Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Teveten Plus 600 mg/12.5 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains eprosartan mesylate equivalent to 600 mg eprosartan and 12.5 mg hydrochlorothiazide.

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

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Butterscotch-coloured, capsule-shaped film-coated tablets.

The inscription of the tablet is “5147” on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Essential hypertension. Teveten Plus 600 mg/12.5 mg is indicated in patients whose blood pressure is not adequately controlled on eprosartan alone.

4.2 Posology and method of administration

The recommended dose is one tablet Teveten Plus 600 mg/12.5 mg once daily, which should be taken in the morning. The switch from eprosartan monotherapy to the fixed combination can be considered after 8 weeks of blood pressure stabilization. Teveten Plus 600 mg/12.5 mg can be taken with or without food.

Elderly
No dose adjustment is required in the elderly, although limited information is available in this population.

Paediatric Population
As safety and efficacy of administration to children have not been established, treatment of children and adolescents < 18 years with Teveten Plus 600 mg/12.5 mg is not recommended.

Hepatic Impairment
The use of Teveten Plus in patients with mild to moderate hepatic impairment is not recommended since there is currently only limited experience of eprosartan mesylate in this patient group. In patients with severe hepatic impairment Teveten Plus is contraindicated (see section 4.3).

Renal Impairment
In patients with mild to moderate renal impairment (creatinine clearance ≥ 30 ml/min) dose adjustment is not necessary. Teveten Plus is contraindicated in patients with severe renal impairment (see sections 4.3 and 4.4).

4.3 Contraindications

- Hypersensitivity to eprosartan, sulfonamide-derived substances (ashydrochlorothiazide) or to any of the excipients listed in section 6.1.
- Second and third trimesters of pregnancy (see sections 4.4 and 4.6)
- Severe hepatic impairment

- Cholestasis and biliary obstructive disorders
- Severe renal impairment (creatinine clearance < 30 ml/min)
- Haemodynamically significant bilateral renovascular disease or severe stenosis of a solitary functioning kidney
- Therapy resistant hypokalaemia or hypercalcaemia
- Refractory hyponatraemia
- Symptomatic hyperuricaemia/gout
- The concomitant use of Teveten Plus 600 mg/12.5mg 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

Hypersensitivity reactions to hydrochlorothiazide are more likely in patients with a history of allergies including hypersensitivity to sulfonamide-derived substances.

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. Renal function should be monitored closely, because there is an increased risk for severe hypotension and renal insufficiency in these patients.

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 section 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.

Renal impairment and renal transplant
When eprosartan + hydrochlorothiazide is to be used in patients with renal impairment, renal function, serum potassium, and uric acid 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.

There is no experience with Teveten Plus 600 mg/12.5 mg in patients with renal transplants.

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. Hydrochlorothiazide should only be used with care in patients with mild to moderate hepatic insufficiency as it may cause intrahepatic cholestasis. Alterations of fluid and electrolyte balance may precipitate hepatic coma.

Metabolic and endocrine disturbances
Hydrochlorothiazide may impair glucose tolerance and this may require dose adjustment of antidiabetic medication (see section 4.5). Latent diabetes mellitus may become manifest during Teveten Plus 600 mg/12.5 mg treatment. At doses of 12.5 mg hydrochlorothiazide in Teveten Plus 600 mg/12.5 mg only mild metabolic and endocrine undesirable effects were observed (increase in serum cholesterol and triglycerides).

Electrolyte imbalance
Hydrochlorothiazide may cause fluid or electrolyte imbalance (hypokalaemia, hyponatraemia, hypercalcaemia, hypomagnesaemia and hypochloremic alkalosis).
As for any patients receiving diuretic therapy, periodic determination of serum electrolytes should be considered.
Potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium or other medicinal products which

may increase the potassium level (e.g. trimethoprim containing medicines) may lead to an increase in serum potassium and should be co-administered cautiously with eprosartan (see section 4.5).

Choroidal effusion, Acute Myopia and Secondary Angle-Closure Glaucoma
Hydrochlorothiazide, a sulfonamide, can cause an idiosyncratic reaction, resulting in choroidal effusion with visual field defect, acute transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue hydrochlorothiazide as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy.

Hypotension
Symptomatic hypotension may occur in patients with severe sodium or volume depletion, e.g. as a result of high doses of diuretics, dietary salt restriction, diarrhoea or vomiting. Sodium and/or volume depletion should be corrected before treatment with Teveten Plus 600 mg/12.5 mg.

Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy
As with other vasodilators patients with aortic or mitral valve stenosis or obstructive hypertrophic cardiomyopathy should be treated with caution.

Primary Hyperaldosteronism
Patients with primary hyperaldosteronism do not react sufficiently on antihypertensives which act through inhibition of the Renin-Angiotensin-Aldosterone system. Therefore, treatment with Teveten Plus 600 mg/12.5 mg is not recommended.

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

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 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 (see sections 4.3 and 4.6).

Non-melanoma skin cancer
An increased risk of non-melanoma skin cancer (NMSC) [basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)] with increasing cumulative dose of hydrochlorothiazide (HCTZ) exposure has been observed in two epidemiological studies based on the Danish National Cancer Registry. Photosensitizing actions of HCTZ could act as a possible mechanism for NMSC. Patients taking HCTZ should be informed of the risk of NMSC and advised to regularly check their skin for any new lesions and promptly report any suspicious skin lesions. Possible preventive measures such as limited exposure to sunlight and UV rays and, in case of exposure, adequate protection should be advised to the patients in order to minimize the risk of skin cancer. Suspicious skin lesions should be promptly examined potentially including histological examinations of biopsies. The use of HCTZ may also need to be reconsidered in patients who have experienced previous NMSC (see also section 4.8).

Acute Respiratory Toxicity
Very rare severe cases of acute respiratory toxicity, including acute respiratory distress syndrome (ARDS) have been reported after taking hydrochlorothiazide. Pulmonary oedema typically develops within minutes to hours after hydrochlorothiazide intake. At the onset, symptoms include dyspnoea, fever, pulmonary deterioration and hypotension. If diagnosis of ARDS is suspected, Teveten Plus HCT 600 mg/12.5 mg should be withdrawn and appropriate treatment given. Hydrochlorothiazide should not be administered to patients who previously experienced ARDS following hydrochlorothiazide intake.

Other warnings and precautions
Thiazide diuretics have been reported to exacerbate or activate systemic lupus erythematosus.

Patients with rare hereditary problems of galactose intolerance, the total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Hydrochlorothiazide may lead to a positive result in doping tests.

4.5 Interaction with other medicinal products and other forms of interaction

Potential interactions related to both eprosartan and hydrochlorothiazide:
Concomitant use not recommended
Lithium:
Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin converting enzyme inhibitors and, rarely, with angiotensin II receptor blockers. In addition, renal clearance of lithium is reduced by thiazides and consequently the risk of lithium toxicity may be increased. Therefore use of Teveten Plus 600 mg/12.5 mg and lithium in combination is not recommended (see section 4.4). If use of the combination proves necessary, careful monitoring of serum lithium levels is recommended.

Concomitant use requiring caution
Baclofen:
Potentiation of antihypertensive effect may occur.

Non-steroidal anti-inflammatory medicinal products:
As with ACE inhibitors, concomitant use of angiotensin II receptor blockers and NSAIDs may lead to an increased risk of worsening 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 of 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.

Concomitant use to be taken into account
Amifostine:
Potentiation of antihypertensive effect may occur.

Other antihypertensive agents:
The blood pressure lowering effect of Teveten Plus 600 mg/12.5 mg can be increased by concomitant use of other antihypertensive medicinal products.

Alcohol, barbiturates, narcotics or antidepressants:
Potentiation of orthostatic hypotension may occur.

Potential interactions related to eprosartan:
Concomitant use not recommended
Medicinal products affecting potassium levels:
Based on experience with the use of other medicinal products that affect the renin-angiotensin system, concomitant use of potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium or other medicinal products that may increase serum potassium levels (eg heparin, trimethoprim containing medicines, ACE inhibitors) may lead to increases in serum potassium. If medicinal product which affect potassium levels are to be prescribed in combination with Teveten Plus 600 mg/12.5 mg, monitoring of potassium plasma levels is advised (see section 4.4).

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).

Potential interactions related to hydrochlorothiazide:
Concomitant use not recommended
Medicinal products affecting potassium levels:
The potassium-depleting effect of hydrochlorothiazide may be potentiated by the coadministration of other medicinal products associated with potassium loss and hypokalaemia (eg other kaliuretic diuretics, laxatives, corticosteroids, ACTH,

amphotericin, carbenoxolone, penicillin G sodium or salicylic acid derivatives). Such concomitant use is therefore not recommended (see section 4.4).

Concomitant use requiring caution
Calcium salts and Vitamin D:
Thiazide diuretics may increase serum calcium levels due to decreased excretion. If calcium supplements or medicinal products affecting serum calcium levels (e.g. Vitamin D therapy) must be prescribed, serum calcium levels should be monitored and calcium dosage adjusted accordingly.

Cholestyramine and colestipol resins:
Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins such as cholestyramine or colestipol. However, the interaction might be minimized by graded intake of hydrochlorothiazide and the resin in the way that hydrochlorothiazide is taken at least 4 hours before or 4-6 hours after the resins.

Digitalis glycosides:
Thiazide-induced hypokalaemia or hypomagnesaemia may favour the onset of digitalis-induced cardiac arrhythmias.

Medicinal products affected by serum potassium disturbances:
Periodic monitoring of serum potassium and ECG is recommended when Teveten Plus 600 mg/12.5 mg is administered with medicinal products affected by serum potassium disturbances (e.g. digitalis glycosides and antiarrhythmics) and with the following torsades de pointes (ventricular tachycardia)-inducing medicinal products (including some antiarrhythmics), hypokalaemia being a predisposing factor to torsades de pointes (ventricular tachycardia):

- Class Ia antiarrythmics (e.g. quinidine, hydroquinidine, disopyramide).
- Class III antiarrythmics (e.g. amiodarone, sotalol, dofetilide, ibutilide).
- Some antipsychotics (e.g. thioridazine, chlorpromazine, levomepromazine, trifluoperazine, cyamemazine, sulpiride, sultopride, amisulpride, tiapride, pimozide, haloperidol, droperidol).
- Others (e.g. bepridil, cisapride, diphemanil, erythromycin IV, halofantrin, mizolastin, pentamidine, terfenadine, vincamine IV).

Non-depolarizing skeletal muscle relaxants (eg tubocurarine):
The effect of nondepolarizing skeletal muscle relaxants may be potentiated by hydrochlorothiazide.

Anticholinergic agents (eg atropine, biperiden):
Increase of the bioavailability of thiazide-type diuretics by decreasing gastrointestinal motility and stomach emptying rate.

Antidiabetic medicinal products (oral agents and insulin):
The treatment with a thiazide may influence the glucose tolerance. Dosage adjustment of the antidiabetic medicinal product may be required (see section 4.4).

Metformin:
Metformin should be used with caution because of the risk of lactic acidosis induced by possible functional renal failure linked to hydrochlorothiazide.

Beta-blockers and diazoxide:
The hyperglycaemic effect of beta-blockers and diazoxide may be enhanced by thiazides.

Pressor amines (eg noradrenaline):
The effect of pressor amines may be decreased.

Medicinal products used in the treatment of gout (probenecid, sulfinpyrazone and allopurinol):
Dosage adjustment of uricosuric medicinal products may be necessary since hydrochlorothiazide may raise the level of serum uric acid. Increase in dosage of probenecid or sulfinpyrazone may be necessary. Coadministration of a thiazide may increase the incidence of hypersensitivity reactions to allopurinol.

Amantadine:
Thiazides may increase the risk of adverse effects caused by amantadine.

Cytotoxic agents (eg cyclophosphamide, methotrexate):

Thiazides may reduce the renal excretion of cytotoxic medicinal products and potentiate their myelosuppressive effects.

Tetracyclines:
Concomitant administration of tetracyclines and thiazides increases the risk of tetracycline-induced increase in urea. This interaction is probably not applicable to doxycycline.

Medicinal products lowering serum sodium level:
The hyponatraemic effect of hydrochlorothiazide may be intensified by concomitant administration of drugs such as antidepressants, antipsychotics, antiepileptics, etc. Caution is advised in long-term administration of these drugs.

4.6 Fertility, pregnancy and lactation

Pregnancy
Angiotensin II receptor blocker:

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 the second and third trimesters 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 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).

Hydrochlorothiazide:
There is limited experience with hydrochlorothiazide during pregnancy especially during the first trimester. Animal studies are insufficient. Hydrochlorothiazide crosses the placenta. Based on the pharmacological mechanism of action of hydrochlorothiazide its use during the second and third trimesters may compromise the foetoplacental perfusion and may cause foetal and neonatal effects like icterus, disturbance of electrolyte balance and thrombocytopenia.
Hydrochlorothiazide should not be used for gestational oedema, gestational hypertension or pre-eclampsia due to the risk of decreased plasma volume and placental hypoperfusion without a beneficial effect on the course of the disease.
Hydrochlorothiazide should not be used for essential hypertension in pregnant women except in rare situations where no other treatment could be used.

Breast-feeding
Angiotensin II receptor blocker:
Because no information is available regarding the use of Teveten Plus 600 mg/12.5 mg during breastfeeding, Teveten Plus 600 mg/12.5 mg is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

Hydrochlorothiazide:
Hydrochlorothiazide is excreted in human milk in small amounts. Thiazides in high doses causing intense diuresis can inhibit the milk production. The use of Teveten Plus 600 mg/12.5 mg during breast feeding is not recommended. If Teveten Plus 600 mg/12.5 mg is used during breast feeding, doses should be kept as low as possible.

Fertility
There are no clinical data on fertility.

Nonclinical data on eprosartan did not reveal any effects on male and female fertility. No preclinical information on possible effects of hydrochlorothiazide on fertility is available.

4.7 Effects on ability to drive and use machines

No studies on the ability to drive and use machines have been performed, but based on its pharmacodynamic properties, Teveten Plus 600 mg/12.5 mg 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

a. Summary of the safety profile

The most commonly reported adverse drug reactions of patients treated with eprosartan+ hydrochlorothiazide are headache and unspecific gastrointestinal complaints occurring in approximately 11% and 8% of patients (versus 14% and 8% with placebo) respectively.

b. Summary of adverse reactions

Adverse drug reactions (ADRs) that occurred in placebo-controlled clinical trials or reported from the scientific literature are summarized in the Table below. Under each frequency category, ADRs are listed based on data from eprosartan, the combination eprosartan+hydrochlorothiazide, as well as hydrochlorothiazide alone (see table footnotes).

ADVERSE DRUG REACTIONS REPORTED IN PLACEBO CONTROLLED TRIALS AND SCIENTIFIC LITERATURE

MedDRA system organ class	**Very common ≥1/10**	**Common ≥1/100 to <1/10**	**Uncommon ≥1/1,000 to <1/100**	**Rare ≥1/10,000 to <1/1,000**	**Very rare <1/ 10,000**	**Unknown** (cannot be estimated from available data)
Blood & lymphatic system disorders			Leukopenia		Haemo-lytic an-aemia[1]	Agranulocytosis, Aplastic anaemia, Thrombocytopenia
Immune system disorders			Hypersensitivity			Anaphylactic reactions
Metabolism and nutrition disorders		Hyperglycaemia	Hypokalaemia, Hyponatraemia, Hypochloraemia, Hyperuricaemia, Gout, Hypercholesterolaemia			Hypercalcaemia, Hypomagnesaemia, Hypertriglyceridaemia, Anorexia
Psychiatric disorders			Depression, Anxiety, Insomnia, Nervousness, Libido disorder			Restlessness
Nervous system disorders	Head-Ache[2]	Dizziness, Paraesthesia				
Eye disorders						Acute myopia and secondary angle-closure glaucoma *, choroidal

MedDRA system organ class	Very common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 to <1/100	Rare ≥1/10,000 to <1/1,000	Very rare <1/ 10,000	Unknown (cannot be estimated from available data)
						effusion[4]
Ear and labyrinth disorders			Vertigo[2]			
Vascular disorders		Hypotension (e.g. orthostatic)				Vasculitis
Respiratory disorders		Rhinitis		Pulmonary oedema[1] Pneumo-nitis[1]	Acute respiratorydistress syndrome (ARDS)[5]	
Gastro-intestinal disorders		Unspecific gastrointestinal complaints (e.g. nausea, diarrhoea, vomiting)	Constipation[2]	Pancrea-titis[1]		
Hepatobiliary disorders						Jaundice (intrahepatic cholestatic jaundice)
Skin and subcutaneous tissue disorders		Allergic skin reactions (e.g. rash, pruritus)	Angioedema			Toxic epidermal necrolyis, Photosensitivity, Cutaneous lupus erythematosus
Musculoskeletal and connective tissue disorders			Muscle spasms[2]			Systemic lupus erythematosus, Arthralgia
Renal and urinary disorders						Interstitial nephritis, Renal failure/ im-paired renal function in patients at risk (e.g. renal artery stenosis)

MedDRA system organ class	Very common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 to <1/100	Rare ≥1/10,000 to <1/1,000	Very rare <1/ 10,000	Unknown (cannot be estimated from available data)
Reproductive system/breast disorders			Sexual dysfunction			
General disorders and administration site reactions		Asthenia	Pyrexia			
Neoplasms benign, malignantand unspecified (incl cysts and polyps)						Non-melanoma skincancer (Basal cell carcinoma and Squamous cell carcinoma)[3]

[1] Frequency based on data from the hydrochlorothiazide scientific literature
[2] Did not occur in a higher frequency than in placebo
[3] Based on available data from epidemiological studies, cumulative dose-dependent association between HCTZ and NMSC has been observed (see also sections 4.4 and 5.1)
[4] Cases of choroidal effusion with visual field defect have been reported after the use of thiazide and thiazide-like diuretics.
[5] See section 4.4

c. Description of selected adverse reactions
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 national reporting system:
HPRA Pharmacovigilance
Website: www.hpra.ie

4.9 Overdose

Limited data are available in regard to overdose in humans. There have been individual reports from postmarketing experience where doses up to 12,000 mg of eprosartan had been ingested. Although most patients reported no symptoms, it has to be noted that in one subject circulatory collapse occurred after ingestion of 12,000 mg eprosartan. The subject recovered completely. For eprosartan + hydrochlorothiazide a maximum ingested dose was 3600 mg eprosartan/75 mg hydrochlorothiazide. It was reported in a case of a suicide attempt.

The most likely manifestation of overdose would be hypotension.

Other symptoms may be due to dehydration and electrolyte depletion (hypokalaemia, hypochloraemia, hyponatraemia) and will most likely present as nausea and somnolence. Treatment should be symptomatic and supportive. Eprosartan is not removed by haemodialysis. The degree to which hydrochlorothiazide is removed by haemodialysis has not been established.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Eprosartan and diuretics: ATC code: C09DA02.

Eprosartan
Eprosartan is a non-peptide, orally active non-biphenyl non-tetrazole angiotensin II receptor blocker, which selectively binds to the AT_1-receptor.

Angiotensin II plays a major role in the pathophysiology of hypertension. It is the primary active hormone of the Renin-Angiotensin-Aldosterone system and a potent vasoconstrictor.

Eprosartan antagonised the effect of angiotensin II on blood pressure, renal blood flow and aldosterone secretion in man. 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 healthy adult males eprosartan has been shown to increase mean effective renal plasma flow.

Eprosartan does not potentiate effects relating to bradykinin (ACE mediated) e.g. cough.

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 NEPHRON-D 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.

Hydrochlorothiazide
Hydrochlorothiazide is an established thiazide diuretic. Thiazides affect the renal tubular mechanisms of electrolyte re-absorption, increasing excretion of fluid, sodium and chloride. The diuretic action of hydrochlorothiazide reduces plasma volume, increases plasma renin activity, increases aldosterone secretion, with consequential 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.

Non-melanoma skin cancer: Based on available data from epidemiological studies, cumulative dose-dependent association between HCTZ and NMSC has been observed. One study included a population comprised of 71,533 cases of BCC and of 8,629 cases of SCC matched to 1,430,833 and 172,462 population controls, respectively. High HCTZ use (≥50,000 mg cumulative) was associated with an adjusted OR of 1.29 (95% CI: 1.23-1.35) for BCC and 3.98 (95% CI: 3.68-4.31) for SCC. A clear cumulative dose response relationship was observed for both BCC and SCC. Another study showed a possible association between lip cancer (SCC) and exposure to HCTZ: 633 cases of lip-cancer were matched with 63,067 population controls, using a risk-set sampling strategy. A cumulative dose-response relationship was demonstrated with an adjusted OR 2.1 (95% CI: 1.7-2.6) increasing to OR 3.9 (3.0-4.9) for high use (~25,000 mg) and OR 7.7 (5.7-10.5) for the highest cumulative dose (~100,000 mg) (see also section 4.4).

Teveten Plus 600 mg/12.5 mg
In a placebo-controlled, 8 weeks clinical trial in 473 patients with essential hypertension it was shown that the combination of 600 mg eprosartan and 12.5 mg hydrochlorothiazide is well tolerated and efficacious. Teveten Plus 600 mg/12.5 mg reduced systolic and diastolic blood pressure to a clinically relevant degree and was statistically significant superior to both individual components and placebo, despite a high placebo response (p=0.08 for comparison of eprosartan alone and placebo). Tolerability was equal for both eprosartan/hydrochlorothiazide 600 mg/12.5 mg, eprosartan and placebo.

In another clinical trial patients with a diastolic blood pressure between 98 and 114 mmHg, who were not treated sufficiently with a 3-weeks treatment ofeprosartan 600 mg alone, were given either eprosartan/hydrochlorothiazde 600 mg/12.5 mg or 600 mg eprosartan alone for 8 weeks. The combination caused a statistically significant and clinically relevant additional decrease in systolic and diastolic blood pressure in patients not reacting sufficiently to eprosartan monotherapy. Tolerability was equally satisfactory for both the combination and monotherapy.

Only limited data is available in patients over 80 years of age.

The effect of the combination of eprosartan and hydrochlorothiazide on morbidity and mortality was not investigated. Epidemiological studies showed that long term treatment with hydrochlorothiazide reduces the risk for cardiovascular mortality and morbidity.

5.2 Pharmacokinetic properties

Eprosartan
Absolute bioavailability following oral administration of eprosartan is approx. 13%. Eprosartan plasma concentrations peak at 1 to 2 hours after dosing in the fasted state. The terminal elimination half-life of eprosartan is typically 5 to 9 hours. A slight accumulation (14 %) is seen with chronic use of eprosartan. Administration of eprosartan with food delays absorption, but does not decrease the bioavailability.

In the dose range between 100 to 800 mg there is a slight less than dose-proportional increase in exposure to eprosartan, most likely due to the physicochemical properties of the drug.

Plasma protein binding of eprosartan is 98% and is not influenced by gender, age, hepatic dysfunction or mild-to moderate renal impairment. Plasma protein binding is decreased in a small number of patients with severe renal impairment.

The volume of distribution of eprosartan is approx. 13 litres. Total plasma clearance is approx. 130 ml/min. After oral administration of [^{14}C] eprosartan approximately 90% of radioactivity was recovered from faeces. Approximately 7% was excreted in urine, 80% of which as eprosartan. Both AUC and C_{max} values for eprosartan are higher in the elderly (on average twofold), but dose adjustment is not necessary. AUC values (but not C_{max}) for eprosartan are increased on average by 40% in patients with hepatic impairment, but this does not necessitate dose 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), approximately 50% higher in patients with severe renal impairment (creatinine clearance 5-29 ml/min). There is no difference in the pharmacokinetics between males and females.

It was shown in vitro that eprosartan does not inhibit human Cytochrome P450 isoenzymes CYP1A, 2A6, 2C9/8, 2C19, 2D6, 2E and 3A.

Hydrochlorothiazide
After oral administration absorption of hydrochlorothiazide is relatively rapid. When given in fasted state the mean elimination half-life is 5-15 hours. Hydrohlorothiazide is not metabolized and is rapidly excreted by the kidneys. At least 61% of an oral dose is excreted unchanged within 24 hours. Hydrochlorothiazide crosses the placental but not the blood-brain barrier and is excreted in breast milk.

Teveten Plus 600 mg/12.5 mg
Co-administration of eprosartan and hydrochlorothiazide has no clinical significant effect on the pharmacokinetics of either active substance. The bioavailability of eprosartan and hydrochlorothiazide is not influenced by food, but absorption is delayed. Peak plasma concentrations are reached after 4 hours for eprosartan and after 3 hours for hydrochlorothiazide.

5.3 Preclinical safety data

The potential toxicity of the combination eprosartan/hydrochlorothiazide after oral administration was investigated in mice and dogs in studies lasting up to 3 months. No findings emerged that would exclude the use of therapeutic doses in man.

The toxicologic target organ was the kidney. The combination eprosartan/hydrochlorothiazide induced functional renal changes (increases in serum urea and in serum creatinine). Furthermore, tubular de- and regeneration in the kidneys were induced at higher doses in mice and dogs, probably by way of altered renal haemodynamics (reduced renal perfusion as a consequence of hypotension leading to tubular hypoxia with tubular cellular degeneration).

Furthermore, the combination induced juxtaglomerular cell hyperplasia, decreases in red blood cell parameters and a decrease in heart weight. These effects appear to be due to the pharmacological effects of high doses eprosartan and also occur with ACE-inhibitors. The relevance of these findings to the use of therapeutic doses of the combination eprosartan/hydrochlorothiazide in humans is unknown.

Findings from in vitro and in vivo studies with eprosartan and hydrochlorothiazide both alone and in combination did not reveal a relevant genotoxic potential.

Carcinogenicity studies were not performed with the combination eprosartan/hydrochlorothiazide. Carcinogenicity was not observed in rats and mice, administered eprosartan up to 600 mg or 2000 mg/kg daily respectively for 2 years.

In pregnant rabbits, eprosartan has been shown to produce maternal and fetal mortality at 10 mg/kg per day during late pregnancy only. Hydrochlorothiazide did not enhance maternal and embryo-fetal toxicity of eprosartan. The combination eprosartan/hydrochlorothiazide administered orally at doses up to 3/1 mg/kg/day (eprosartan/hydrochlorothiazide) resulted in neither maternal nor fetal developmentally toxic effects.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Lactose monohydrate
Microcrystalline cellulose
Pregelatinised starch (from maize)
Crospovidone
Magnesium stearate
Purified water

Film coat:
Polyvinyl alcohol
Talc
Titanium dioxide (E171)
Macrogol 3350
Iron oxide yellow (E172)
Iron oxide black (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage condition.

6.5 Nature and contents of container

White PVC/PCTFE/Aluminium foil blisters or white PVC/PVDC/Aluminium foil blisters

Blister packs: 28 film-coated tablets
56 film-coated tablets
98 film-coated tablets
280 (10 x 28) film-coated tablets
Sample : film-coated 14 tablets

Not all pack sizes may be marketed

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Viatris Healthcare Limited
Damastown Industrial Park
Mulhuddart
Dublin 15
Dublin
Ireland

8 MARKETING AUTHORISATION NUMBER

PA23355/021/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28th January 2005
Date of last renewal: 1st November 2006

10 DATE OF REVISION OF THE TEXT

March 2025