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Read this leaflet before you take your medicine as it gives you some important information.
If you have any questions or are not sure about anything, ask your doctor or a pharmacist.

TEVETEN™ 400 mg

SOLVAY

Film coated, oval shaped, pink tablets for oral administration containing eprosartan mesylate dihydrate, equivalent to 400 mg eprosartan free base.

Excipients: lactose monohydrate, microcrystalline cellulose, pregelatinised starch, croscarmellose sodium, magnesium stearate, hydroxypropylmethylcellulose, titanium dioxide (E171), red and yellow iron oxide (E172), polysorbate 80 and polyethylene glycol.

Indication
Treatment of essential hypertension.

Posology and method of administration
The recommended dose is 600 mg once daily, to be taken in the morning.

The dose may be increased to a maximum of 800 mg daily, depending on the blood pressure response, until satisfactory response is achieved. Achievement of maximal blood pressure reduction in most patients may take 2 to 3 weeks of treatment.
Doses up to 1200 mg per day, for 8 weeks, have been shown in clinical trials to be effective with no apparent dose relationship in the incidence of adverse experiences reported.

Teveten™ may be used alone or in combination with other antihypertensives, e.g. thiazide-type diuretics or calcium channel blockers, if a greater blood pressure lowering effect is required.

Teveten™ may be taken with or without food.

No dose adjustment is required in the elderly, or in patients with hepatic impairment or renal insufficiency (creatinine clearance > 5 mL/min).

Contra-indications
Known hypersensitivity to components of the product.
Pregnancy and lactation.

Special warnings and precautions for use
Patients whose renal function is dependent on the activity of the renin-angiotensin-aldosterone system (e.g. patients with severe cardiac insufficiency, bilateral renal artery stenosis, or renal artery stenosis of a solitary kidney) have developed oliguria and/or progressive azotaemia and rarely acute renal failure during therapy with angiotensin converting enzyme (ACE) inhibitors. Since there is currently inadequate therapeutic experience in patients with severe cardiac insufficiency or renal artery stenosis, it cannot be ruled out that renal function may be impaired with Teveten™ due to inhibition of the renin-angiotensin-aldosterone system.
When eprosartan is 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.
As safety and efficacy in children have not been established, treatment of children is not recommended.

Interaction with other medicaments and other forms of interaction
No clinically significant drug interactions have been observed. No effect on the pharmacokinetics of digoxin and the pharmacodynamics of warfarin or glyburide (glibenclamide) has been shown with Teveten™. Similarly no effect on Teveten™ pharmacokinetics has been shown with ranitidine, ketoconazole or fluconazole.

Teveten™ has been safely used concomitantly with thiazide diuretics (e.g. hydrochlorothiazide) and calcium channel blockers (e.g. sustained-release nifedipine) without evidence of clinically significant adverse interactions. It has been safely co-administered with hypolipidaemic agents (e.g. lovastatin, simvastatin, pravastatin, fenofibrate, gemfibrozil, niacin).

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors. While this is not documented with Teveten™, 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*.

Pregnancy and lactation
There is little experience with the use of Teveten™ during pregnancy. Drugs that act directly on the renin-angiotensin-aldosterone system can cause foetal and neonatal morbidity and death when administered to pregnant women during the second and third trimester. As with other drugs affecting the renin-angiotensin-aldosterone system, Teveten™ should not be used in pregnancy, and if pregnancy is detected, Teveten™ should be discontinued as soon as possible.

Lactation: Breast feeding women should not be treated with Teveten™.

Effects on ability to drive and use machines
Based on its pharmacodynamic properties, Teveten™ is unlikely to affect the ability to drive or use machines. When driving vehicles or operating machines, it should be taken into account that occasionally dizziness or weariness may occur during treatment of hypertension.

Undesirable effects
In placebo-controlled clinical trials, the overall incidence of adverse experiences reported with Teveten™ was comparable to placebo. Adverse experiences have usually been mild and transient in nature and have only required discontinuation of therapy in 4.1% of patients treated with Teveten™ (6.5% for placebo).

Facial swelling and/or angioedema have been very rarely reported.

Overdose
Limited data are available in regard to overdosage in humans. Eprosartan was well tolerated after oral dosing (maximum unit dose taken to date in humans 1200 mg).The most likely manifestation of overdosage would be hypotension. If symptomatic hypotension should occur, supportive treatment should be instituted.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties
Angiotensin II receptor antagonists can be subdivided into three groups: non-biphenyl tetrazoles, biphenyl tetrazoles and non-heterocyclics. Eprosartan is a potent, non-peptide, orally active non-biphenyl 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, suprarenals, 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. In hypertensive patients, comparable blood pressure control is achie-

ved when Teveten™ is administered as a single dose or in two divided doses. The blood pressure control is maintained in a consistent and smooth manner over a 24 hour period with no first dose postural hypotension. Discontinuation of treatment with Teveten™ 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 hypertensive patients Teveten™ does not affect fasting triglycerides, total cholesterol, or LDL (low density lipoprotein) cholesterol levels. In addition Teveten™ has no effect on fasting blood sugar levels.

Teveten™ does not compromise renal autoregulatory mechanisms. In normal adult males Teveten™ has been shown to increase mean effective renal plasma flow. Teveten™ maintains renal function in patients with essential hypertension and patients with renal insufficiency. Teveten™ does not reduce glomerular filtration rate in normal males, in patients with hypertension or in patients with varying degrees of renal insufficiency. Teveten™ has a natriuretic effect in normal subjects on a salt restricted diet. Teveten™ 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.

Teveten™ does not significantly affect the excretion of urinary uric acid.

Teveten™ 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 Teveten™ and an angiotensin converting enzyme inhibitor, the incidence of dry persistent cough in patients treated with Teveten™ (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 Teveten™ (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 Teveten™, 2.7% on placebo, and 25% on an angiotensin converting enzyme inhibitor. The difference in the incidence of dry, persistent cough between the Teveten™ and angiotensin converting enzyme inhibitor groups was statistically significant ($p<0.01$), while the difference between the Teveten™ and placebo groups was not. The incidence of cough of any description was also significantly lower ($p<0.01$) on Teveten™ 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 Teveten™ 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 Teveten™ has been shown to be at least as great as the ACE inhibitor enalapril with a tendency for greater efficacy with Teveten™.

Pharmacokinetic properties
Absolute bioavailability following a single 300 mg oral dose of Teveten™ 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 Teveten™ 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 Teveten™ between males and females.

Incompatibilities
None.

Shelf life
The expiry date is indicated on the packaging.

Special precautions for storage
Do not store above 25°C.

Nature and contents of container
Opaque PVC/PVdC/Al or PVC/Aclar/Al blister packs.

Instruction for use/handling
None.

Date of information
November 24, 2000

Keep medicines out of the reach of children!

Teveten™ is a trade mark of Solvay Pharmaceuticals Marketing & Licensing AG, Allschwil, Switzerland.
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