Abbott

Read this entire leaflet carefully before you start taking this medicine.
Keep this leaflet. You may need to read it again. If you have questions not answered by this pamphlet, please ask your doctor or pharmacist. This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

Teveten 600 mg tablets are capsule-shaped, white, film-coated tablets for oral administration marked "5046" on one side and "SOLVAY" on the other side. Each tablet contains 600 mg eprosartan mesylate.

Excipients (non-medicinal ingredients):
Tablet Core
Lactose monohydrate, microcrystalline cellulose, pregelatinised starch, crospovidone, magnesium stearate, purified water

Tablet Coating
Hypromellose (E464), macrogol 400, polysorbate 80 (E433), titanium dioxide (E171)

Indications
Teveten is indicated for the treatment of essential hypertension.

Dosage and administration
Always take Teveten exactly as your doctor has prescribed. If you have any questions, you should check with your doctor or pharmacist.

If you forget to take your tablet(s), do not take a double dose to compensate for it. If you require further information, please ask your doctor or pharmacist for advice.

The recommended dose is 600 mg of eprosartan once daily and it is best to take your medicine in the morning. However, your doctor will decide the dose and frequency that is right for you.

It may take 2–3 weeks for the best results (best blood pressure lowering effect) to be achieved.

Doses up to 1200 mg per day, for 8 weeks, have been shown in clinical trials to be effective with no increase in the frequency of adverse reactions.

Teveten may be used alone or in combination with other anti-hypertensives. The use of thiazide-type diuretics is especially recommended in combination with Teveten. Furthermore, a combination of Teveten with calcium channel blockers has been shown to be likewise effective if a greater blood pressure lowering effect is required.

Teveten may be taken with or without food.

The duration of treatment is not limited.

Geriatric Patients
No dose adjustment is required in the elderly.

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

Dosage in Hepatically Impaired Patients
No dose adjustment is required in patients with hepatic (liver) impairment.

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

Contraindications
Do not take Teveten if any of the following applies to you:
- you are allergic (hypersensitive) to the active substance (eprosartan mesylate) or to any of the excipients (see above section "Excipients")
- you are in your second or third trimester of pregnancy
- you have severe kidney disease (specifically hemodynamically significant bilateral renovascular disease or severe stenosis of a solitary functioning kidney).

Warnings and special precautions for use
Pregnancy
Treatment with Teveten should not be started during pregnancy. If you are planning to become pregnant or if you become pregnant while on Teveten, talk to your doctor as soon as possible. He will decide if and when to stop the treatment and which alternative therapy is best for you (see sections "Contraindications" and "Pregnancy and Lactation").

Patients at risk of renal impairment
Information for the doctor:
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. There has not been adequate experience with angiotensin II receptor blockers, such as eprosartan, 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 Teveten and at intervals during the course of therapy. If worsening of renal function is observed during therapy, treatment with Teveten should be reassessed.

Information for patient:
If you suffer from renal impairment and your doctor has prescribed Teveten to you, he will check your renal function before you start the therapy. Kidney function tests should be repeated at intervals during the course of therapy. If a deterioration in your renal function is observed your doctor will reassess the treatment plan.

Hypotension
Symptomatic hypotension (low blood pressure) may occur in patients with severe volume and/or salt depletion (e.g. those on high dose diuretic therapy). These conditions should be corrected prior to commencing therapy.

Other conditions
If you have been diagnosed with galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption (which are rare hereditary problems) you should not take this medicine.

Interactions with other medications
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines including medicines obtained without a prescription.

No clinically significant drug interactions have been observed. No effect on the pharmacokinetics of digoxin (a medicine used to treat congestive heart failure) and the pharmacodynamics of warfarin (an anti-coagulant/blood thinner) or glyburide (glibenclamide) (a medicine used to treat type II diabetes) has been shown with eprosartan. Similarly no effect on eprosartan pharmacokinetics has been shown with ranitidine (a medicine used to treat dyspepsia), ketoconazole or fluconazole (anti-fungals).

Eprosartan has been safely used concomitantly with thiazide diuretics (e.g. hydrochlorothiazide) (this class of drug is used to treat high blood pressure and congestive heart failure) and calcium channel blockers (e.g. sustained-release nifedipine) (calcium channel blockers are used to treat high blood pressure and/or some types of heart disease) without evidence of clinically significant adverse interactions. It has been safely co-administered with hypolipidaemic agents (e.g.: lovastatin, simvastatin, pravastatin, fenofibrate, gemfibrozil and niacin) (these drugs are used to treat people with high cholesterol levels).

Reversible increases in serum lithium concentrations and toxicity have been reported when lithium and ACE inhibitors were taken together. The possibility of a similar effect with the use of eprosartan can not be excluded. Your doctor will carefully monitor your serum lithium levels if you take these kinds of medicines concomitantly.

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

Pregnancy and lactation
Information for patient:
Pregnancy
Ask your doctor or pharmacist for advice before taking any medicine during pregnancy.

It is strongly recommended not to take Teveten during the first trimester (first three months) of pregnancy (see also section "Warnings and special precautions for use"). Furthermore, you must not take Teveten during the second or third trimesters of pregnancy (from the fourth month on), as Teveten is strictly contraindicated during these times (see sections "Contraindications" and "Warnings and special precautions for use"). ***Do not take Teveten if you are pregnant.***

Lactation
There is no information available on the use of Teveten during breast feeding.
Therefore, the safety of this product in breastfeeding women is not known. The use of Teveten during this time is not recommended. Your doctor will switch you to an alternative treatment with better established safety profiles, especially if you are nursing a newborn or preterm infant.
Do not take Teveten if you are breast feeding.

Information for the doctor:
Pregnancy
The use of Teveten is not recommended during the first trimester of pregnancy (see section "Warnings and special precautions for use"). The use of eprosartan is contraindicated during second and third trimester of pregnancy (see sections "Contraindications" and "Warnings and special precautions for use").

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. While 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 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.
Angiotensin II receptor blocker therapy exposure during the second and third trimesters is known to induce human foetotoxicity (e.g.: decreased renal function, oligohydramnios, retardation of skull ossification) and neonatal toxicity (e.g.: renal failure, hypotension, hyperkalaemia). Should exposure to eprosartan have occurred from the second trimester of pregnancy, ultrasound checks of the kidneys and the skull, as well as renal function assessment are recommended.
Infants whose mothers have taken eprosartan should be closely observed for hypotension (see sections "Contraindications" and "Warnings and special precautions for use").

Lactation
See above.

Effects on ability to drive and use machines
Based on its pharmacodynamic properties, eprosartan is unlikely to affect the ability to drive or use machines. However, you should take into account that you may occasionally experience dizziness or weakness during treatment of hypertension.

Important information about the ingredients
This product contains lactose monohydrate. If you have been told by your doctor that you have an intolerance to some sugars, especially lactose, contact your doctor before taking this product.

Undesirable effects
Like all medicines, Teveten may have side effects. If you notice any side effects not mentioned in this leaflet, or if any of the side effects gets serious, inform your doctor or pharmacist immediately.

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 experiences by eprosartan-treated patients participating in clinical trials (n=2316)

The frequencies of study related side effects are ranked according to the following:
Very Common: More than 10 cases in 100 treated patients
Common: Between 1 and 10 cases in 100 treated patients
Uncommon: Less than one case in 100 treated patients

Undesirable Effects by System Organ Class:
Immune system disorders:
Uncommon: Hypersensitivity*

Nervous system disorders
Very common: Headache*
Common: Dizziness*

Vascular disorders
Uncommon: Hypotension (low blood pressure)

Skin and subcutaneous tissue disorders
Common: Allergic skin reaction (e.g. rash, pruritus (itching))
Uncommon: Angioedema* (rapid swelling of the skin and subcutaneous tissues, particularly in the head and neck area)

Gastrointestinal disorders
Common: Unspecific gastrointestinal complaints (e.g.: nausea, diarrhoea vomiting)

General disorders and administration site reactions:
Common: Asthenia (weakness)

* Did not occur in a higher frequency than in placebo (this comment refers to those conditions marked by a * above).

In addition to those adverse events reported during clinical trials, the following side effects have been reported spontaneously during post-marketing use of Teveten (a frequency is not known and cannot be estimated from the available data):
- *Renal and urinary disorders:* Impaired renal (kidney) function including renal failure in patients at risk (e.g. renal artery stenosis (narrowing))

Overdose
There is only limited data available with regard to overdose in humans. Teveten was well tolerated after oral dosing (maximum single dose reported taken to date by a human is 1200 mg). The most likely manifestation of overdose would be hypotension (symptoms of low blood pressure, including dizziness and feeling faint). If symptomatic hypotension should occur, supportive treatment should be instituted.

Pharmacodynamics
Information for the doctor:
Pharmacotherapeutic group: Angiotensin II antagonists

Eprosartan is a potent, non-peptide, orally active non-biphenyl non-tetrazole angiotensin II receptor antagonist, 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, adrenals, kidney, heart) and produces important biological effects such as vasoconstriction, sodium retention and release of aldosterone. More recently, 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. The blood pressure control is maintained over a 24 hour period with no first dose postural hypotension. Discontinuation of treatment with eprosartan does not lead to a rapid rebound increase in blood pressure.
In patients with hypertension, blood pressure reduction did not produce a change in heart rate.

In the MOSES trial (morbidity and mortality after stroke, eprosartan compared with nitrendipine for secondary prevention) 1405 hypertensive patients with a history of cerebrovascular events were treated either with eprosartan or with nitrendipin. In the eprosartan group, 78% of the patients received 600 mg o.d.; 12% up to 800 mg per day; in the nitrendipine group, 47% received 10 mg and 42% 20 mg per day (11% up to 40 mg) in an open label observer blinded randomized prospective design. The primary composite endpoint included all cause mortality, cerebrovascular events (TIA, PRIND, Stroke), and cardiovascular events (unstable angina, myocardial infarction, heart failure, pulmonary embolism and fatal cardiac arrhythmia) including recurrent events. Blood pressure targets were well met in both treatment arms and maintained throughout the course of the study. The primary endpoint showed a significantly better result in the eprosartan group (risk reduction by 21%). In the first event analysis the numerical risk reduction was 12% for the cerebrovascular and 30% for the cardiovascular endpoints. These results were mainly driven by a reduction in the incidence of TIA/PRIND, unstable angina, and heart failure. Overall mortality was numerically in favour of nitrendipine; in the eprosartan group, 57 from 681 patients died vs. 52 from 671 patients in the nitrendipine group (hazard ratio 1.07, 95% CI 0.73 – 1.56, p= 0.725). Fatal and nonfatal myocardial infarction occurred in 18 vs. 20 and stroke in 36 vs. 42 patients, i.e. numerically in favour of eprosartan. For the primary endpoint, the effect of eprosartan appeared to be more pronounced in patients not receiving betablockers.

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 maintains renal function in patients with essential hypertension and patients with renal insufficiency. 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 patients with essential hypertension and to patients with varying degrees of renal insufficiency without causing sodium retention or a deterioration of renal function.

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%). The incidence of cough of any description was also significantly lower ($p<0.05$) in patients treated with eprosartan (21.2%) than in patients treated with an angiotensin converting enzyme inhibitor (29.9%). 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% on an angiotensin converting enzyme inhibitor. The difference in the incidence of dry, persistent cough between the eprosartan and angiotensin converting enzyme inhibitor groups was statistically significant ($p<0.01$), while the difference between the eprosartan and placebo groups was not. The incidence of cough of any description was also significantly lower ($p<0.01$) on eprosartan than on the angiotensin converting enzyme inhibitor, and not significantly different from that on placebo. In addition, in an overall analysis bringing together 6 double-blind clinical trials involving 1554 patients, the incidence of cough reported spontaneously by patients treated with eprosartan was of the same order (3.5%) as that observed in patients treated with placebo (2.6%).

In three clinical studies (n=791) the blood pressure lowering effect of eprosartan has been shown to be at least as great as the ACE inhibitor enalapril with a tendency for greater efficacy with eprosartan.

Pharmacokinetics
Information for the doctor:
Absolute bioavailability following a single 300 mg oral dose of eprosartan is about 13%, due to limited oral absorption. Eprosartan plasma concentrations peak at 1 to 2 hours after an oral dose in the fasted state. In a dose-proportionality study, plasma concentrations of eprosartan were dose proportional from 100 to 200 mg, but less than proportional for 400 and 800 mg doses. The terminal elimination half-life of eprosartan following oral administration is typically 5 to 9 hours. Eprosartan does not significantly accumulate with chronic use. Administration of eprosartan with food delays absorption with minor changes (<25%) observed in C_{max} and AUC which are not of clinical consequence.

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 [^{14}C]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 130 ml/min. Biliary and renal excretion contribute to the elimination of eprosartan. Following intravenous [^{14}C]eprosartan, about 61% of radioactivity is recovered in the faeces and about 37% in the urine. Following an oral dose of [^{14}C]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 2 fold), but this does not necessitate alterations in dosing.

AUC values of eprosartan (but not C_{max}) are increased, on average, approximately 40% in patients with hepatic impairment, but this does not necessitate alterations in dosing.

Compared to subjects with normal renal function mean AUC and C_{max} values were approximately 30% higher in patients with moderate renal impairment (creatinine clearance 30–59 ml/min) and approximately 50% higher in patients with severe renal impairment (creatinine clearance 5–29 ml/min). No alterations in dosing are needed.

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

Incompatibilities
Not applicable.

Shelf life and storage conditions
This product can be stored for up to 3 years at temperatures not exceeding 25°C.

Do not use the medicine after the expiry date stated on the carton.

Store in the original package.

Keep this medicine out of the reach and sight of children.

Pack sizes
Teveten comes in packages containing 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 24, 27, 28, 30, 32, 40, 42, 48, 49, 50, 56, 98, 100, 500, or 1000 film-coated tablets.

The blister packs are made of opaque or clear PVC/PCTFE/Alu.

Not all pack sizes may be marketed.

Further information
Any unused product or waste material should be disposed of in accordance with local requirements.

The information in this leaflet is limited. For further information, please contact your doctor or pharmacist.

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Abbott Healthcare SAS
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for
Abbott Healthcare Products B.V., THE NETHERLANDS

THIS MEDICATION
is a product which affects your health and its use contrary to instructions is dangerous to you. Strictly follow the doctor's prescription, the method of use and the instructions of the pharmacist who sold you the medication.
– The doctor and the pharmacist are the experts in medicines, their benefits and risks.
– Do not interrupt the period of treatment prescribed.
– Do not repeat the same prescription without first consulting your doctor.
– Keep all medications out of reach of children.

Council of Arab Health Ministers,
Union of Arab Pharmacists.