cancer. Suspicious skin lesions should be promptly examined potentially including histological examinations of biopsies. The use of HCTZ may also need to be reconsidered in patients who have experienced previous NMSC (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

Acute Respiratory Toxicity

Very rare severe cases of acute respiratory toxicity, including acute respiratory distress syndrome (ARDS) have been reported after taking hydrochlorothiazide. Pulmonary oedema typically develops within minutes to hours after hydrochlorothiazide intake. At the onset, symptoms include dyspnoea, fever, pulmonary deterioration and hypotension. If diagnosis of ARDS is suspected, TEVETEN PLUS should be withdrawn and appropriate treatment given. Hydrochlorothiazide should not be administered to patients who previously experienced ARDS following hydrochlorothiazide intake.

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.

Thiazide diuretics have been reported to exacerbate or activate systemic lupus erythematosus

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

Hydrochlorothiazide may lead to a positive result in doping tests.

Use in Hepatic Impairment

Hydrochlorothiazide should be used with caution in patients with mild to moderate impairment of hepatic function as it may cause intra-hepatic cholestasis. Alterations of fluid and electrolyte balance may precipitate hepatic coma.

Use in Renal Impairment

No dose adjustment is required in patients with mild to moderate renal insufficiency (creatinine clearance ≥ 30 ml/min). TEVETEN PLUS is contraindicated in severe renal impairment (creatinine clearance < 30 mL/min) (see Section 4.3 CONTRAINDICATIONS). Caution is recommended for use in patients undergoing dialysis There is no experience with TEVETEN PLUS in patients with renal transplants.

Hydrochlorothiazide-associated azotaemia may occur in patients with impaired renal function.

When eprosartan + hydrochlorothiazide is to be used in patients with renal impairment, renal function, serum potassium and uric acid should be assessed before starting treatment with eprosartan + hydrochlorothiazide and at intervals during therapy.

Use in the Elderly

In clinical studies, no significant difference was observed in efficacy and safety between older patients (> 65 years of age) and younger patients.

Paediatric Use

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

Effects on Laboratory Tests

Treatment with TEVETEN PLUS for up to 2 years was associated with small increases in serum uric acid, plasma glucose and triglycerides. These were not clinically significant.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Potential Interactions Related to both Eprosartan and Hydrochlorothiazide

Lithium

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors and, rarely, with angiotensin II receptor blockers. While this has not been documented with eprosartan, the possibility of a similar effect cannot be excluded. In addition, the renal clearance of lithium is reduced by thiazides and consequently the risk of lithium toxicity may be increased. Therefore, use of TEVETEN PLUS and lithium in combination is not recommended. If use of the combination proves necessary, careful monitoring of serum lithium levels is recommended.

Baclofen

The potentiation of antihypertensive effect may occur with concomitant baclofen therapy.

Other Antihypertensive Agents

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

Non-Steroidal and Anti-Inflammatory Medicinal Products (NSAIDs)

NSAIDs may attenuate the diuretic and antihypertensive effects of TEVETEN PLUS. 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.

Amifostine

The potentiation of antihypertensive effect may occur with concomitant amifostine therapy.

Alcohol, Barbiturates, Narcotics or Antidepressants

The potentiation of orthostatic hypotension may occur with concurrent use of alcohol, barbiturates, narcotics and antidepressants.

Potential Interactions Related to Eprosartan

Cytochrome P450

In vitro human cytochrome P450 enzymes CYP1A, 2A6, 2C9/8, 2C19, 2D6, 2E, and 3A, associated with drug-metabolism, are not inhibited by eprosartan. Ranitidine, ketoconazole and fluconazole have shown no effects on the pharmacokinetics of eprosartan.

Medicinal Products Affecting Potassium Levels

Based on the reported experience with the use of drugs which affect the renin-angiotensin system, potassium-sparing diuretics, potassium supplements or potassium-containing salts substitutes or other medicinal products that may increase serum potassium levels (e.g. heparin, ACE inhibitors, trimethoprim containing medicines) may lead to increases in serum potassium. If medicinal products which affect potassium levels are to be prescribed in combination with TEVETEN PLUS, monitoring of potassium plasma levels is advised.

Renin-angiotensin-aldosterone System (RAAS)

Clinical trial data has shown that dual blockade of the 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.

Potential Interactions Related to Hydrochlorothiazide

Medicinal Products Affecting Potassium Levels

Hydrochlorothiazide increases the risk of hypokalaemia particularly if it is concomitantly administered with drugs associated with potassium loss, such as kaliuretic diuretics, laxatives, corticosteroids, ACTH, amphotericin, carbenoxolone, penicillin G sodium or salicylic acid derivatives. Concomitant use of these products is not recommended.

Calcium Salts and Vitamin D

Thiazide diuretics may increase serum calcium levels due to decreased excretion. If calcium supplements or medicinal products affecting serum calcium levels (e.g. Vitamin D therapy) must be prescribed, serum calcium levels should be monitored, and calcium dosage adjusted accordingly.

Digitalis Glycosides

Thiazide-induced hypokalaemia or hypomagnesaemia may favour the onset of digitalis-induced cardiac arrhythmias. By lowering serum potassium levels, hydrochlorothiazide can increase the effects and side-effects of digitalis and anti-arrhythmic drugs.

Medicinal Products Affected by Serum Potassium Disturbances

Periodic monitoring of serum potassium and ECG is recommended when TEVETEN PLUS is administered with medicinal products affected by serum potassium disturbances (e.g. digitalis glycosides and antiarrhythmics) and with the following torsades de pointes (ventricular tachycardia)-inducing medicinal products (including some antiarrhythmics), hypokalaemia being a predisposing factor to torsades de pointes (ventricular tachycardia):

- Class Ia antiarrythmics (e.g. quinidine, hydroquinidine, disopyramide)
- Class III antiarrythmics (e.g. amiodarone, sotalol, dofetilide, ibutilide)
- Some antipsychotics (e.g. thioridazine, chlorpromazine, levomepromazine, trifluoperazine, cyamemazine, sulpiride, sultopride, amisulpride, tiapride, pimozide, haloperidol, droperidol)
- Others (e.g. bepridil, cisapride, diphemanil, erythromycin IV, halofantrine, mizolastin, pentamidine, terfenadine, vincamine IV)

Non-depolarising Skeletal Muscle Relaxants (e.g. tubocurarine)

The effect of non-depolarizing skeletal muscle relaxants may be potentiated by hydrochlorothiazide.

Anticholinergic Agents (e.g. atropine, biperiden)

Increase of the bioavailability of thiazide-type diuretics by decreasing gastrointestinal motility and stomach emptying rate.

Colestyramine and Colestipol Resins

Absorption of hydrochlorothiazide is reduced by anionic exchange resins such as colestyramine or colestipol.

Antidiabetic Medicinal Products (oral agents and insulin)

The treatment with a thiazide may influence the glucose tolerance. Dosage adjustment of the antidiabetic medicinal product may be required.

Metformin

Metformin should be used with caution because of the risk of lactic acidosis induced by possible functional renal failure linked to hydrochlorothiazide.

Beta-blockers and Diazoxide

The hyperglycaemic effect of beta-blockers and diazoxide may be enhanced by thiazides.

Pressor Amines (e.g. noradrenaline (norepinephrine))

The effect of pressor amines may be decreased.

Medicinal Products Used in the Treatment of Gout (probenecid, sulfinpyrazone and allopurinol)

Dosage adjustment of uricosuric medicinal products may be necessary since hydrochlorothiazide may raise the level of serum uric acid. Increase in dosage of probenecid or sulfinpyrazone may be necessary. Co-administration of a thiazide may increase the incidence of hypersensitivity reactions to allopurinol.

Amantadine

Thiazides may increase the risk of adverse effects caused by amantadine.

Cytotoxic Agents (e.g. cyclophosphamide, methotrexate)

Thiazides may reduce the renal excretion of cytotoxic medicinal products and potentiate their myelosuppressive effects.

Tetracyclines

Concomitant administration of tetracyclines and thiazides increases the risk of tetracycline-induced increase in urea. This interaction is probably not applicable to doxycycline.

Medicinal Products Lowering Serum Sodium Levels

The hyponatraemic effect of hydrochlorothiazide may be intensified by concomitant administration of drugs such as antidepressants, antipsychotics, antiepileptics, etc. Caution is advised in long-term administration of these drugs.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

The effects of eprosartan and hydrochlorothiazide in combination and hydrochlorothiazide monotherapy on fertility have not been investigated. However, administration of eprosartan to male or female rats during gametogenesis at oral doses up to 1000 mg/kg/day did not impair fertility or fetal development (approximately 0.7 times the human exposure at the maximum recommended clinical dose, based on AUC).

Use in Pregnancy – Category D

TEVETEN PLUS is contraindicated in pregnancy.

There is little experience with the use of eprosartan and hydrochlorothiazide in combination during pregnancy. It has been reported that drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death. Several dozen cases have been reported in the world literature in patients who were taking ACE inhibitors. When pregnancy is detected, TEVETEN PLUS should be discontinued as soon as possible.

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

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 PLUS should be discontinued unless it is considered lifesaving. Patients and physicians should be aware that oligohydramnios might not appear until after the fetus has sustained irreversible injury. Infants with a history of in utero exposure to an angiotensin II receptor antagonist should be closely observed for hypotension, oliguria and hyperkalaemia.

Intra-uterine exposure to the drug during the first trimester only, does not appear to result in these adverse events. However, mothers whose embryos and fetuses have been exposed to an angiotensin II receptor antagonist during the first trimester should be informed of the potential risks. Women of childbearing age should be warned of the potential hazards to their fetus and asked to report pregnancies to their physician as soon as possible.

Thiazides cross the placental barrier and appear in cord blood.

Studies in pregnant rabbits showed an increased incidence of late resorptions and dead fetuses when eprosartan/hydrochlorothiazide were administered at non-maternotoxic doses of 10/3 mg/kg/day during late gestation. These doses are associated with drug exposure similar to those expected in humans after administration of TEVETEN PLUS.

Eprosartan alone 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 fetal 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 on the infant, women should not breastfeed while taking TEVETEN PLUS. Eprosartan is excreted in the milk of lactating rats, however there is no information on excretion of the drug in human breast milk. Hydrochlorothiazide is excreted in human breast milk.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Based on its pharmacodynamic properties, TEVETEN PLUS is unlikely to affect the ability to drive or operate machinery. However, it should be taken into account that occasionally dizziness or asthenia may occur during treatment of hypertension.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Eprosartan in combination with hydrochlorothiazide at doses equal to or greater than those provided by TEVETEN PLUS has been evaluated for safety in more than 1600 subjects worldwide, including more than 500 patients treated for 1 year or longer. The incidence of adverse events was unrelated to age, gender or race. Most adverse events were generally mild to moderate in severity and transient by nature and similar to those seen with the individual components taken separately.

In controlled clinical trials involving 782 patients (8 weeks duration), withdrawals due to treatment related adverse events were, 2.6% for eprosartan/hydrochlorothiazide, 2.5% for placebo, 1.8% for eprosartan and 5.1% for hydrochlorothiazide

Table 1 lists adverse events that occurred at an incidence of 1% or more among eprosartan + hydrochlorothiazide (HCTZ)-treated patients who participated in a placebo-controlled trial of 8 weeks' duration, using doses of 600/12.5 mg once-daily.

Table 1: Adverse Events Reported by ≥ 1% of Patients Receiving TEVETEN PLUS in a Placebo-Controlled Clinical Study

	Frequency (% of patients)			
Event	**Eprosartan + HCTZ (n=116)**	**Eprosartan (n=118)**	**HCTZ (n=117)**	**Placebo (n=122)**
Body as a Whole				
Fatigue	2.6	1.7	0.9	0.8
Insomnia	1.7	0.8	1.7	0.0
Oedema dependent	2.8	1.8	0.0	0.9
Cardiovascular				
Palpitations	1.7	0.8	1.7	2.5
Heart disorder	2.6	0.8	0.0	0.8
Musculoskeletal				
Back pain	2.6	5.1	1.7	3.3
Arthrosis	1.7	0.8	0.0	0.8
Arthralgia	1.7	0.0	0.0	0.8
Nervous System				
Headache	5.1	11.0	9.4	10.6
Dizziness	5.2	3.4	1.7	1.6
Neuralgia	2.6	1.7	0.0	1.6
Paraesthesia	1.7	1.7	0.0	0.8
Nervousness	1.7	0.8	0.0	1.6
Respiratory				
Bronchitis	2.6	2.5	2.6	0.0
Respiratory disorder	1.7	0.0	1.7	1.6
Rhinitis	1.7	0.0	0.0	0.0

Urogenital				
Albuminuria	3.4	1.7	1.7	1.6
Pyuria	2.6	2.5	1.7	0.8
Haematuria	1.7	2.5	1.7	0.8

Adverse events that occurred in more than two (2) hypertensive patients when taking TEVETEN PLUS during controlled and uncontrolled clinical trials and that were not reported in Table 1 are listed below. Events are listed within body systems and categorised by frequency according to the following definitions:

- *Common (frequency ≥1% and <10%)*
- *Uncommon (frequency ≥ 0.1% and < 1%)*
- *Rare (frequency ≥ 0.01% and < 0.1%)*

Table 2

Body as a Whole	Common: asthenia, injury, pain Uncommon: fever, syncope, allergy
Cardiovascular	Uncommon: hypotension
Nervous System	Uncommon: hypaesthesia, vertigo
Gastrointestinal	Common: abdominal pain, diarrhoea, nausea, gastroenteritis Uncommon: dyspepsia
Liver and Biliary System	Uncommon: SGPT increased
Metabolic and Nutritional	Common: hyperglycaemia, hypokalaemia
Muscular System	Uncommon: bursitis, myalgia
Psychiatric	Uncommon: anxiety, depression, insomnia
Respiratory	Uncommon: coughing, dyspnoea, epistaxis, pharyngitis, sinusitis, upper respiratory tract infection
Skin and Appendages	Uncommon: rash
Urinary System	Common: urinary tract infection, cystitis

Eprosartan monotherapy: Adverse events with eprosartan have usually been mild and transient in nature and have only required discontinuation of therapy in 4.1% of patients in placebo-controlled studies (6.5% for placebo). The adverse events reported are similar to those reported for the combination product.

Post-marketing Reports

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

As with other angiotensin II receptor antagonists, very rare cases of facial swelling and/or angioedema have been reported. Reports of hypotension, including orthostatic hypotension have been uncommon. Rare cases of skin reactions (rash, pruritus, urticaria) have been reported. Headache, dizziness, asthenia, anxiety, insomnia, nervousness, paraesthesia, somnolence and vertigo have been reported rarely.

The following adverse events have been reported spontaneously during post-marketing use of eprosartan.

Table 3

Renal and Urinary disorders	Impaired renal function including renal failure in patients at risk (e.g. renal artery stenosis)
Musculoskeletal and Connective Tissue Disorders	Arthralgia

Hydrochlorothiazide Monotherapy

The following reactions have been reported in addition to those reported for the combination therapy:

Table 4

Gastrointestinal Disorders	Anorexia, stomach discomfort, vomiting, cramps, constipation[2], pancreatitis, sialoadenitis
Immune System Disorders	Anaphylactic reactions
Nervous System Disorders	Restlessness, xanthopsia
Vascular Disorders	Orthostatic hypotension, vasculitis
Blood and Lymphatic System Disorders	Leukopenia, agranulocytosis, thrombocytopenia, aplastic anaemia, haemolytic anaemia
Metabolism and Nutrition Disorders	hyperuricaemia, gout, hyponatraemia, hypochloraemia, hypercalcaemia, hypomagnesaemia, hypercholesterolaemia, hypertriglyceridaemia
Psychiatric Disorders	Libido disorder
Hepatobiliary Disorders	Jaundice (intrahepatic cholestatic jaundice),
Renal and Urinary Disorders	Renal impairment, interstitial nephritis, renal failure
Respiratory, Thoracic and Mediastinal Disorders	Pneumonitis, pulmonary oedema, acute respiratory distress syndrome (ARDS)
Musculoskeletal and Connective Tissue Disorders	Systemic lupus erythematosus, muscle spasms
Skin and Subcutaneous Tissue Disorders	Photosensitivity reaction, toxic epidermal necrolysis, purpura, urticaria
Reproductive System and Breast Disorders	Sexual dysfunction
General Disorders and Administration Site Conditions	Asthenia, pyrexia
Eye Disorders	Choroidal effusion, acute myopia and secondary angle-closure glaucoma

The following adverse events have been reported spontaneously during post-marketing use of eprosartan + hydrochlorothiazide.

Table 5

Psychiatric Disorders	Depression, anxiety, insomnia, nervousness, restlessness

Skin and Subcutaneous Tissue Disorders	Photosensitivity reaction, toxic epidermal necrolysis, purpura, cutaneous lupus, erythematosus

Neoplasms Benign, Malignant and Unspecified (including cysts and polyps)

Frequency 'not known': non-melanoma skin cancer (Basal cell carcinoma and Squamous cell carcinoma)

Based on available data from epidemiological studies, cumulative dose-dependent association between HCTZ and NMSC has been observed (see Sections 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and 5.1 PHARMACODYNAMIC PROPERTIES – MECHANISM OF ACTION, HYDROCHLOROTHIAZIDE).

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 http://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Limited data is available in regard to overdose in humans. Overdose may be expected to cause hypotension, dehydration and electrolyte abnormalities (including hypo or hyperkalaemia, hypochloraemia and hyponatraemia). These may be associated with cardiac arrhythmias, somnolence or nausea.

Treatment should be symptomatic and supportive. If hypotensive, the patient should be placed in a supine position. Electrolyte and volume replacements should be given as required and the patient should be monitored for electrolyte disturbances and cardiac arrhythmias. Activated charcoal may be administered.

Eprosartan is not removed by haemodialysis. The degree to which hydrochlorothiazide is removed by haemodialysis has not been established.

For information on the management of overdose, contact the Poison Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

Eprosartan

Eprosartan is a potent angiotensin II receptor antagonist, which selectively binds to the AT1 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 AT1 receptors in many tissues (e.g. vascular smooth muscle, kidney adrenal glands and heart) and produces biological effects such as vasoconstriction, sodium retention and release of aldosterone. In addition, in animals, eprosartan has been shown to block the direct vasoconstrictor response to angiotensin as well as the indirect effects mediated by enhanced neurotransmission, indicating the potential to antagonise overactivity of the sympathetic nervous system.

Eprosartan blocks the binding of angiotensin II to the AT1 receptors, which prevents vasoconstriction, thus lowering blood pressure and aldosterone secretion.

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 does not significantly affect urinary uric acid excretion and does not potentiate effects related to bradykinin e.g. Angiotensin Converting Enzyme (ACE) mediated cough.

Hydrochlorothiazide

Hydrochlorothiazide is a thiazide with diuretic, natriuretic and antihypertensive effects. Thiazides affect the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of fluid, sodium and chloride in approximately equivalent amounts.

The diuretic action of hydrochlorothiazide reduces plasma volume, increases plasma renin activity, increases aldosterone secretion, with consequent increases in urinary potassium and bicarbonate loss, and decreases in serum potassium.

The antihypertensive action of hydrochlorothiazide appears to be due to a combined diuretic effect and reduction of vascular resistance.

Clinical Trials

The efficacy and safety of eprosartan plus hydrochlorothiazide have been studied in patients with mild to moderate hypertension.

In a 2x2 factorial study with 116 – 122 hypertensive patients per arm, reductions in systolic and diastolic blood pressure were significantly greater with once-daily eprosartan plus hydrochlorothiazide than with the individual components. The mean placebo subtracted reduction in systolic/diastolic blood pressure after 8 weeks was 3.5/1.8 mmHg on eprosartan 600 mg, 5.5/1.5 mmHg on hydrochlorothiazide and 9.3/4.5 mmHg on the combination eprosartan plus hydrochlorothiazide.

In a second study, patients with an inadequate response to 3 weeks of eprosartan 600 mg once daily were randomised to eprosartan 600 mg once daily plus placebo or eprosartan 600 mg plus hydrochlorothiazide 12.5 mg once daily. After a further 8 weeks, the mean post-randomization systolic/diastolic blood pressure reduction was 5.8/7.9 mmHg on eprosartan 600 mg plus placebo and 9.2/10.7 mmHg on eprosartan 600 mg plus hydrochlorothiazide 12.5 mg (i.e. 3.4/2.8 mmHg more with the combination; $p < 0.05$). Diastolic blood pressure was normalised (≤ 90 mmHg) in 49% of patients who continued eprosartan 600 mg once daily, compared with 59% of patients switched to eprosartan 600 mg plus hydrochlorothiazide 12.5 mg. Diastolic blood pressure responded (was normalised or reduced by ≥10 mmHg from baseline) in 57% of patients who continued eprosartan 600 mg once daily, compared with 79% of patients who switched to eprosartan 600 mg plus hydrochlorothiazide 12.5 mg.

No specific data is available on use of TEVETEN PLUS in patients with severe hypertension. However, a study using Teveten monotherapy evaluated the efficacy of eprosartan and enalapril in patients with severe systolic hypertension. The reduction of 25.7 mmHg in sitting systolic blood pressure produced by eprosartan once-daily (in titrated doses of 600, 800, 1200 mg, hydrochlorothiazide 25 mg could be added further) was comparable to enalapril once-daily (in titrated doses of 10, 20, 40 mg, hydrochlorothiazide 25 mg could be added further). The percentage of patients receiving hydrochlorothiazide either as study medication or as concomitant medication continued from screening was similar between the two treatment groups.

In long-term open-label studies, the antihypertensive effect of eprosartan/ hydrochlorothiazide was maintained for 24 months. The long-term effects of eprosartan plus hydrochlorothiazide on mortality and cardiovascular morbidity have not been studied.

Non-melanoma skin cancer: based on available data from epidemiological studies, cumulative dose-dependent association between HCTZ and NMSC has been observed.

One study included a population comprised of 71,553 cases of BCC and of 8,629 cases of SCC matched to 1,430,883 and 172,462 population controls, respectively. High HCTZ use (≥50,000 mg cumulative) was associated with an adjusted OR of 1.29 (95% CI: 1.23 - 1.35) for BCC and 3.98 (95% CI: 3.68 - 4.31) for SCC. A clear cumulative dose response relationship was observed for both BCC and SCC.

Another study showed a possible association between lip cancer (SCC) and exposure to HCTZ: 633 cases of lip-cancer were matched with 63,067 population controls, using a risk-set sampling strategy. A cumulative dose-response relationship was demonstrated with an adjusted OR 2.1 (95% CI: 1.7-2.6) increasing to OR 3.9 (3.0-4.9) for high use (~25,000 mg) and OR 7.7 (5.7-10.5) for the highest cumulative dose (~100,000 mg) (see Sections 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

5.2 PHARMACOKINETIC PROPERTIES

Absorption

The absolute bioavailability of eprosartan has been shown to be approximately 13% when administered alone. The bioavailability of eprosartan was increased by approximately 20% when administered with hydrochlorothiazide. This increase is not considered to be of clinical consequence. The absolute bioavailability of hydrochlorothiazide is reported to be 50–80% when administered alone. When administered concurrently with eprosartan, the bioavailability decreased by approximately 20%. This decrease is not considered to be of clinical consequence. Peak plasma concentrations of eprosartan and hydrochlorothiazide occurred 0.5–4 hours and 1–4 hours, respectively, after a fasting oral dose when administered in combination. Administration of eprosartan plus hydrochlorothiazide with food does not alter the bioavailability of the hydrochlorothiazide component. Food decreases the rate of absorption of the eprosartan component, leading to a 40% decrease in the peak plasma concentration of eprosartan. The extent of absorption of the eprosartan component is reduced by approximately 10%. These changes are unlikely to be clinically significant.

Distribution

Eprosartan is highly bound to plasma proteins (approximately 98%). 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. Hydrochlorothiazide is approximately 68% bound to plasma proteins. The volume of distribution of hydrochlorothiazide is 0.83 to 1.41 L/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. Hydrochlorothiazide is not metabolised.

Excretion

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. Hydrochlorothiazide is eliminated rapidly via the kidneys.

Special Populations

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

In the elderly, eprosartan AUC and Cmax values (on average) increased approximately 2-fold, compared with young subjects.

In patients with hepatic impairment, AUC (but not Cmax) values of eprosartan are on average increased approximately 40%.

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

The combination of eprosartan and hydrochlorothiazide (600 mg/12.5 mg) did not induce gene mutations (in vitro in bacterial cells). The combination caused chromosomal aberrations when tested in vitro (human lymphocytes) but was negative in an in vivo assay (mouse micronucleus assay).

Eprosartan was not genotoxic in a series of assays for gene mutations and chromosomal damage. Hydrochlorothiazide was not genotoxic in a gene mutation assay in bacterial cells, or in tests for clastogenic activity in vitro and in vivo. However, positive results were obtained in a mammalian cell assay for gene mutation (mouse lymphoma cell assay) and in two other tests (sister chromatid exchange assay in Chinese hamster ovary cells and non-disjunction assay in Aspergillus nidulans).

Carcinogenicity

The carcinogenic potential of eprosartan and hydrochlorothiazide in combination has not been investigated in animal studies. Studies to investigate the carcinogenic potential of eprosartan indicated no carcinogenicity 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.

Two year feeding studies in mice and rats with hydrochlorothiazide uncovered no evidence of carcinogenic potential in female mice at doses up to approximately 600 mg/kg/day, or in male and female rats at doses up to approximately 100 mg/kg/day. The studies, however, uncovered equivocal evidence for hepatocarcinogenecity in male mice treated with hydrochlorothiazide at approximately 600 mg/kg/day.

6 PHARMACEUTICAL PROPERTIES

6.1 LIST OF EXCIPIENTS

The tablets contain the following excipients: microcrystalline cellulose, lactose monohydrate, pregelatinised maize starch, crospovidone, magnesium stearate and OPADRY II complete film coating system 85F27320 Butterscotch (ARTG PI No: 12291).

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 PLUS tablets should be stored at or below 25˚C.

6.5 NATURE AND CONTENTS OF CONTAINER

Available in PVC/PCTFE (Aclar)/Aluminium blister packs of 7, 14, 28 or 56 tablets per carton.

Some strengths, pack sizes and/or pack types may not be marketed.

Australian Register of Therapeutic Goods (ARTG)

AUST R 143172 – TEVETEN PLUS 600/12.5 eprosartan 600mg/hydrochlorothiazide 12.5mg tablet blister pack

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

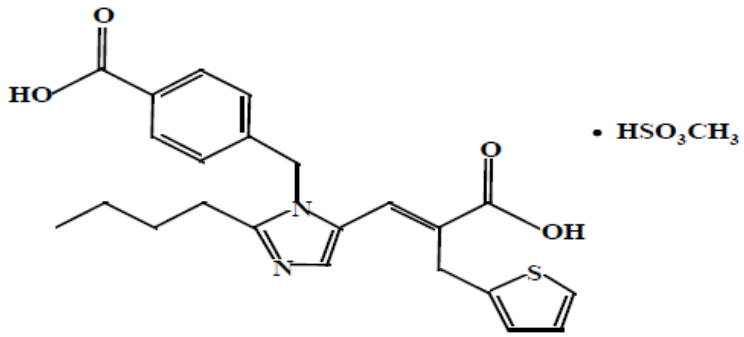
6.7 PHYSIOCHEMICAL PROPERTIES

Chemical Structure

Eprosartan mesilate

Chemical name: (E)-α-[[2-butyl-1-[(4-carboxyphenyl) methyl]-1H-imidazol-5-yl] methylene]-2-thiophenepropanoic acid, monomethanesulphonate.

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

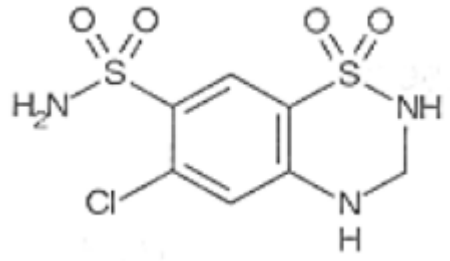


Eprosartan mesilate is a white to off-white powder with a melting point range of 248°C to 250°C and at room temperature has a solubility of 0.91 mg/mL in water at a pH of 7.

Hydrochlorothiazide

Chemical name: 6-chloro-3, 4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-di-oxide.

Hydrochlorothiazide has a molecular weight (MW) of 297.73 and maybe represented structurally as:



$C_7H_8ClN_3O_4S_2$

Hydrochlorothiazide is a white to off white crystalline powder. It is slightly soluble in water, soluble in acetone and freely soluble in alkali hydroxides.

CAS Number

Eprosartan mesilate: 144143-96-4

Hydrochlorothiazide: 58-93-5

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

Viatris Pty Ltd

Level 1, 30 The Bond

30-34 Hickson Road

Millers Point NSW 2000

www.viatris.com.au

Phone: 1800 274 276

9 DATE OF FIRST APPROVAL

28/03/2002

10 DATE OF REVISION

03/06/2022

Summary Table of Changes

Section Changed	Summary of New Information
4.4	Added Acute Respiratory Toxicity
4.8	Added acute respiratory distress syndrome (ARDS) in Table 4.

TEVETEN® PLUS is a Viatris company trade mark

TEVETEN PLUS_pi\Jun22/01 (CCDS 06-Dec-2021)