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 Plus is a butterscotch-coloured, capsule-shaped, film-coated tablet for oral administration, with the inscription "5147" on one side of the tablet and "SOLVAY" on the other side. Each tablet contains 600 mg eprosartan mesylate and 12.5 mg hydrochlorothiazide.

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

Tablet Coating
Polyvinylalcohol, macrogol 3350, talc, titanium dioxide (E171), iron oxide black (E172), iron oxide yellow (E172)

Indications
Teveten Plus is indicated for the treatment of essential hypertension.

Dosage and administration
Always take Teveten Plus 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 one tablet per day, to be taken in the morning.

Teveten Plus may be used alone or in combination with other antihypertensives.

Teveten Plus may be taken with or without food.

Geriatric population
No dose adjustment is required in the elderly.

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

Dosage in hepatically impaired patients
No dosage adjustment of Teveten Plus is necessary in patients with mild to moderate hepatic (liver) impairment (see section "Warnings and precautions for use").

Dosage in renally impaired patients
No dosage adjustment is necessary in patients with renal (kidney) impairment whose creatinine clearance is above 30 ml/min (see section "Warnings and precautions for use").

Contraindications
Do not take Teveten Plus if any of the following applies to you:
- you are allergic (hypersensitive) to eprosartan mesylate, hydrocholothiazide, to any of the excipients or to sulfonamides.
- you are in your second or third trimester of pregnancy (see sections "Warnings and special precautions for use" and "Pregnancy and lactation")
- you have severe kidney impairment (with a creatinine clearance of less than 30 ml/min), or
- you have severe kidney disease (specifically, haemodynamically 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").

Information for the patient:
Talk to your doctor if you have any type of kidney or liver disease or diabetes as these problems can become worse while taking Teveten Plus. Furthermore, tell your doctor if you are currently taking a diuretic or potassium supplement.

If you have any type of kidney disease and your doctor has prescribed Teveten Plus to you, he will check your kidney function before you start the therapy. Furthermore, kidney function tests should be repeated at intervals during the course of therapy. If a worsening in your kidney function is detected your doctor will reassess the treatment plan.

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.

Information for the doctor:
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. 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 + hydrochlorothiazide is to be used in patients with renal impairment, renal function should be assessed before starting treatment with eprosartan + hydrochlorothiazide and at intervals during the course of therapy. If worsening of renal function is observed during therapy, treatment with eprosartan + hydrochlorothiazide should be reassessed (see section 4.3). Hydrochlorothiazide-associated azotaemia may occur in patients with impaired renal function.

Hepatic impairment
Hydrochlorothiazide should be used with caution in patients with moderately to severely impaired hepatic function. There is no clinical experience with Teveten Plus in patients with severe hepatic impairment.

Metabolic and endocrine effects
Hydrochlorothiazide may impair glucose tolerance, and this may require dosage adaptation of antidiabetic medication (see section "Interactions with other medications"). Latent diabetes mellitus may become manifest during therapy with Teveten Plus.

At the 12.5 mg hydrochlorothiazide dose of Teveten Plus, only minor metabolic or endocrine effects have been reported.

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 or potassium-containing salts substitutes should be co-administered cautiously with Teveten Plus (see section "Interactions with other medications").

Hypotension
Symptomatic hypotension may occur especially in patients with severe volume and/or salt depletion (e.g. after diuretic therapy, dietary salt restriction, diarrhoea, or vomiting) which should be corrected before treatment with Teveten Plus.

Other conditions
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption 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.

Eprosartan + hydrochlorothiazide
The blood pressure lowering effect of Teveten Plus may increase with the concomitant use of other medicines that lower blood pressure.

NSAIDs (non-steroidal anti-inflammatories) may mildly decrease the diuretic and antihypertensive effects of Teveten Plus.

Eprosartan
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 calcium channel blockers (e.g. sustained release nifedipine) (this class of medicine is used to treat hypertension and congestive heart failure) without evidence of clinically significant adverse interactions.

Reversible increased serum (blood) lithium concentrations and toxicity have been reported when lithium and ACE inhibitors were taken together. The possibility of a similar effect after use of eprosartan cannot 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 isozymes CYP1A, 2A6, 2C9/8, 2C19, 2D6, 2E, and 3A *in vitro.*

Hydrochlorothiazide
By lowering serum potassium levels, hydrochlorothiazide can increase the effects and side-effects of digitalis and anti-arrhythmic medicines (these are used to treat some abnormal heart conditions).

Hydrochlorothiazide increases the risk of hypokalemia if it is concomitantly administered with medicines associated with potassium loss, such as kaliuretic diuretics, laxatives, corticosteroids and ACTH (see section "Warnings and special precautions for use").

Hydrochlorothiazide may impair glucose tolerance. A dosage adjustment of antidiabetic medicines may be required (see section "Warnings and special precautions for use").

Absorption of hydrochlorothiazide is reduced by anionic exchange resins such as colestyramine or colestipol (these medicines are mainly used to lower cholesterol).

Hydrochlorothiazide may increase effects of non-depolarizing (tubocurarin-type) skeletal muscle relaxants.

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

Lactation:
There is no adequate information on the use of Teveten Plus in nursing mothers (see section "Contraindications"). Therefore, the safety of this product in breastfeeding women is not known. The use of Teveten Plus during this time is not recommended. ***Do not take Teveten Plus if you are breast-feeding.***

Information for the doctor:
Pregnancy
Due to the effects on the pregnancy of each of the active substances of this medicinal product, the use of Teveten Plus is not recommended during the first trimester of pregnancy (see section "Warnings and special precautions for use"). The use of Teveten Plus 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. 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 blocker therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive 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 blocker therapy during the second and third trimesters is known to induce human fetotoxicity (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).

The experience of the use of hydrochlorothiazide during pregnancy is limited, in particular during the first trimester. Animal studies are insufficient. Hydrochlorothiazide crosses the placental barrier. Considering the mechanism of action of hydrochlorothiazide the use of this product during the second and third trimesters may compromise the foetoplacental perfusion and may cause neonatal and foetal effects, such as jaundice, electrolyte disturbances and thrombocytopenia. Hydrochlorothiazide should not be used for gestational oedema, hypertension in pregnancy or pre-eclampsia due to the risk of the plasma volume reduction and placental hypoperfusion without any benefits during the course of the disease. Hydrochlorothiazide should not be used for essential hypertension in pregnant women, unless in the rare situation where there is no therapeutic alternative.

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

Effects on ability to drive and use machines
No studies on the effects on the ability to drive and use machines have been performed, but based on its pharmacodynamic properties, Teveten Plus is unlikely to affect this ability. When driving vehicles or operating machines 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 Plus may have side effects. If you notice any side effects not mentioned in this leaflet, or if any of the side effects get serious, please inform your doctor or pharmacist.

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).

None of the listed adverse drug reactions occurred in studies with the combination product (eprosartan + hydrochlorothiazide) in a higher frequency category than with eprosartan alone. Only hypotension occurred in a limited number of patients (n = 372) in a higher frequency (therefore regarded as common side effect) with the combination product compared to eprosartan mono therapy.

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 (kidney) function including renal failure in patients at risk (e.g. renal artery stenosis (narrowing of the kidneys' arteries))

Hydrochlorothiazide administed alone is known to have the following undesirable effects (the frequencies are not known):
- Blood and lymphatic system disorders Aplastic anaemia, agranulocytosis, haemolytic anaemia (the loss of red blood cells in the circulation), leucopenia (the loss of white blood cells), thrombocytopenia (the loss of platelets)
- Immune system disorders:
  Anaphylactic (severe allergic) reactions
- Metabolism and nutrition disorders: Anorexia, hypokalaemia, hyponatraemia, hypercalcaemia, hypomagnesaemia, hypochloraemia, hyperuricaemia, gout, hyperglycaemia, hypercholesterolaemia, hypertriglyceridaemia (these conditons describe the loss or excess of various electrolytes and other substances from the circulation)
- Psychiatric disorders:
  Libido (sex drive) disorder
- Nervous system disorders:
  Paraesthesia (a feeling of tingling or numbness of the skin), headache, dizziness
- Ear and labyrinth disorders:
  Vertigo
- Vascular disorders:
  Hypotension, including orthostatic hypotension, vasculitis (inflammation of the walls of small blood vessels)
- Respiratory, thoracic and mediastinal disorders:
  Pulmonary oedema (swelling/fluid accumulation in the lungs), pneumonitis (inflammation of the lungs)
- Gastrointestinal disorders:
  Pancreatitis (inflammation of the pancreas), abdominal pain, vomiting, diarrhoea, nausea, constipation, stomach discomfort
- Hepatobiliary disorders:
  Jaundice (intrahepatic cholestatic jaundice) (jaundice is a yellowing discoloration of the skin and sclera due to liver disease)
- Skin and subcutaneous tissue disorders:
  Toxic epidermal necrolysis (a life threatening skin disorder, the main symptom of which is widespread rash with skin sloughing, which can lead to sepsis and death), photosensitivity reaction (allergy to sunlight), rash
- Musculoskeletal and connective tissue disorders:
  Systemic lupus erythematosus (an auto-immune disease, symptoms of which include skin eruptions, joint pain, pleurisy and kidney disease), muscle spasms
- Renal and urinary disorders:
  Renal (kidney) failure, interstitial nephritis (a certain type of kidney swelling), renal impairment
- Reproductive system and breast disorders:
  Sexual dysfunction
- General disorders and administration site conditions:
  Pyrexia (fever), asthenia (weakness)

The following adverse events have been reported spontaneously during postmarketing use of the combination **eprosartan plus hydrochlorothiazide.** A frequency cannot be estimated from the available data (not known).
- Psychiatric disorders: Depression, anxiety, insomnia, nervousness, restlessness

All the conditions mentioned for the single products may also appear when the combination product is used.

Overdose
No cases of overdose with Teveten Plus have been reported. Eprosartan plus hydrochlorothiazide was well tolerated after oral dosing (maximum unit dose taken to date in humans is 1200 mg eprosartan with 25 mg hydrocholothiazide). Overdose will most likely result in hypotension (low blood pressure). Other symptoms can be related to dehydration and electrolyte depletion (hypokalaemia, hypochloraemia, hyponatraemia), and are most likely to present as nausea and somnolence (sleepiness).

Treatment should be symptomatic (based on your symptoms) and supportive (directed at supporting your body functions). Depending on the time since ingestion, your doctor may take the following measures: induction of emesis (forced vomiting), gastric lavage (emptying of the stomach), and/or application of activated charcoal (used to absorb toxins from the intestines). If you become hypotensive (i.e.: your blood pressure drops too low, symptoms of which include feeling dizzy and weak), you should lay down and salt and volume replacements (intravenous and/or oral fluid therapy) should be initiated.

Eprosartan is not removed by haemodialysis (blood cleansing). The degree to which hydrochlorothiazide is removed by haemodialysis has not been established.

Pharmacodynamics
Information for the doctor:
Pharmacotherapeutic group: eprosartan and diuretics.

Eprosartan
Eprosartan is a potent, non-peptide, orally active non-biphenyl non-tetrazole angiotensin II antagonist, which binds selectively to the AT_1 receptor. Angiotensin II is a potent vasoconstrictor and the primary active hormone of the reninangiotensin-aldosterone system, playing a major part in the pathophysiology of hypertension.
In addition, in animals eprosartan was shown to block the direct vasoconstrictor response to angiotensin as well as the indirect effects mediated by enhanced neurotransmission, indicating the potential to antagonize overactivity of the sympathetic nervous system.
Eprosartan antagonised the effect of angiotensin II on blood pressure, renal blood flow and aldosterone secretion in normal volunteers. Blood pressure control is maintained over a 24 hour period with no first dose postural hypotension or reflex tachycardia. Discontinuation of treatment with eprosartan does not lead to a rapid rebound increase in blood pressure.

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 potentiate effects relating to bradykinin (mediated by ACE inhibition) e.g. cough.

Hydrochlorothiazide
Hydrochlorothiazide is an established thiazide diuretic. Thiazides affect the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of fluid, sodium and chloride. 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 combined diuretic and direct vascular activity (reduction of vascular resistance) mechanism.

Teveten Plus
Combined i.v. administration of eprosartan and hydrochlorothiazide to spontaneously hypertensive rats showed significant antihypertensive activity.

In patients with isolated systolic hypertension eprosartan alone provided a statistically significant reduction in systolic blood pressure compared to placebo. The addition of once daily hydrochlorothiazide (12.5 mg/day) to once daily eprosartan (600 or 1200 mg/day) provided a statistically significant further reduction in systolic blood pressure compared with once daily eprosartan (600 or 1200 mg/day) alone.
Co-administration of eprosartan reverses the potassium loss associated with the diuretic effect of hydrochlorothiazide, presumably through blockade of the renin-angiotensin-aldosterone system. Onset of diuresis occurs within 2 hours, with peak effect at about 4 hours.

Pharmacokinetics
Information for the doctor:
Eprosartan
After oral administration, absolute bioavailability of eprosartan is about 13%. Eprosartan plasma concentrations peak at 1 to 2 hours. The elimination half-life of eprosartan is typically 5 to 9 hours. Eprosartan does not significantly accumulate with chronic use.

Plasma protein binding of eprosartan is 98%, and not influenced by gender, age, liver disease or mild-to-moderate renal impairment.
The volume of distribution of eprosartan is 13 litres. Total plasma clearance is 130 ml/min. After oral dosing of [^{14}C]eprosartan, about 90% of radioactivity is recovered in the faeces. About 7% was excreted in urine, 80% of which as eprosartan.

Both AUC and C_{max} values of eprosartan are higher in the elderly (on average, twofold), but no dosage adjustment is necessary.
AUC values of eprosartan (but not C_{max}) are increased, on average, approximately 40% in patients with hepatic impairment, but this does not necessitate dosage adjustment.
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).

The pharmacokinetics of eprosartan is not different in males and females.

Hydrochlorothiazide
Hydrochlorothiazide is not metabolized but is eliminated rapidly by the kidneys. At least 61% of the oral dose is eliminated unchanged within 24 hours. Hydrochlorothiazide crosses the placental but not the blood-brain barrier, and is excreted in breast milk.

Teveten Plus
Concomitant administration of hydrochlorothiazide and eprosartan has no clinically significant effect on the pharmacokinetics of either drug.

The bioavailability of eprosartan and hydrochlorothiazide is not influenced by food, but absorption is delayed. Peak plasma concentrations occur at 4 hours after dosing for eprosartan and 3 hours for hydrochlorothiazide.

Incompatibilities
Not applicable.

Shelf life and storage conditions
This product can be stored for up to 3 years.

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

Store in the original package.

Do not store above 25°C.

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

Pack sizes
Teveten Plus comes in packages containing 7, 14, 28, 56, or 98 film-coated tablets.

The blister packs are made of opaque 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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for
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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.