SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Teveten 600mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains eprosartan mesilate equivalent to 600 mg eprosartan.

Excipient with known effect:
Each film-coated tablet contains 43.3 mg lactose (as lactose monohydrate).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablets.

Capsule-shaped, biconvex, white film-coated tablet with the inscription ‘5046’.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Eprosartan is indicated for the treatment of essential hypertension

4.2 Posology and method of administration

The recommended dose is 600 mg eprosartan once daily.

Achievement of maximal blood pressure reduction in most patients may take 2 to 3 weeks of treatment.

Eprosartan may be used alone or in combination with other anti-hypertensives (see sections 4.3,4.4,4.5 and 5.1). In particular, addition of a thiazide-type diuretic such as hydrochlorothiazide or a calcium channel blocker such as sustained release nifedipine has been shown to have an additive effect with eprosartan.

Eprosartan may be taken with or without food.

Geriatric patients

No dose adjustment is required in the elderly.

Dosage in Hepatically Impaired Patients:
There is limited experience in patients with hepatic insufficiency (see section 4.3).

Dosage in Renally Impaired Patients:
In patients with moderate or severe renal impairment (creatinine clearance <60 ml/min), the daily dose should not exceed 600 mg.

Paediatric patients
Teveten is not recommended for use in children and adolescents due to lack of data on safety and efficacy

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.
Second and third trimester of pregnancy (see sections 4.4 and 4.6).
Severe hepatic impairment.
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 < 60 ml/min/1.73 m^2) (see sections 4.5 and 5.1)

4.4 Special warnings and precautions for use

Hepatic impairment
When Eprosartan is used in patients with mild to moderate hepatic impairment, special care should be exercised due to the fact that there is limited experience in this patient population

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

Patients at risk of renal impairment
Some patients whose renal function is dependent on the continued inherent activity of the renin-angiotensin-aldosterone system (e.g., patients with severe cardiac insufficiency [NYHA-classification: class IV], bilateral renal artery stenosis, or renal artery stenosis of a solitary kidney), have risks of developing oliguria and/or progressive azotaemia and rarely acute renal failure during therapy with an angiotensin converting enzyme (ACE) inhibitor. These events are more likely to occur in patients treated concomitantly with a diuretic. Angiotensin II receptor blockers such as eprosartan have not had adequate

therapeutic experience to determine if there is a similar risk of developing renal function compromise in these susceptible patients. When eprosartan is to be used in patients with renal impairment, renal function should be assessed before starting treatment with eprosartan and at intervals during the course of therapy. If worsening of renal function is observed during therapy, treatment with eprosartan should be reassessed.
The following precautions have been included based on experience with other agents in this class and also ACE inhibitors:

Hypotension
Symptomatic hypotension may occur in patients with severe sodium depletion and/or volume depletion (e.g. high dose diuretic therapy). These conditions should be corrected before commencing therapy.

Coronary Heart Disease
There is limited experience in patients with coronary heart disease.

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.

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 4.5 and 5.1).

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.

Primary hyperaldosteronism
Patients with primary hyperaldosteronism are not recommended to be treated with eprosartan.

Renal Transplantation
There is no experience in patients with recent kidney transplantation.

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 potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium or

other medicinal products which may increase the potassium level (e.g. heparin, trimethoprim containing medicines) may lead to an increase in serum potassium and should therefore be co-administered cautiously with Teveten.

Intestinal angioedema
Intestinal angioedema has been reported in patients treated with angiotensin II receptor antagonists (see section 4.8). These patients presented with abdominal pain, nausea, vomiting and diarrhoea. Symptoms resolved after discontinuation of angiotensin II receptor antagonists. If intestinal angioedema is diagnosed, eprosartan should be discontinued and appropriate monitoring should be initiated until complete resolution of symptoms has occurred.

Pregnancy
Angiotensin II receptor blockers should not be initiated during pregnancy. Unless continued angiotensin II receptor blocker 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 angiotensin II receptor blockers should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

Other warnings and precautions
As observed for angiotensin converting enzyme inhibitors, eprosartan and the other angiotensin II receptor blockers are apparently less effective in lowering blood pressure in black people than in non-blacks, possibly because of higher prevalence of low-renin states in the black hypertensive population.
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Since in placebo-controlled clinical studies significantly 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, trimethoprim containing medicines) may lead to increase in serum potassium.

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 a 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 (see sections 4.3, 4.4 and 5.1).

The antihypertensive effect may be potentiated by other antihypertensives.
Toxicity and a reversible increase in serum lithium concentrations have been reported during concomitant administration of lithium with ACE inhibitors. The possibility of

a similar effect cannot be excluded and careful monitoring of serum lithium levels is recommended during concomitant use.

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

As with ACE inhibitors, concomitant use of Angiotensin II receptor blockers and NSAIDs may lead to an increased risk of worsening of renal function, including possible acute renal failure, and an increase in serum potassium, especially in patients with poor pre-existing renal function. The combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy, and periodically thereafter.

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 Pregnancy and lactation

Pregnancy

The use of angiotensin II receptor blockers is not recommended during the first trimester of pregnancy (see section 4.4). The use of angiotensin II receptor blockers is contraindicated during second and third trimester of pregnancy (see sections 4.3 and 4.4).

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however, a small increase in risk cannot be excluded. Whilst there is no controlled epidemiological data on the risk with angiotensin II receptor blockers, similar risks may exist for this class of drugs. Unless continued angiotensin II receptor blockers 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 angiotensin II receptor blockers should be stopped immediately and, if appropriate, alternative therapy should be started.

Exposure to angiotensin II receptor blockers therapy during the second and third trimesters is known to induce human foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (see section 5.3).

Should exposure to angiotensin II receptor blockers have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.

Infants whose mothers have taken angiotensin II receptor blockers should be closely observed for hypotension (see sections 4.3 and 4.4).

Lactation

Because no information is available regarding the use of Teveten during breast-feeding, Teveten is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

4.7 Effects on ability to drive and use machines

The effect of eprosartan on the ability to drive and use machines has not been studied, but based on its pharmacodynamic properties, eprosartan is unlikely to affect this ability. When driving vehicles or operating machines, it should be taken into account, that occasionally dizziness or weariness may occur during treatment of hypertension.

4.8 Undesirable effects

Clinical Trials

The most commonly reported adverse drug reactions of patients treated with eprosartan are headache and unspecific gastrointestinal complaints, occurring in approximately 11% and 8%, respectively, of patients.

ADVERSE EVENTS REPORTED DURING CLINICAL TRIALS IN PATIENTS TREATED WITH EPROSARTAN (n = 2316)

MedDRA system organ class	**Very common ≥1/10**	**Common ≥1/100 to <1/10**	**Uncommon ≥1/1,000 to < 1/100**
Immune system disorders			Hypersensitivity*
Nervous system disorders	Headache*	Dizziness*	
Vascular disorders			Hypotension
Respiratory, thoracic and mediastinal disorders		Rhinitis	
Gastrointestinal disorders		Unspecific gastrointestinal complaints (e.g., nausea, diarrhoea, vomiting)	
Skin and subcutaneous tissue disorders		Allergic skin reactions (e.g. rash, pruritus)	Angioedema*
General disorders and administration site reactions		Asthenia	

(*)Did not occur in a higher frequency than in placebo

Postmarketing experience

In addition to those adverse events reported during clinical trials, the following side effects have been reported spontaneously during postmarketing use of eprosartan. A frequency cannot be estimated from the available data (not known).

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

Gastrointestinal disorders

Cases of intestinal angioedema have been reported after the use of angiotensin II receptor antagonists (see section 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation 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 via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Limited data are available with regard to overdosage in humans. Eprosartan was well tolerated after oral dosing with no mortality in rats and mice up to 3000 mg/kg and in dogs up to 1000 mg/kg.

In humans, there have been individual reports from postmarketing experience where doses up to 12,000 mg had been ingested. Most patients reported no symptoms. In one subject circulatory collapse occurred after ingestion of 12,000 mg eprosartan. The subject recovered completely.

The most likely manifestation of overdosage would be hypotension. If symptomatic hypotension occurs, supportive treatment should be instituted.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Angiotensin II antagonists, ATC code: C09CA02

Eprosartan is a potent, synthetic, orally active non-biphenyl non-tetrazole angiotensin II receptor blocker, which binds selectively 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 the AT_1 receptor in many tissues (e.g. smooth vascular musculature, suprarenals, kidney, heart) and produces important biological effects such as vasoconstriction, sodium retention and release of aldosterone. Angiotensin II has been implicated in the genesis of cardiac and vascular hypertrophy through its effect on cardiac and smooth muscle cell growth.
Eprosartan antagonised the effect of angiotensin II on blood pressure, renal blood flow and aldosterone secretion in normal volunteers. In hypertensive patients, comparable blood pressure control is achieved when eprosartan is administered as a single dose or in two divided doses. In placebo-controlled studies, in 299 patients treated receiving 600-800 mg once daily, there was no evidence of first dose postural hypotension. Discontinuation of treatment with eprosartan does not lead to a rapid rebound increase in blood pressure.
Eprosartan was evaluated in mild to moderate hypertensive patients (sitting DBP ≥95 mmHg and <115 mmHg) and severe hypertensive patients (sitting DBP ≥115 mmHg and ≤125 mmHg).
A dose of 1200 mg once daily, for 8 weeks, has been shown in 72 patients in clinical trials to be effective. In placebo-controlled studies using doses up to 1200 mg once daily, there is no apparent dose relationship in the incidence of adverse experiences reported.

In patients with hypertension, blood pressure reduction did 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. Effective renal plasma flow is not altered in patients with essential hypertension and patients with renal insufficiency treated with eprosartan. 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 the excretion of urinary uric acid.
Eprosartan does not potentiate effects relating to bradykinin (ACE-mediated), e.g. cough. In a study specifically designed to compare the incidence of cough in patients treated with eprosartan and an angiotensin converting enzyme inhibitor, the incidence of dry persistent cough in patients treated with eprosartan (1.5%) was significantly lower ($p<0.05$) than that observed in patients treated with an angiotensin converting enzyme inhibitor (5.4%). In a further study investigating the incidence of cough in patients who had previously coughed while taking an angiotensin converting enzyme inhibitor, the incidence of dry, persistent cough was 2.6% on eprosartan, 2.7% on placebo, and 25.0% on an angiotensin converting enzyme inhibitor ($p<0.01$, eprosartan versus angiotensin converting enzyme inhibitor).

Two large randomised, controlled trials (ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) and VA NEPHRON-D (The Veterans Affairs Nephropathy in Diabetes)) have examined the use of the combination of an ACE-inhibitor with an angiotensin II receptor blocker.

ONTARGET was a study conducted in patients with a history of cardiovascular or cerebrovascular disease, or type 2 diabetes mellitus accompanied by evidence of end-organ damage. VA NEPHROND was a study in patients with type 2 diabetes mellitus and diabetic nephropathy. These studies have shown no significant beneficial effect on renal and/or cardiovascular outcomes and mortality, while an increased risk of hyperkalaemia, acute kidney injury and/or hypotension as compared to monotherapy was observed. Given their similar pharmacodynamic properties, these
results are also relevant for other ACE- inhibitors and angiotensin II receptor blockers. ACE-inhibitors and angiotensin II receptor blockers should therefore not be used concomitantly in patients with diabetic nephropathy.

ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints) was a study designed to test the benefit of adding aliskiren to a standard therapy of an ACE-inhibitor or an angiotensin II receptor blocker in patients with type 2 diabetes mellitus and chronic kidney disease, cardiovascular disease, or both. The study was terminated early because of an increased risk of adverse outcomes. Cardiovascular death and stroke were both numerically more frequent in the aliskiren group than in the placebo group and adverse events and serious
adverse events of interest (hyperkalaemia, hypotension and renal dysfunction) were more frequently reported in the aliskiren group than in the placebo group.

5.2 Pharmacokinetic properties

Absolute bioavailability following a single 300mg oral dose of eprosartan is about 13%, due to limited oral absorption. Eprosartan plasma concentrations peak at one to two hours after an oral dose in the fasted state. Plasma concentrations are dose proportional from 100 to 200mg, but less than proportional for 400 and 800mg doses. The terminal elimination half-life of eprosartan following oral administration is typically five to nine hours. A slight accumulation (14%) is seen with chronic use of eprosartan. Administration of eprosartan with food delays absorption with minor increases (<25%) observed in C_{max} and AUC.

Plasma protein binding of eprosartan is high (approximately 98%) and constant over the concentration range achieved with therapeutic doses. The extent of plasma protein binding is not influenced by gender, age, hepatic dysfunction or mild-moderate renal impairment but has shown to be decreased in a small number of patients with severe renal impairment.

Following oral and intravenous dosing with [14C]eprosartan in human subjects, eprosartan was the only drug-related compound found in the plasma and faeces. In the urine, approximately 20% of the radioactivity excreted was an acyl glucuronide of eprosartan with the remaining 80% being unchanged eprosartan.

The volume of distribution of eprosartan is about 13 litres. Total plasma clearance is about 130ml/min. Biliary and renal excretion contribute to the elimination of eprosartan. Following intravenous [14C]eprosartan, about 61% of radioactivity is recovered in the faeces and about 37% in the urine. Following an oral dose of [14C] eprosartan, about 90% of radioactivity is recovered in the faeces and about 7% in the urine.

Both AUC and C_{max} values of eprosartan are increased in the elderly (on average, approximately two-fold).

Following administration of a single 100mg dose of eprosartan, AUC values of eprosartan (but not C_{max}) are increased, on average, approximately 40% in patients with hepatic impairment. Since an intravenous dose of eprosartan was not administered to patients with hepatic impairment, the plasma clearance of eprosartan could not be measured.

Compared to subjects with normal renal function (n=7), mean AUC and C_{max} values were approximately 30% higher in patients with creatinine clearance 30-59ml/min (n=11) and approximately 50% higher in patients with creatinine clearance 5-29ml/min (n=3). In a separate investigation, mean AUC was approximately 60% higher in patients undergoing dialysis (n=9) compared to subjects with normal renal function (n=10).

There is no difference in the pharmacokinetics of eprosartan between males and females.

5.3 Preclinical safety data

General toxicology

Eprosartan given orally at dosages up to 1000 mg/kg per day for up to six months in rats and up to one year in dogs did not result in any significant drug-related toxicity.

Reproductive and developmental toxicity

In pregnant rabbits, eprosartan has been shown to produce maternal and foetal mortality at 10 mg/kg per day during late pregnancy only. Maternal toxicity but no foetal effects were observed at 3 mg/kg per day.

Genotoxicity

Genotoxicity was not observed in a battery of *in vitro* and *in vivo* tests.

Carcinogenicity

Carcinogenicity was not observed in rats and mice given up to 600 or 2000 mg/kg per day respectively for two years.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet cores

Lactose
Microcrystalline cellulose
Pregelatinised starch
Magnesium stearate
Crospovidone

Film coat

6.2 Incompatibilities

None known

6.3 Shelf life

36 months

6.4 Special precautions for storage

Do not store above 25°C

Keep container in the outer carton

6.5 Nature and contents of container

White PVC/PCTFE/Alu blister packs or,

White PVC/PVDC/Alu blister packs containing 28 tablets or 56 tablets

6.6 Special precautions for disposal

No special instructions

7 MARKETING AUTHORISATION HOLDER

Viatris Products Limited,
Station Close,
Potters Bar,
EN6 1TL,
United Kingdom.

8 MARKETING AUTHORISATION NUMBER(S)

PL 46302/0051

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

05/06/2009

10 DATE OF REVISION OF THE TEXT

29/09/2025