IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0749/029/001
Case No: 2072784

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Teva Pharma B.V.

Computerweg 10, **3542 DR Utrecht**, **Netherlands**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Enalapril Maleate Hydrochlorothiazide Teva 20 mg/12.5 mg Tablets

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **30/03/2010** until **31/05/2012**.

Signed on behalf of the Irish Medicines Board this

_____

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Enalapril Maleate Hydrochlorothiazide Teva 20 mg/12.5 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 20 mg of enalapril maleate and 12.5 mg of hydrochlorothiazide (HCT).

Excipients:
Each tablet contains 140 mg of lactose monohydrate.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

White, round, slightly arched tablets, debossed “EL”, “20” and scoreline on one side and plain on the other.
The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of essential hypertension.

This fixed dose combination is indicated in patients whose blood pressure is not adequately controlled with

enalapril alone.

This fixed dose may also replace the combination of 20 mg enalapril maleate and 12.5 mg hydrochlorothiazide in patients who have been stabilised on the individual active substances given in the same proportions as separate medications.

This fixed dose combination is not suitable for initial therapy

4.2 Posology and method of administration

Enalapril/HCT can be administered in a single dose/day with or without food.

Individual dose titration with both active substances can be recommended.

When clinically appropriate, direct change from ACE inhibitor monotherapy to the fixed combination may be considered.

Dosage in patients with normal renal function

The usual dosage is one tablet, taken once daily.

Dosage in renal insufficiency

- Creatinine clearance ≥ 30 ml/min: The dose of enalapril should be titrated in patients with renal impairment whose creatinine clearance is ≥ 30 ml/min before switching to the fixed combination. Loop diuretics are preferred to thiazides in this population. The dose of enalapril maleate and hydrochlorothiazide should be kept as low as possible (see section 4.4).

Potassium and creatinine should be monitored periodically in these patients, e.g. every 2 months when the treatment has been stabilised (see section 4.4).

- Creatinine clearance < 30 ml/min: see section 4.3.

Special population

In salt/volume depleted patients, the starting dose is 5 mg enalapril or lower. Individual dose titration with enalapril and hydrochlorothiazide is recommended.

Use in the elderly

The use in elderly has been shown as good as in younger hypertensive patients. In case of physiological renal impairment, titration with the monocomponent enalapril is recommended prior to using the fixed combination.

Use in children and adolescents

Safety and effectiveness of Enalapril/HCT in children has not been established.

4.3 Contraindications

Associated with enalapril:

This medicinal product must not be used in patients with:

- hypersensitivity to enalapril, other ACE inhibitors or to any of the excipients,

- a history of angiooedema (Quincke's oedema) linked to previous treatment with an ACE inhibitor and/or in patients with inherited or idiopathic angioedema.

- during the second and third trimesters of pregnancy (see section s 4.4 and 4.6).

Associated with hydrochlorothiazide:

This medicinal product must not be used in patients with:

- hypersensitivity to hydrochlorothiazide or other sulphonamides

- severe renal impairment (creatinine clearance < 30 ml/min)

- Severe hepatic impairment/hepatic encephalopathy

- Lactation

4.4 Special warnings and precautions for use

Warnings

ASSOCIATED WITH THE EXCIPIENTS

This medicinal product contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

ASSOCIATED WITH ENALAPRIL

Symptomatic hypotension

Symptomatic hypotension is rarely seen in uncomplicated hypertensive patients. In hypertensive patients receiving enalapril, symptomatic hypotension is more likely to occur if the patient has been volume-depleted e.g. by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting (see section 4.5). In patients with heart failure, with or without associated renal insufficiency, symptomatic hypotension has been observed. This is most likely to occur in those patients with more severe degrees of heart failure, as reflected by the use of high doses of loop diuretics, hyponatremia or functional renal impairment. In these patients, therapy should be started under medical supervision and the patients should be followed closely whenever the dose of enalapril and/or diuretic is adjusted. Similar considerations may apply to patients with ischemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, should receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses, which can be given usually without difficulty once the blood pressure has increased after volume expansion.

In some patients with heart failure who have normal or low blood pressure, additional lowering of systematic blood pressure may occur with enalapril. This effect is anticipated and usually is not a reason to discontinue treatment. If hypotension becomes symptomatic, a reduction of dose and/or discontinuation of the diuretic and/or enalapril may be necessary.

Aortic or mitral valve stenosis/hypertophic cardiomyopathy

As with all vasodilators, ACE inhibitors should be given with caution in patients with left ventricular valvular and outflow tract obstruction and avoided in cases of cardiogenic shock and haemodynamically significant obstruction.

Renal function impairment

In cases of renal impairment (creatinine clearance < 80 ml/min), the initial enalapril dosage should be adjusted according to the patient's creatinine clearance (see section 4.2) and then as a function of the patient's response to treatment. Routine monitoring of potassium and creatinine are part of normal medical practice for these patients.

Renal failure has been reported in association with enalapril, and has been mainly in patients with severe heart failure or underlying renal disease, including renal artery stenosis. If recognised promptly and treated appropriately, renal failure when associated with therapy with enalapril is usually reversible.

Some hypertensive patients, with no apparent pre-existing renal disease have developed increases in blood urea and creatinine when enalapril has been given concurrently with a diuretic. Dosage reduction of enalapril and /or discontinuation of the diuretic may be required. This situation should raise the possibility of underlying renal artery stenosis (see section 4.4. – renovascular hypertension).

Renovascular hypertension

There is an increased risk of hypotension and renal insufficiency when patients with bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney are treated with ACE inhibitors. Loss of renal function may occur with only mild changes in serum creatinine. In these patients, therapy should be initiated under close medical supervision with low doses, careful titration and monitoring of renal function.

Kidney transplantation

There is no experience regarding the administration of enalapril in patients with a recent kidney transplantation. Treatment with enalapril is therefore not recommended

Hepatic failure

Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice or hepatitis and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up.

Neutropenia/agranulocytosis

Neutropenia/agranulocytosis, thrombocytopenia and anaemia have been reported in patients receiving ACE inhibitors. In patients with normal renal function and no other complicating factors, neutropenia occurs rarely. Enalapril should be used with extreme caution in patients with collagen vascular disease, immunosuppressant therapy, treatment with allopurinol or procainamide, or a combination of these complicating factors, especially if there is pre-existing impaired renal function. Some of these patients developed serious infections which in a few instances did not respond to intensive antibiotic therapy. If enalapril is used in such patients, periodical monitoring of white blood cell counts is advised and patients should be instructed to report any sign of infection

Hypersensitivity/angioneurotic oedema

Angioneurotic oedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with angiotensin converting enzyme inhibitors, including enalapril. This may occur at any time during treatment. In such cases, enalapril should be discontinued promptly, and appropriate monitoring should be instituted to ensure complete resolution of symptoms prior to dismissing the patient. In those instances where swelling has been confined to the face and lips the condition generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Even in those instances where swelling of only the tongue is involved, without respiratory distress, patients may require prolonged observation since treatment with antihistamines and corticosteroids may not be sufficient.

Angioneurotic oedema associated with laryngeal oedema may be fatal. Very rarely, fatalities have been reported due to angiooedema associated with laryngeal oedema or tongue oedema. Patients with involvement of the tongue glottis or larynx are likely to experience airway obstruction, especially those with a history of airway surgery.

Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, appropriate therapy, which may include subcutaneous epinephrine solution 1:1000 (0.3 ml to 0.5 ml) and/or measures to ensure a patent airway, should be administered promptly.

Black patients taking ACE inhibitors have been reported to have a higher incidence of angioedema compared to non-blacks.

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see section 4.3.)

Anaphylactoid reactions during hymenoptera desensitization

Rarely, patients receiving ACE inhibitors during desensitization with hymenoptera venom have experienced life-threatening anaphylactoid reactions. These reactions were avoided by temporarily withholding ACE-inhibitor therapy prior to each desensitization.

Anaphylactoid reactions during LDL apheresis

Rarely, patients receiving ACE inhibitors during low density lipoprotein (LDL)-apheresis with dextran sulphate have experienced life-threatening anaphylactoid reactions. These reactions were avoided by temporarily withholding ACE-inhibitor therapy prior to each apheresis.

Haemodialysis patients

Anaphylactoid reactions have been reported in patients dialysed with high-flux membranes (e.g., AN 69®) and treated concomitantly with an ACE inhibitor. In these patients consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent.

Diabetic patients

In diabetic patients treated with oral antidiabetic agents or insulin, glycemic control should be closely monitored during the first month of treatment with an ACE inhibitor. (see section 4.5).

Cough

Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is non-productive, persistent and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

Surgery/anaesthesia

In patients undergoing major surgery or during anesthesia with agents that produce hypotension, enalapril blocks angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Hyperkalaemia

Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including enalapril. Patients at risk for the development of hyperkalemia include those with renal insufficiency, diabetes mellitus, or those using concomitant potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes; or those patients taking other drugs associated with increases in serum potassium (e.g. heparin). If concomitant use of the above mentioned agents is deemed appropriate, regular monitoring of serum potassium is recommended.

Ethnic differences

As with other angiotensin converting enzyme inhibitors, enalapril is apparently less effective in lowering blood pressure in black people than in non-blacks, possibly because of a higher prevalence of low-renin states in the black hypertensive population.

Pregnancy

ACE inhibitors should not be initiated during pregnancy. Unless continued ACE inhibitor 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 ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

Interactions

This medicinal product IS GENERALLY NOT RECOMMENDED in combination with potassium-sparing diuretics, potassium salts and estramustine (see section 4.5).

ASSOCIATED WITH HYDROCHLOROTHIAZIDE

Hepatic impairment

Thiazide should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic encephalopathy in patients with hepatic disease. In this case, treatment with the diuretic must be stopped immediately.

Enalapril/HCT is generally not recommended in combination with sultopride (see section 4.5).

ASSOCIATED WITH ENALAPRIL AND HYDROCHLOROTHIAZIDE

Interaction

This medicinal product is generally not recommended in combination with lithium due to the potentialisation of lithium toxicity (see section 4.5).

PRECAUTIONS FOR USE

ASSOCIATED WITH HYDROCHLOROTHIAZIDE

Fluid/electrolyte balance
As for any patient receiving diuretic therapy, periodic determination of serum electrolytes should be performed at appropriate intervals.

Thiazides (including hydrochlorothiazide) can cause fluid or electrolyte imbalance (hypokalaemia, hyponatraemia, and hypochloraemic alkalosis). Warning signs of fluid or electrolyte imbalance are dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pain or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea or vomiting.

Although hypokalaemia may develop with the use of thiazide diuretics, concurrent therapy with enalapril may reduce diuretic-induced hypokalaemia. The risk of hypokalaemia is greatest in patients with cirrhosis of the liver, in patients experiencing brisk diuresis, in patients who are receiving inadequate oral intake of electrolytes and in patients receiving concomitant therapy with corticosteroids or ACTH (see section 4.5).

Dilutional hyponatraemia may occur in oedematous patients in hot weather. Chloride deficit is generally mild and usually does not require treatment.

Natraemia

Sodium levels must be assessed before the initiation of treatment, and at regular intervals thereafter. All diuretic treatment can cause hyponatraemia, with potentially serious consequences. Since a decrease in natraemia may initially be asymptomatic, regular monitoring is essential and must be even more frequent in at-risk populations such as the elderly, malnourished and cirrhotic (see section 4.8 and section 4.9).

Kalaemia

Potassium depletion and hypokalaemia are the major risks associated with thiazide and related diuretics. Hypokalaemia (< 3.5 mmol/l) must be prevented in certain at-risk populations, such as elderly and/or malnourished patients, especially when receiving combination therapy, cirrhotic patients with oedema and ascites, coronary patients, patients with heart failure. In these cases, hypokalaemia increases the cardiotoxicity of digitalis glycosides and the risk of arrhythmia.

In patients with a long QT interval, whether congenital or substance-induced, hypokalaemia increases the risk of severe arrhythmia, in particular potentially fatal torsade de pointes, especially in patients with bradycardia.

Potassium levels must be regularly monitored, starting in the first week of treatment.

Calcaemia

Thiazide may decrease urinary calcium excretion and may cause intermittent and slight elevation of serum calcium.

Marked hypercalcaemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Magnesium plasma levels

Thiazides have been shown to increase the urinary excretion of magnesium, which may result in hypomagnesaemia.

Metabolic and endocrine effects

Thiazide therapy may impair glucose intolerance. In diabetic patients dosage adjustments of insulin or oral hypoglycaemic agents may be required. Latent diabetes mellitus may become manifest during thiazide therapy.

Increases in cholesterol and triglyceride levels have been associated with thiazide diuretic therapy. The salt and volume depletion caused by thiazides reduces the urinary elimination of uric acid. Hyperuricaemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy.

Renal impairment

Thiazide diuretics are fully efficacious only in patients with normal renal function or mild renal impairment (evaluated, for example, according to creatinine clearance). In the elderly, the value for creatinine clearance must be adjusted for age, weight and sex.

Hypovolaemia, secondary to diuretic-induced fluid and sodium loss at the beginning of treatment, leads to reduced glomerular filtration. This can cause an increase in blood urea and creatinine.

This transient functional renal impairment is without consequence in patients with normal renal function, but can aggravate pre-existing renal impairment.

Thiazides should be used with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotaemia. Cumulative effects of the drug may develop in patients with impaired renal function. If progressive renal impairment becomes evident, as indicated by a rising non-protein nitrogen, careful reappraisal of therapy is necessary, with consideration given to discontinuing diuretic therapy.

Athletes/anti-doping test

The attention of athletes is drawn to the fact that this medicinal product contains an active substance which may induce a positive reaction in anti-doping tests.

Other

Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. The possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

ASSOCIATED WITH ENALAPRIL AND HYDROCHLOROTHIAZIDE

Functional renal impairment

Some hypertensive patients with no apparent pre-existing renal disease have developed signs of functional renal impairment. If this occurs, treatment must be discontinued.Reinstitution of therapy at reduced dosage may be possible, or either of the components may be used appropriately alone.

Hypotension and fluid/electrolyte imbalance

Patients must be systematically monitored for clinical signs of fluid/electrolyte imbalance, which may occur during intercurrent diarrhoea or vomiting. Regular monitoring of plasma electrolytes must be undertaken in such patients.

Significant hypotension may require the initiation of intravenous isotonic saline.

Transient hypotension is not a contra-indication to continued treatment. After volume repletion and establishment of satisfactory blood pressure, treatment can be reinstituted, either at a lower dosage or either of the components may be used appropriately alone.

Risk of hypokalaemia

The combination of an ACE inhibitor and non-potassium-sparing diuretic does not preclude the development of hypokalaemia, in particular in diabetic or renally impaired patients. Plasma potassium must be regularly monitored.

Paediatric use

The safety and efficacy of this product have not been demonstrated in controlled studies in children.

4.5 Interaction with other medicinal products and other forms of interaction

RELATED TO ENALAPRIL

Some active substances or therapeutic classes may favour the development of hyperkalaemia: potassium salts, potassium-sparing diuretics, ACE inhibitors, angiotensin II inhibitors, non-steroidal anti-inflammatory agents, heparins (low molecular weight or unfractionned), ciclosporin and tacrolimus, trimethoprim.

The occurrence of hyperkalaemia may depend on the existence of associated risk factors.

This risk is increased in combination with the above-mentioned medicinal products.

Not recommended combinations

- Potassium-sparing diuretics alone or in combination: amiloride, potassium canrenoate, spironolactone, triamterene, potassium (salts) Hyperkalaemia (potentially lethal), especially in conjunction with renal impairment (additive hyperkalaemic effects)

ACE inhibitors must not be associated with hyperkalaemic substances, except in hypokalaemia.

- Estramustine:

Risk of increased adverse effects such as angioneurotic oedema (angioedema).

Combinations requiring precautions for use

- Antidiabetic agents (insulin, hypoglycaemic sulphonamides):

The use of ACE inhibitors may increase the hypoglycaemic effect in diabetic patients treated with insulin or hypoglycaemia sulphonamides.

Hypoglycaemic episodes appear to be rare (improved glucose tolerance which could lead to reduced need for insulin).

Self-monitoring of glycaemia should be reinforced.

- Non-potassium-sparing diuretics:

Risk of sudden hypotension and/or acute renal impairment on initiation of treatment with an ACE inhibitor in patients with pre-existing salt/volume depletion

In arterial hypertension, when prior diuretic therapy has caused salt/volume depletion, either the diuretic must be discontinued before initiating the ACE inhibitor, in which case a non-potassium-sparing diuretic can be thereafter reintroduced or the ACE inhibitor must be initiated with a low dosage and progressively increased.

- In diuretic-treated congestive heart failure, the ACE inhibitor must be initiated at a very low dosage, possibly after reducing the dosage of the associated non-potassium-sparing diuretic.

In all cases, renal function (creatinine levels) must be monitored during the first few weeks of ACE inhibitor therapy.

RELATED TO HYDROCHLOROTHIAZIDE

Not recommended associations

- Sultopride:

Increased risk of ventricular arrhythmia, especially torsade de pointes (hypokalaemia favours the occurrence of this adverse reaction).

Combinations requiring precautions for use

- Substances that cause torsade de pointes (except sultopride):

Class IA antidysrhythmic agents (quinidine, hydroquinidine, disopyramide); class III antidysrhythmic agents (amiodarone, dofetilide, ibutilide, sotalol); some neuroleptics (chlorpromazine, cyamemazine, levomepromazine, thioridazine, trifluoperazine), benzamides (amisulpride, sulpiride, tiapride), butyrophenones (droperidol, haloperidol), other neuroleptics (pimozide); other substances such as bepridil, cisapride, diphemanil, IV erythromycin, halofantrine, mizolastine, moxifloxacin, pentamidine, sparfloxacin, IV vincamine, methadone.

Increased risk of ventricular arrhythmia, especially torsade de pointes (hypokalaemia favours the occurrence of this adverse reaction).

Hypokalaemia must be corrected before administration, and clinical, electrolyte and electrocardiographic monitoring instituted.

- Other hypokalaemic agents:

amphotericin B (intravenous), glucocorticoids (systemic), tetracosactide, stimulant laxatives.

Increased risk of hypokalaemia (additive effect).

Potassium levels must be monitored and, if necessary, corrected. Take particularly into account with concomitant digitalis therapy. Use non-stimulant laxatives.

- Digitalis glycosides:

Hypokalaemia favouring the toxic effects of digitalis glycosides.

Monitor potassium and possibly ECG.

- Metformin:

Metformin-induced lactic acidosis may be triggered by possible functional renal impairment induced by diuretics, especially loop diuretics.

Metformin must not be used when creatinine levels exceed 15 mg/l (135 micromol/l) in men and 12 mg/l (110 micromol/l) in women.

- Iodinated contrast media:

Increased risk of acute renal failure, in particular when high doses of iodinated contrast media are used, in patients dehydrated as a consequence of diuretic use.

Patients must be re-hydrated before administration of the iodinated product.

- Carbamazepine:

Risk of symptomatic hyponatraemia.

Clinical and biological monitoring. If possible, use another class of diuretics.

Combinations to be taken into account

- Calcium (salts):

Risk of hypercalcaemia through decreased urinary calcium excretion.

- Ciclosporin:

Risk of increased creatinine levels without alteration of plasma ciclosporin concentration, even in the absence of salt/volume depletion.

INTERACTIONS COMMON TO ENALAPRIL AND HYDROCHLOROTHIAZIDE

Not recommended combinations

Lithium:

Increased lithium concentration, potentially to toxic levels (decreased renal lithium excretion).

- Alpha-blocking agents used as anti-hypertensive drugs: prazosin, timazosin, urapidal: increased antihypertensive effect. Increased risk of orthostatic hypotension (additive effect).

Combinations requiring precautions for use

- Non-steroidal anti-inflammatory agents (NSAIDs, systemic), including selective cyclooxygenase (COX) 2 inhibitors, high-dose acetylsalicylic acid (aspirin) (≥ 3 g/day):

Acute renal failure in at-risk patients (elderly and/or dehydrated) through reduced glomerular filtration (NSAID-induced inhibition of vasodilating prostaglandins).

Also reduced antihypertensive effect.

Hydrate the patient; monitor renal function at the beginning of treatment.

- Baclofen: Increased antihypertensive effect.

Monitor blood pressure and adapt antihypertensive dosage if necessary.

Combinations to be taken into account

- Amifostine: Increased antihypertensive effect.

- Tricyclic antidepressants, neuroleptics: Increased antihypertensive effect and risk of orthostatic hypotension (additive effect).

- Corticosteroids, tetracosactide (systemic) (except hydrocortisone used as a substitute in Addison's disease):

Reduced antihypertensive effect (corticosteroid-induced salt/volume retention).

Alpha-blockers agents used in urology: alfuzosin, doxazosin, prazosin, tamsulosin, terazosin: increased hypotensive effect. Increased risk of ortostatic hypotension (additive effect).

4.6 Pregnancy and lactation

Given the effects of the individual components in this combination product on pregnancy and lactation:

Enalapril/HCT is not recommended during the first trimester of pregnancy. Enalapril/HCT is contraindicated during the second and third trimesters of pregnancy.

Enalapril/HCT is contraindicated during lactation. A decision should therefore be made whether to discontinue nursing or to discontinue Enalapril/HCT taking account the importance of this therapy for the mother.

Pregnancy

Linked to enalapril

The use of ACE inhibitors is not recommended during the first trimester of pregnancy (see section 4.4). The use of ACE inhibitors is contra-indicated during the 2nd and 3rd trimester 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. Unless continued ACE inhibitor 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 ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started.

Exposure to ACE inhibitor therapy during the second and third trimesters is known to induce human foetoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (see section 5.3). Should exposure to ACE inhibitor have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Infants whose mothers have taken ACE inhibitors should be closely observed for hypotension (see sections 4.3 and 4.4).

Linked to 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 trimester may compromise foeto-placental 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 preeclampsia 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.

Lactation

Both enalapril and hydrochlorothiazide are excreted in breast milk.

Enalapril

Limited pharmacokinetic data demonstrate very low concentrations in breast milk (see section 5.2). Although these concentrations seem to be clinically irrelevant, the use of enalapril in breastfeeding is not recommended for preterm infants and for the first few weeks after delivery, because of the hypothetical risk of cardiovascular and renal effects and because there is not enough clinical experience. In the case of an older infant, the use of enalapril in a breast-feeding mother may be considered if this treatment is necessary for the mother and the child is observed for any adverse effect.

Hydrochlorothiazide

Thiazides during breast feeding have been associated with decrease or even suppression of milk lactation. Hypersensitivity to sulphonamide-derived drugs, hypokalaemia and nuclear icterus might occur.

A decision should be made whether to discontinue nursing or to discontinue therapy taking into account the importance of this therapy for the mother.

4.7 Effects on ability to drive and use machines

When driving vehicles or operating machines it should be taken into account that occasionally vertigo or fatigue may occur (see section 4.8).

4.8 Undesirable effects

RELATED TO ENALAPRIL

Undesirable effects reported for enalapril include: Very common (> 1/10), Common (≥ 1/100 to < 1/10), Uncommon (≥ 1/1000 to < 1/100), Rare (≥ 1/10,000 to < 1/1000), Very rare (< 10, 000), Not known (cannot be estimated from the available data)

Blood and lymphatic system disorders:

uncommon: anaemia (including aplastic and haemolytic)

rare: neutropenia, decreases in haemoglobin, decreases in haematocrit, thrombocytopenia, agranulocytosis, myelosuppression, pancytopenia, lymphadenopathy, autoimmune diseases.

Metabolic and nutrition disorders:

uncommon: hypoglycemia (see section 4.4, diabetic patients).

Nervous system and psychiatric disorders

Common; headache, depression

Uncommon: confusion, somnolence, insomnia, nervousness, paraesthesia, vertigo

Rare: dream abnormality, sleep disorders

Eye disorders:

very common: blurred vision.

Cardiac and vascular disorders:

very common: dizziness

common: hypotension (including orthostatic hypotension), syncope, myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in risk patients (see section 4.4), chest pain, rhythm disorders, angina pectoris, tachycardia

uncommon: orthostatic hypotension, palpitations

rare: Raynaud's syndrome.

Respiratory, thoracic and mediastinal disorders:

very common: cough

common: dyspnea

uncommon: rhinorrhea, sore throat and hoarseness, bronchospasm/asthma

rare: pulmonary infiltrates, rhinitis, allergic alveolitis/eosinophilic pneumonia.

Gastrointestinal disorders:

very common: nausea

common: diarrhoea, abdominal pain, taste alteration

uncommon: ileus, pancreatitis, vomiting, dyspepsia, constipation, anorexia, gastric irritations, dry mouth, peptic ulcer

rare: stomatitis/aphthous ulcerations, glossitis.

Very rare: intestinal angioedema

Hepatobiliary disorders:

rare: hepatic failure, hepatitis - either hepatocellular or cholestatic, hepatitis including necrosis, cholestasis (including jaundice).

Skin and subcutaneous tissue disorders:

common: rash, hypersensitivity/angioneurotic oedema, angioneurotic oedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported (see 4.4).

uncommon: diaphoresis, pruritus, urticaria, alopecia

rare: erythema multiforme, Stevens-Johnson syndrome, exfoliative dermatitis, toxic epidermal necrolysis, pemphigus, erythroderma

A symptom complex has been reported which may include some or all of the following: fever, serositis, vasculitis, myalgia/myositis, arthralgia/arthritis, positive ANA, elevated ESR, eosinophilia, and leukocytosis. Rash, photosensitivity or other dermatologic manifestations may occur.

Renal and urinary disorders:

uncommon: renal dysfunction, renal failure, proteinuria

rare: oliguria.

Reproductive system and breast disorders:

uncommon: impotence

rare: gynaecomastia.

General disorders and administration site conditions:

very common: asthenia

common: fatigue

uncommon: muscle cramps, flushing, tinnitus, malaise, fever.

Investigations:

common: hyperkalaemia, increases in serum creatinine

uncommon: increases in blood urea content, hyponatraemia

rare: elevations of liver enzymes, elevations of serum bilirubin.

RELATED TO HYDROCHLOROTHIAZIDE

Infections and infestations:

Sialadenitis

Blood and lymphatic system disorders:

Leucopenia, neutropenia/agranulocytosis, thrombocytopenia, aplastic anaemia, haemolytic anaemia, bone marrow depression

Metabolism and nutrition disorders:

Anorexia, hyperglycaemia, glycosuria, hyperuricaemia, electrolyte imbalance (including hyponatraemia and hypokalemia), increases in cholesterol and triglycerides

Psychiatric disorders:

Restlessness, depression, sleep disturbances

Nervous system disorders:

Loss of appetite, paraesthesia, light-headedness

Eye disorders:

Xanthopsia, transient blurred vision

Ear and labyrinth disorders:

Vertigo

Cardiac disorders:

Postural hypotension, cardiac arrhythmias

Vascular disorders:

Necrotising angiitis (vasculitis, cutaneous vasculitis)

Respiratory, thoracic and mediastinal disorders:

Respiratory distress (including pneumonitis and pulmonary oedema)

Gastrointestinal disorders:

Gastric irritation, diarrhoea, constipation, pancreatitis

Hepato-billary disorders:

Jaundice (intrahepatic cholestatic jaundice)

Skin and subcutaneous tissue disorders:

Photosensitivity reactions, rash, cutaneous lupus erythematosus-like reactions, reactivation of cutaneous lupus erythematosus, urticaria, anaphylactic reactions, toxic epidermal necrolysis

Musculoskeletal, connective tissue and bone disorders:

Muscle spasm

Renal and urinary disorders:

Renal dysfunction, interstitial nephritis

General disorders and administration site conditions:

Fever, weakness

4.9 Overdose

No specific information is available with respect to the treatment of an overdose of Enalapril/HCT 20 mg/12.5 mg.

Symptoms of overdose are severe hypotension, shock, stupor, bradycadia, electrolyte disturbances and renal failure.

ASSOCIATED WITH ENALAPRIL

Limited data are available on overdose in humans.

Symptoms

The most prominent features of overdose reported to date are marked hypotension beginning some six hours after ingestion of the tablets, concomitant with blockade of the renin-angiotensin system, and stupor.

Symptoms associated with overdose of ACE inhibitors may include circulatory shock, electrolyte disturbances, renal failure, hyperventilation, tachycardia, palpitations, bradycardia, dizziness, anxiety and cough. Serum enalaprilat levels 100- and 200-fold higher than usually seen after therapeutic doses have been reported after ingestion of 300 mg and 440 mg of enalapril respectively.

ASSOCIATED WITH HYDROCHLOROTHIAZIDE

The signs of acute intoxication are primarily related to fluid/electrolyte imbalance (hyponatramia, hypokalaemia).

In addition to the expected diuresis, overdose of thiazides may produce varying degrees of lethargy, which may progress to coma within a few hours, with minimal depression of respiration and cardiovascular function, and without evidence of serum electrolyte changes or dehydration. The mechanism of thiazide-induced CNS depression is unknown.

Gastrointestinal irritation in BUN has been reported, and serum electrolyte changes may occur, especially in patients with impaired renal function.

Clinically, nausea, vomiting, hypotension, cramps, dizziness, somnolence, confusional states, polyuria or oliguria to the point of anuria (through hypovolaemia) may occur.

COMBINATION

Treatment is symptomatic and supportive. Treatment with Enalapril/HCT 20 mg/12.5 mg should be discontinued and the patient should be carefully monitored. Recommended measures include induction of vomiting, administration of activated charcoal and administration of a laxative and/or gastric lavage if the tablets were taken recently. Any dehydration, disturbances in the electrolyte balance and hypotension should be treated in an appropriate manner. Enalaprilat can be eliminated from blood circulation via haemodialysis (see section 4.4). The extent to which hydrochlorothiazide is removed is not established.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ACE inhibitors and diuretics

ATC code: C09B A02

Pharmacological mechanism of action

ASSOCIATED WITH ENALAPRIL

Enalapril maleate is the maleate salt of enalapril, a derivative of two amno-acids , Lalanine and L-proline. Angiotensin converting enzyme (ACE) is a peptidyl dipeptidase which catalyses the conversion of angiotensin I to the pressor substance angiotensin II. After absorbtion, enalapril is hydrolysed to enalaprilat, which inhibits ACE. Inhibition of ACE results in decreased plasma angiotensin II, which leads to increased plasma rennin activity (due to removal of negative feedback of rennin release), and decreased aldosterone secretion.

ACE is identical to kininase II. Thus enalapril may also block the degradation of bradykinin, a potent vasodepressor peptide. However, the role that this plays in the therapeutic effects of enalapril remains to be elucidated.

ASSOCIATED WITHN HYDROCHLOROTHIAZIDE

Hydrochlorothiazide is a thiazide diuretic which acts by inhibiting fluid-expelling and blood pressure-lowering agent which increase the tubular re-absorption of sodium in the cortical diluting segment.

It increases the urinary excretion of sodium and chloride and, to a lesser degree, the excretion of potassium and magnesium, thus increasing diuresis and exerting an antihypertensive effect.

Characteristics of the antihypertensive therapy

While the mechanism through which enalparil lowers blood pressure is believed to be primarily suppression of the renin-angiotensin aldosterone system, enalapril is antihypertensive even in patients with low-renin hypertension.

Administration of enalapril to patients with hypertension results in a reduction of both supine and standing blood pressure without a significant increase in heart rate.

Symptomatic postural hypotension is infrequent. In some patients the development of optimal blood pressure reduction may require several weeks of therapy. Abrupt withdrawal of enalapril has not been associated with rapid increase in blood pressure.

Effective inhibition of ACE activity usually occurs 2 to 4 hours after oral administration of an individual dose of enalapril. Onset of antihypertensive activity was usually seen at one hour, with peak reduction of blood pressure achieved by 4 to 6 hours after administration. The duration of effect is dose-related. However, at recommended doses, antihypertensive and haemodynamic effects have been shown to be maintained for at least 24 hours.

In haemodynamic studies in patients with essential hypertension, blood pressure reduction was accompanied by a reduction in peripheral arterial resistance with an increase in cardiac output and little or no change in heart rate. Following administration of enalapril there was an increase in renal blood flow; glomerular filtration rate was unchanged. There was no evidence of sodium or water retention. However, in patients with low pre-treatment glomerular filtration rates, the rates were usually increased.

In short-term clinical studies in diabetic and non-diabetic patients with renal disease, decreases in albuminuria and urinary excretion of IgG and total urinary protein were seen after the administration of enalapril.

When given together with thiazide-type diuretics, the blood pressure-lowering effects of enalapril are at least additive. Enalapril may reduce or prevent the development of thiazide-induced hypokalaemia.

ASSOCIATED WITH HYDROCHLROTHIAZIDE

The time to onset of diuretic activity is approximately 2 hours. Diuretic activity reaches a peak after 4 hours and is maintained for 6 to 12 hours.

Above a certain dose, thiazide diuretics reach a plateau in terms of therapeutic effect whereas adverse reactions continue to multiply. When treatment is ineffective, increasing the dose beyond recommended doses serves no useful purpose and often gives rise to adverse reactions.

ASSOCIATED WITH THE COMBINATION

In clinical studies, the concomitant administration of enalapril and hydrochlorothiazide reduced blood pressure more significantly than either substance alone.

The administration of enalapril inhibits the renin-angiotensin-aldosterone system and tends to reduce the hydrochlorothiazide-induced potassium.

Combination of an ACE inhibitor with a thiazide diuretic produces a synergistic effect and also lessens the risk of hypokalaemia provoked by the diuretic alone.

5.2 Pharmacokinetic properties

Co-administration of enalapril and hydrochlorothiazide in various doses has little or no effect on the bioavailability of these two substances.

ASSOCIATED WITH ENALAPRIL

Absorption

Oral enalapril is rapidly absorbed, with peak serum concentrations of enalapril occurring within 1 hour. Based on urinary recovery, the extent of absorption of enalapril from oral enalapril maleate is approximately 60%. The absorption of oral enalapril is not influenced by the presence of food in the gastrointestinal tract.

Distribution

Following absorption, oral enalapril is rapidly and extensively hydrolysed to enalaprilat, a potent angiotensin converting enzyme inhibitor. Peak serum concentrations of enalaprilat occur 3 to 4 hours after an oral dose of enalapril maleate. The effective half-life for accumulation of enalapril following concentrations of enalaprilat were reached after four days of treatment.

Over the range of concentrations which are therapeutically relevant, enalapril binding to human plasma proteins does not exeed 60%

Biotransformation

Except for conversion to enalaprilat, there is no evidence for significant metabolism of enalapril.

Elimination

Excretion of enalaprilat is primarily renal. The principal components in urine are enalaprilat, accounting for about 40% of the dose, and intact enalapril (about 20%).

Renal impairment

The exposure of enalapril and enalaprilat is increased in patients with renal insufficiency. In patients with mild to moderate renal insufficiency (creatanince clearance 40-60 ml/min) steady state AUC of enalaprilat was approximately two-fold higher than in patients with normal renal function after administration of 5 mg once daily. In severe renal impairment (creatinine clearance ≤30 ml/min), AUC was increased approximately 8-fold. The effective half-life of enalaprilat following multiple doses of enalapril maleate is prolonged at this level of renal insufficiency and time to steady state is delayed. (See section 4.2, Dosage in renal Insufficiency).

Enalaprilat may be removed from the general circulation by hemodialysis. The dialysis clearance is 62 ml/min.

Lactation

After a single 20 mg oral dose in five postpartum women, the average peak enalapril milk level was 1.7μg/L (range 0.54 to 5.9 μg/L) at 4 to 6 hours after the dose. The average peak enalaprilat level was 1.7μg/L (range 1.2 to 2.3μg/L); peaks occurred at various times over the 24-hour period. Using the peak milk level data, the estimated maximum intake of an exclusively breastfed infant would be about 0.16% of the maternal weightadjusted dosage. A woman who had been taking oral enalapril 10 mg daily for 11 months had peak enalapril milk levels of 2 μg/L 4 hours after a dose and peak enalaprilat levels of 0.75 μg/L about 9 hours after the dose. The total amount of enalapril and enalaprilat measured in milk during the 24 hour period was 1.44μg/L and 0.63 μg/L of milk respectively. Enalaprilat milk levels were undetectable (<0.2μg/L) 4 hours after a single dose of enalapril 5 mg in one mother and 10mg in two mothers; enalapril levels were not determined.

ASSOCIATED WITH HYDROCHLOROTHIAZIDE

Absorption

Oral absorption of hydrochlorothiazide is relatively rapid.

The bioavailability of hydrochlorothiazide varies between 60 and 80%. The time to peak plasma concentration (Tmax) varies between 1.5 and 5 hours, with a mean of about 4 hours.

Distribution

Protein binding is approximately 40%.

The mean plasma half-life in fasted individuals has been reported to be 5 to 15 hours.

Elimination

Hydrochlorothiazide is eliminated rapidly by the kidney and excreted unchanged (> 95%) in the urine. At least 61% of the oral dose is eliminated unchanged within 24 hours.

In renal and cardiac impairment, as in the elderly, the renal clearance of hydrochlorothiazide is reduced, and the elimination half-life increased. Elderly subjects also show increased peak plasma concentrations.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential.

Reproductive toxicity studies suggest that enalapril has no effects on fertility and reproductive performance in rats, and is not teratogenic. In a study in which female rats were dosed prior to mating through gestation, an increased incidence of rat pup deaths occurred during lactation.

The compound has been shown to cross the placenta and is secreted in milk.

Angiotensin converting enzyme inhibitors, as a class, have been shown to be fetotoxic (causing injury and/or death to the fetus) when given in the second or third trimester.

Hydrochlorothiazide crosses the placental but not the blood-brain barrier.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Maize starch
Pregelatinised starch (maize)
Sodium hydrogen carbonate
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

2 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Oriented Polyamide (OPA)/Alu/PVC cold formable foil/Aluminium foil blister packs containing 14, 20, 28, 28 (4x7), 30, 49, 49 (49x1), 50, 56, 60, 90, 98, 98 (14x7) and 100 tablets. Hospital packs of 50 and 300 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

Teva Pharma B.V.
Computerweg 10
3542 DR Utrecht
The Netherlands

8 MARKETING AUTHORISATION NUMBER

PA 749/29/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 1st June 2007.

10 DATE OF REVISION OF THE TEXT

April 2009