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™ 600 mg

SOLVAY

Film coated, capsule shaped, white tablets for oral administration containing eprosartan mesylate dihydrate, equivalent to 600 mg eprosartan free base.

Excipients: lactose monohydrate, microcrystalline cellulose, pregelatinised starch, crospovidone, magnesium stearate, hydroxypropylmethylcellulose, titanium dioxide (E171), 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.

Elderly (> 75 years): As clinical experience is limited in patients over 75 years, a starting dose of 300 mg once daily is recommended.

Dosage in hepatically impaired patients: There is limited experience in patients with hepatic impairment (see section Contra-indications and section Pharmacokinetic properties). In patients with mild to moderate hepatic impairment, a starting dose of 300 mg once daily is recommended.

Dosage in renally impaired patients: No dose adjustment is required in patients with creatinine clearance 60-80 ml/min. As clinical experience is limited in patients with creatinine clearance <60ml/min, a starting dose of 300mg once daily is recommended (see Special warnings and precautions for use).

Contra-indications

Known hypersensitivity to components of the product. Pregnancy and lactation. Severe hepatic impairment.

The concomitant use of Teveten™ with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73m^2) (see Interactions).

Special warnings and precautions for use

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 Interactions).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.

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

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-angiotensinaldosterone 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.

Although eprosartan has no significant effect on serum potassium, there is no experience of concomitant administration with K-sparing diuretics or K-supplements. Consequently, as with other angiotensin II antagonists, the risk of hyperkalaemia when taken with K-sparing diuretics or K-supplements cannot be excluded. Regular monitoring for serum potassium levels is recommended when drugs that may increase potassium are administered with eprosartan in patients with renal impairment.

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

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 Contraindications and Warnings/Precautions).

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 coadministered 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).

Headache, dizziness, asthenia, arthralgia, rhinitis, flatulence and hypertriglyceridemia have been reported rarely.

Hypotension, including postural hypotension, has been reported very rarely. Skin reactions (rash, pruritus, urticaria) have been reported rarely. Facial swelling and/or angioedema have been very rarely reported.

In placebo-controlled clinical studies, significantly elevated serum potassium concentrations were observed in 0.9% of patients treated with eprosartan and 0.3% of patients who received placebo.

Significantly low values of haemoglobin were observed in 0.1% and 0% patients treated with eprosartan and placebo respectively.

In rare cases elevations of BUN values were reported in patients treated with eprosartan. In rare cases increases in liver function values were also observed but were not considered to be causally related to eprosartan treatment.

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 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 the AT1 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 achieved 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™ 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%).

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 Cmax 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 [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 130 mL/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 Cmax values of eprosartan are increased in the elderly (on average, approximately 2 fold).

Following administration of a single 100mg dose of eprosartan, AUC values of eprosartan (but not Cmax) are increased, on average, approximately 40% in patients with hepatic impairment.

Compared to subjects with normal renal function mean AUC and Cmax 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).

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/Aclar/AI blister packs.

Instruction for use/handling

None.

Date of information

March 13, 2015

Keep medicines out of the reach of children!

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