



The European Agency for the Evaluation of Medicinal Products
Pre-authorisation Evaluation of Medicines for Human Use

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COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP)
SUMMARY INFORMATION ON REFERRAL OPINION FOLLOWING ARBITRATION
PURSUANT TO ARTICLE 30 OF COUNCIL DIRECTIVE 2001/83/EC FOR

Ecazide and associated names

International NonProprietary Name (INN): captopril/hydrochlorothiazide

BACKGROUND INFORMATION

Captopril is a highly specific, competitive inhibitor of angiotensin-I converting enzyme, belonging to the category of ACE inhibitors. Hydrochlorothiazide is a thiazide diuretic. Hydrochlorothiazide has been widely used as an antihypertensive agent and captopril has also been indicated in the treatment of hypertension, among others. The addition of a thiazide diuretic to an ACE inhibitor produces at least an additive antihypertensive effect. The combination product captopril/ hydrochlorothiazide got the first national authorisation in 1984 and has since been registered in all EU countries in the second line treatment of hypertension, i.e. in patients who did not respond sufficiently to monotherapy.

From the registrations in Member States, different Summaries of Product Characteristics have been issued, based on national, divergent decisions. On 24 August 2000, France presented to the EMA a referral under Article 30 of Directive 2001/83/EC¹.

The referral procedure started on 1 March 2001 in order to harmonise the Summaries of Product Characteristics (SPC) within the Member States and Norway and Iceland. The CPMP having considered the Rapporteur and the Co-Rapporteur assessment reports, scientific discussion within the Committee and comments from the Marketing Authorisation Holders, was of the opinion that the benefit/risk ratio of captopril/hydrochlorothiazide is considered to be favourable for the agreed indications. The CPMP issued a positive opinion, on 25 April 2002, recommending the harmonisation of the SPC for Ecazide and associated names. The grounds for referral are appended to this report.

An overall summary of the scientific evaluation is provided together with the amended summary of product characteristics.

A Decision was issued by the European Commission on 22 August 2002.

¹ Corresponding to Article 11 of Directive 75/319/EEC, for referrals presented before 18 December 2001
Public

SCIENTIFIC CONCLUSIONS

Overall Summary of the Scientific Evaluation of Ecazide and Associated names

- Quality issues

No significant issues relating to Quality were identified.

The pharmaceutical particulars of the SPC were harmonised, except the sections, which need to be introduced nationally by the Member States when implementing the harmonised SPC (sections 6.1, 6.3, 6.4 and 6.5).

- Efficacy issues

The divergences that previously existed across the SPCs of EU Member States included:

Section 4.1 Therapeutic Indications

Captopril/Ecazide is approved for the second-line treatment of hypertension, however there was a disharmony in the labelling relating to;

- Whether or not treatment should only be initiated "after failure of captopril or ACE-inhibitor therapy", "after failure of a monotherapy or other treatment in general" or "after failure of captopril or hydrochlorothiazide/diuretic"
- In some Member States, the fixed combination is currently only indicated in patients who are already stabilised on the individual components.
- In some SPCs the lower strength combination (25/12,5) is currently indicated in elderly and other patients requiring low doses, whereas in some the 50/15 combination is indicated for patients requiring a low dose of diuretic.

After an assessment of the documentation provided by the MAH and an evaluation of the current EU-wide clinical practices relating to the use of Ecazide, the following was considered to be the most suitable harmonised Section 4.1 indications text:

4.1 Therapeutic indications

Treatment of essential hypertension.

This fixed dose combination is indicated in patients whose blood pressure is not adequately controlled by captopril alone or hydrochlorothiazide alone.

Section 4.2. Posology and method of administration

The MAH was requested to substantiate scientifically the divergent information across member states and justify a proposed common wording, especially with regard to recommendations for the initiation of treatment and the adjustment of posology in the various targeted sub-populations (adults, patients with renal impairment, elderly, children if relevant).

In the proposed harmonised SPC, the 4 dosages (25/12,5 mg, 25/25 mg, 50/15 mg, 50/25 mg) are included in the therapeutic dose regimen.

After an assessment of the documentation provided by the MAH and an evaluation of the current EU-wide clinical practices relating to the use of Ecazide the following was considered to be the most suitable harmonised Section 4.2 Posology text.

<Ecazide> can be administered in a single or two divided doses/day with or without food in patients whose blood pressure is not adequately controlled by captopril alone (or hydrochlorothiazide alone.) A maximum daily dose of 100 mg captopril/30 mg hydrochlorothiazide should not be exceeded. If satisfactory reduction of blood pressure has not been achieved, additional antihypertensive medication may be added (see 4.5).

Adults: the administration of the fixed combination of captopril and hydrochlorothiazide is usually recommended after dosage titration with the individual components. The usual maintenance dose is 50/25 mg, once a day, in the morning. When clinically appropriate a direct change from monotherapy to the fixed combination may be considered. The 25/25 mg strength may be used once a day for patients whose blood pressure is not adequately controlled by hydrochlorothiazide 25 mg monotherapy and before titration of the captopril component. The 50/25mg and 25/25mg strengths are intended to be used once daily as two tablets would result in an inappropriately high dose of hydrochlorothiazide (50mg/day). The 50/15 mg strength may be administered to start the fixed combination in patients whose blood pressure is not adequately controlled by 50 mg captopril monotherapy, and/or when a lower dose of hydrochlorothiazide is preferred.

Renal impairment: Creatinine clearance between 30 and 80 ml/min: the initial dose is usually 25/12.5 mg once a day, in the morning.

The combination captopril/hydrochlorothiazide is contraindicated in patients with severe renal impairment (creatinine clearance < 30 ml/min).

Special populations: in salt/volume depleted patients, elderly patients, and diabetic patients, the usual starting dose is 25/12.5 mg once a day.

Children: the safety and effectiveness of Ecazide in children has not been established.

- Safety issues

Section 4.3. Contra-indications

The contraindications text was considered to differ to a large extent between Member States. The MAH was requested to propose and scientifically justify a common EU wide approach.

After an assessment of the documentation provided by the MAH and an evaluation of the current EU-wide clinical practices relating to the use of Ecazide, the most suitable harmonised Section 4.3

Contraindications text was approved. The text approved in the harmonised SPC is not so dissimilar to the currently approved SPCs that it will significantly change clinical practices.

Section 4.4. Special warnings and precautions for use

After an assessment of the documentation provided by the MAH and an evaluation of the current EU-wide clinical practices relating to the use of Ecazide, the most suitable harmonised Section 4.4 Special Warnings and Precautions for Use text was approved. The text in the harmonised SPC is not so dissimilar to the currently approved SPCs that it will significantly change clinical practices

All other sections of the SPC were harmonised as a result of the referral procedure (except See Below; Administrative Issues).

- Administrative issues

Other sections of the SPC which were not harmonised and which need to be introduced nationally by the Member States when implementing the harmonised SPC are the following: MAH, MA number, date of first authorisation/renewal of authorisation, Date of revision of the text.

Benefit/Risk considerations

Based on the documentation submitted by the MAH and the scientific discussion within the Committee, the CPMP considered that the benefit/risk ratio of Ecazide is favourable for use relating to hypertension.

GROUNDINGS FOR AMENDMENT OF THE SUMMARIES OF PRODUCT CHARACTERISTICS

Whereas,

- the scope of the referral was the harmonisation of the Summaries of Products Characteristics,
- the Summary of Products Characteristic proposed by the Marketing Authorisation Holders has been assessed based on the documentation submitted and the scientific discussion within the Committee,

the CPMP has recommended the amendment of the Marketing Authorisations for which the Summary of Product Characteristics is set out in Annex III of the Opinion. The major divergences identified at the start of the referral have been resolved.

ANNEX III

SUMMARY OF PRODUCT CHARACTERISTICS

Note: This SPC is the one that was annexed to the Commission Decision concerning this referral for arbitration; the text was valid at that time.

It is not subsequently maintained or updated by the EMEA, and therefore may not necessarily represent the current text.

1. NAME OF THE MEDICINAL PRODUCT

<Ecazide and associated names – see Annex I> <STRENGTH> mg tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains (STRENGTH) mg captopril and (STRENGTH) mg hydrochlorothiazide.
For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of essential hypertension.

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4.2 Posology and method of administration

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Adults: the administration of the fixed combination of captopril and hydrochlorothiazide is usually recommended after dosage titration with the individual components. The usual maintenance dose is 50/25 mg, once a day, in the morning. When clinically appropriate a direct change from monotherapy to the fixed combination may be considered. The 25/25 mg strength may be used once a day for patients whose blood pressure is not adequately controlled by hydrochlorothiazide 25 mg monotherapy and before titration of the captopril component. The 50/25mg and 25/25mg strengths are intended to be used once daily as two tablets would result in an inappropriately high dose of hydrochlorothiazide (50mg/day). The 50/15 mg strength may be administered to start the fixed combination in patients whose blood pressure is not adequately controlled by 50 mg captopril monotherapy, and/or when a lower dose of hydrochlorothiazide is preferred.

Renal impairment: Creatinine clearance between 30 and 80 ml/min: the initial dose is usually 25/12.5 mg once a day, in the morning.

The combination captopril/hydrochlorothiazide is contraindicated in patients with severe renal impairment (creatinine clearance < 30 ml/min).

Special populations: in salt/volume depleted patients, elderly patients, and diabetic patients, the usual starting dose is 25/12.5 mg once a day.

Children: the safety and effectiveness of <Ecazide> in children has not been established.

4.3 Contraindications

- History of hypersensitivity to captopril, to any of the excipients or any other ACE inhibitor.
- History of hypersensitivity to hydrochlorothiazide or other sulphonamide-derived drugs.
- History of angioedema associated with previous ACE inhibitor therapy.
- Hereditary/idiopathic angioneurotic oedema.
- Severe renal impairment (creatinine clearance < 30 ml/min).
- Severe hepatic impairment.

- Second and third trimester of pregnancy (see 4.6).
- Lactation (see 4.6).

4.4 Special warnings and special precautions for use

CAPTOPRIL

Hypotension: rarely hypotension is observed in uncomplicated hypertensive patients.

Symptomatic hypotension is more likely to occur in hypertensive patients who are volume and/or sodium depleted by vigorous diuretic therapy, dietary salt restriction, diarrhoea, vomiting, or haemodialysis. Volume and/or sodium depletion should be corrected before the administration of an ACE inhibitor and a lower starting dose should be considered.

As with any antihypertensive agent, excessive blood pressure lowering in patients with ischaemic cardiovascular or cerebrovascular disease may increase the risk of myocardial infarction or stroke. If hypotension develops, the patient should be placed in a supine position. Volume repletion with intravenous normal saline may be required.

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.

Angioedema: angioedema of the extremities, face, lips, mucous membranes, tongue, glottis or larynx may occur in patients treated with ACE inhibitors particularly during the first weeks of treatment. However, in rare cases, severe angioedema may develop after long-term treatment with an ACE inhibitor. Treatment should be discontinued promptly. Angioedema involving the tongue, glottis or larynx may be fatal. Emergency therapy should be instituted. The patient should be hospitalised and observed for at least 12 to 24 hours and should not be discharged until complete resolution of symptoms has occurred.

Cough: cough has been reported with the use of ACE inhibitors. Characteristically, the cough is non-productive, persistent and resolves after discontinuation of therapy.

Hepatic failure: rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice 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.

Hyperkalaemia: elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including captopril. Patients at risk for the development of hyperkalaemia 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.

Aortic and mitral valve stenosis/Obstructive hypertrophic cardiomyopathy/Cardiogenic shock: ACE inhibitors should be used with caution in patients with left ventricular valvular and outflow tract obstruction and avoided in cases of cardiogenic shock and hemodynamically significant obstruction.

Neutropenia/Agranulocytosis: neutropenia/agranulocytosis, thrombocytopenia and anaemia have been reported in patients receiving ACE inhibitors, including captopril. In patients with normal renal function and no other complicating factors, neutropenia occurs rarely. Captopril 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 captopril is used in such patients, it is advised that white blood cell count and differential counts should be performed prior to therapy, every 2 weeks during the first 3 months of captopril therapy, and periodically thereafter. During treatment all patients should be instructed to report any sign of infection (e.g. sore throat, fever) when a differential white blood cell count should be performed.

Captopril and other concomitant medication (see 4.5) should be withdrawn if neutropenia (neutrophils less than 1000/mm³) is detected or suspected.

In most patients neutrophil counts rapidly return to normal upon discontinuing captopril.

Proteinuria: proteinuria may occur particularly in patients with existing renal function impairment or on relatively high doses of ACE inhibitors.

Total urinary proteins greater than 1 g per day were seen in about 0.7% of patients receiving captopril. The majority of patients had evidence of prior renal disease or had received relatively high doses of captopril (in excess of 150 mg/day), or both. Nephrotic syndrome occurred in about one-fifth of proteinuric patients. In most cases, proteinuria subsided or cleared within six months whether or not captopril was continued. Parameters of renal function, such as BUN and creatinine, were seldom altered in the patients with proteinuria.

Patients with prior renal disease should have urinary protein estimations (dip-stick on first morning urine) prior to treatment, and periodically thereafter.

Anaphylactoid reactions during desensitisation: sustained life-threatening anaphylactoid reactions have been rarely reported for patients undergoing desensitising treatment with hymenoptera venom while receiving another ACE inhibitor. In the same patients, these reactions were avoided when the ACE inhibitor was temporarily withheld, but they reappeared upon inadvertent rechallenge. Therefore, caution should be used in patients treated with ACE inhibitors undergoing such desensitisation procedures.

Anaphylactoid reactions during high-flux dialysis/lipoprotein apheresis membrane exposure: anaphylactoid reactions have been reported in patients haemodialysed with high-flux dialysis membranes or undergoing low-density lipoprotein apheresis with dextran sulphate absorption. In these patients, consideration should be given to using a different type of dialysis membrane or a different class of medication.

Surgery/Anaesthesia: hypotension may occur in patients undergoing major surgery or during treatment with anaesthetic agents that are known to lower blood pressure. If hypotension occurs, it may be corrected by volume expansion.

Diabetic patients: the glycaemia levels should be closely monitored in diabetic patients previously treated with oral antidiabetic drugs or insulin, namely during the first month of treatment with an ACE inhibitor.

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

HYDROCHLOROTHIAZIDE

Renal impairment: 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 (see 4.3).

Hepatic impairment: thiazides 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 coma (see 4.3).

Metabolic and endocrine effects: thiazide therapy may impair glucose tolerance. 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. Hyperuricaemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy.

Electrolyte imbalance: 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 captopril 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 4.5).

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

Thiazides may decrease urinary calcium excretion and cause an intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcaemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

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

Anti-doping test: hydrochlorothiazide contained in this medication could produce a positive analytic result in an anti-doping test.

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.

CAPTOPRIL/HYDROCHLOROTHIAZIDE COMBINATION

Pregnancy: <Ecazide> is not recommended during the first trimester of pregnancy (see 4.6.). If treatment is discontinued due to pregnancy the prescriber should decide whether treatment of hypertension should be continued.

Risk of hypokalaemia: the combination of an ACE inhibitor with a thiazide diuretic does not rule out the occurrence of hypokalaemia. Regular monitoring of kalaemia should be performed.

Combination with lithium: <Ecazide> is not recommended in association with lithium due to the potentiation of lithium toxicity (see 4.5).

Lactose: <Ecazide> contains lactose, therefore it should not be used in cases of congenital galactosaemia, glucose and galactose malabsorption or lactase deficiency syndromes (rare metabolic diseases).

4.5 Interaction with other medicinal products and other forms of interaction

CAPTOPRIL

Potassium sparing diuretics or potassium supplements: ACE inhibitors attenuate diuretic induced potassium loss. Potassium sparing diuretics (e.g. spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. If concomitant use is indicated because of demonstrated hypokalaemia they should be used with caution and with frequent monitoring of serum potassium (see 4.4).

Diuretics (thiazide or loop diuretics): prior treatment with high dose diuretics may result in volume depletion and a risk of hypotension when initiating therapy with captopril (see 4.4). The hypotensive effects can be reduced by discontinuation of the diuretic, by increasing volume or salt intake or by initiating therapy with a low dose of captopril. However, no clinically significant drug interactions have been found in specific studies with hydrochlorothiazide or furosemide.

Other antihypertensive agents: captopril has been safely co-administered with other commonly used antihypertensive agents (e.g. beta-blockers and long-acting calcium channel blockers). Concomitant use of these agents may increase the hypotensive effects of captopril. Treatment with nitroglycerine and other nitrates, or other vasodilators, should be used with caution.

Treatments of acute myocardial infarction: captopril may be used concomitantly with acetylsalicylic acid (at cardiologic doses), thrombolytics, beta-blockers and/or nitrates in patients with myocardial infarction.

Tricyclic antidepressants/Antipsychotics: ACE inhibitors may enhance the hypotensive effects of certain tricyclic antidepressants and antipsychotics (see 4.4). Postural hypotension may occur.

Allopurinol, procainamide, cytostatic or immunosuppressive agents: concomitant administration with ACE inhibitors may lead to an increased risk for leucopenia especially when the latter are used at higher than currently recommended doses.

Sympathomimetics: may reduce the antihypertensive effects of ACE inhibitors; patients should be carefully monitored.

Antidiabetics: pharmacological studies have shown that ACE inhibitors, including captopril, can potentiate the blood glucose-reducing effects of insulin and oral antidiabetics such as sulphonylurea in

diabetics. Should this very rare interaction occur, it may be necessary to reduce the dose of the antidiabetic during simultaneous treatment with ACE inhibitors.

HYDROCHLOROTHIAZIDE

Amphotericin B (parenteral), carbenoxolone, corticosteroids, corticotropin (ACTH) or stimulant laxatives: hydrochlorothiazide may intensify electrolyte imbalance, particularly hypokalaemia.

Calcium salts: increased serum calcium levels due to decreased excretion may occur when administered concurrently with thiazide diuretics.

Cardiac glycosides: enhanced possibility of digitalis toxicity associated with thiazide induced hypokalaemia.

Cholestyramine resin and colestipol: may delay or decrease absorption of hydrochlorothiazide. Sulphonamide diuretics should be taken at least one hour before or four to six hours after these medications.

Nondepolarising muscle relaxants (e.g. tubocurarine chloride): effects of these agents may be potentiated by hydrochlorothiazide.

Drugs associated with torsades de pointes: because of the risk of hypokalaemia, caution should be used when hydrochlorothiazide is coadministered with drugs associated with torsades de pointes, e.g. some antiarrhythmics, some antipsychotics and other drugs known to induce torsades de pointes.

CAPTOPRIL/HYDROCHLOROTHIAZIDE COMBINATION

Lithium: reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors. Concomitant use of thiazide diuretics may increase the risk of lithium toxicity and enhance the already increased risk of lithium toxicity with ACE inhibitors. The combination of captopril and hydrochlorothiazide with lithium is therefore not recommended and careful monitoring of serum lithium levels should be performed if the combination proves necessary.

Non-steroidal anti-inflammatory medicinal products: it has been described that non-steroidal anti-inflammatory medicinal products (NSAIDs) and ACE inhibitors exert an additive effect on the increase in serum potassium, whereas renal function may decrease. These effects are, in principle, reversible. Rarely, acute renal failure may occur, particularly in patients with compromised renal function such as the elderly or dehydrated. Chronic administration of NSAIDs may reduce the antihypertensive effect of an ACE inhibitor. The administration of NSAIDs may reduce the diuretic, natriuretic and antihypertensive effects of thiazide diuretics.

Clinical Chemistry

Captopril may cause a false-positive urine test for acetone. Hydrochlorothiazide may cause diagnostic interference of the bentiromide test. Thiazides may decrease serum PBI (Protein Bound Iodine) levels without signs of thyroid disturbance.

4.6 Pregnancy and lactation

Pregnancy: <Ecazide> is not recommended during the first trimester of pregnancy. When a pregnancy is planned or confirmed, an alternative treatment should be initiated as soon as possible. Controlled studies with ACE inhibitors have not been done in humans, but limited number of cases of first trimester exposures have not shown malformations.

<Ecazide> is contraindicated during the second and third trimesters of pregnancy. Prolonged captopril exposure during the second and third trimesters is known to induce toxicity in foetuses (decreased renal function, oligohydramnios, skull ossification retardation) and in neonates (neonatal renal failure, hypotension, hyperkalaemia) (see also 5.3).

Hydrochlorothiazide in case of prolonged exposure during the third trimester of pregnancy may cause a foeto-placental ischaemia and risk of growth retardation. Moreover, rare cases of hypoglycaemia and thrombocytopenia in neonates have been reported in case of exposure near the term.

Hydrochlorothiazide can reduce plasma volume as well as the uteroplacental blood flow.

Should exposure to <Ecazide> have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.

Lactation: <Ecazide> is contraindicated in the lactation period.

Both captopril and hydrochlorothiazide are excreted in human milk. Thiazides during breast feeding by lactating mothers have been associated with a decrease or even suppression of the milk lactation. Hypersensitivity to sulfonamide-derived drugs, hypokalaemia and nuclear icterus might occur. Because of the potential for serious adverse reactions in nursing infants from both drugs, a decision should be made whether to discontinue nursing or to discontinue therapy taking account the importance of this therapy to the mother.

4.7 Effects on ability to drive and use machines

As with other antihypertensives, the ability to drive and use machines may be reduced, e.g. at the start of the treatment or when the dose is modified, and also when used in combination with alcohol, but these effects depend on the individual's susceptibility.

4.8 Undesirable effects

CAPTOPRIL

Undesirable effects reported for captopril and/or ACE inhibitor therapy include:

Blood and lymphatic disorders:

very rare: neutropenia/agranulocytosis (see 4.4), pancytopenia particularly in patients with renal dysfunction (see 4.4), anaemia (including aplastic and haemolytic), thrombocytopenia, lymphadenopathy, eosinophilia, auto-immune diseases and/or positive ANA-titres.

Metabolism and nutrition disorders:

rare: anorexia

very rare: hyperkalaemia, hypoglycaemia (see 4.4)

Psychiatric disorders:

common: sleep disorders

very rare: confusion, depression.

Nervous system disorders:

common: taste impairment, dizziness

rare: drowsiness, headache and paraesthesia.

very rare: cerebrovascular incidents, including stroke, and syncope.

Eye disorders:

very rare: blurred vision.

Cardiac disorders:

uncommon: tachycardia or tachyarrhythmia, angina pectoris, palpitations

very rare: cardiac arrest, cardiogenic shock.

Vascular disorders:

uncommon: hypotension (see 4.4), Raynaud syndrome, flush, pallor.

Respiratory, thoracic and mediastinal disorders:

common: dry, irritating (non-productive) cough (see 4.4) and dyspnoea.

very rare: bronchospasm, rhinitis, allergic alveolitis/eosinophilic pneumonia.

Gastrointestinal disorders:

common: nausea, vomiting, gastric irritations, abdominal pain, diarrhoea, constipation, dry mouth

rare: stomatitis/apthous ulcerations

very rare: glossitis, peptic ulcer, pancreatitis.

Hepato-biliary disorders:

very rare: impaired hepatic function and cholestasis (including jaundice), hepatitis including necrosis, elevated liver enzymes and bilirubin.

Skin and subcutaneous tissue disorders:

common: pruritus with or without a rash, rash, and alopecia.

uncommon: angioedema (see 4.4)

very rare: urticaria, Stevens Johnson syndrome, erythema multiforme, photo-sensitivity, erythroderma, pemphigoid reactions and exfoliative dermatitis.

Musculoskeletal, connective tissue and bone disorders:

very rare: myalgia, arthralgia.

Renal and urinary disorders:

rare: renal function disorders including renal failure, polyuria, oliguria, increased urine frequency
very rare: nephrotic syndrome.

Reproductive system and breast disorders:

very rare: impotence, gynaecomastia.

General disorders:

uncommon: chest pain, fatigue, malaise

very rare: fever.

Investigations:

very rare: proteinuria, eosinophilia, increase of serum potassium, decrease of serum sodium, elevation of BUN, serum creatinine and serum bilirubin, decreases in haemoglobin, haematocrit, leucocytes, thrombocytes, positive ANA-titre, elevated ESR.

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 hypokalaemia), 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 angitis (vasculitis, cutaneous vasculitis).

Respiratory, thoracic and mediastinal disorders:

respiratory distress (including pneumonitis and pulmonary oedema).

Gastrointestinal disorders:

gastric irritation, diarrhoea, constipation, pancreatitis.

Hepato-biliary 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:

fever, weakness.

4.9 Overdose

Symptoms of overdosage are: increased diuresis, electrolyte imbalance, severe hypotension, depression of consciousness (including coma), convulsions, paresis, cardiac arrhythmias, bradycardia, renal failure.

Measures to prevent absorption (e.g. gastric lavage, administration of absorbing agents and sodium sulfate within 30 minutes after intake) and hasten elimination should be applied if ingestion is recent. If hypotension occurs, the patient should be placed in the shock position and sodium chloride and volume supplementation should be given rapidly. Treatment with angiotensin-II can be considered. Bradycardia or extensive vagal reactions should be treated by administering atropine. The use of a

pacemaker may be considered. Constant monitoring of water, electrolyte and acid base balance, blood glucose is essential. In case of hypokalaemia, potassium substitution is necessary.

Captopril may be removed from circulation by haemodialysis. The degree to which hydrochlorothiazide is removed by haemodialysis has not been established.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ACE (Angiotensin-Converting-Enzyme) inhibitors, combinations, ATC code: C09BA01.

<Ecazide> is a combination of an ACE inhibitor, captopril, and an antihypertensive diuretic, hydrochlorothiazide. The combination of these agents has an additive antihypertensive effect, reducing blood pressure to a greater degree than either component alone.

- Captopril is an angiotensin converting enzyme (ACE) inhibitor, i.e. it inhibits ACE, the enzyme involved in the conversion of angiotensin I to angiotensin II - a vasoconstrictor which also stimulates aldosterone secretion by the adrenal cortex.

Such inhibition leads to:

- reduced aldosterone secretion,
- increased plasma renin activity, since aldosterone no longer exerts negative feedback,
- a drop in total peripheral resistance (with a preferential effect on muscles and kidneys) which is not accompanied by water and sodium retention or reflex tachycardia during long-term treatment. Captopril also exerts its antihypertensive effect in subjects with low or normal renin concentrations.

Captopril is effective at all stages of hypertension, i.e. mild, moderate or severe. A reduction in supine and standing systolic and diastolic blood pressures is observed.

After a single dose, the antihypertensive effect is evident fifteen minutes post-dose and reaches a maximum between 1 h and 1.5 h after administration of the drug. Its duration of action is dose-dependent and varies from 6 to 12 hours.

Blood pressure becomes normalised (seated DBP < 90 mmHg) in patients after two weeks to one month of treatment and the drug retains its effectiveness over the course of time. Patients are also classified as responders if seated DBP decreased by 10% or more from baseline-BP.

Rebound hypertension does not occur when treatment is discontinued.

The treatment of hypertension with captopril leads to an increase in arterial compliance, a rise in renal blood flow without any significant drop in the glomerular filtration rate, and a decrease in left ventricular hypertrophy.

- Hydrochlorothiazide is a thiazide diuretic which acts by inhibiting the reabsorption of sodium in the cortical diluting segment of renal tubules. It increases the excretion of sodium and chloride in urine and, to a lesser extent, the excretion of potassium and magnesium, thereby increasing urinary output and exerting an antihypertensive effect.

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.

- The concomitant administration of captopril and hydrochlorothiazide in clinical trials led to greater reductions in blood pressure than when either of the products was administered alone.

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

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

Captopril is quickly absorbed after oral administration and maximum serum concentrations are obtained around one hour after administration. Minimum mean absorption is approximately 75%. Peak plasma concentrations are reached within 60-90 minutes. The presence of food in the gastrointestinal tract reduces absorption by about 30-40%. Approximately 25-30% of the circulating drug is bound to plasma proteins. The apparent elimination half-life of unchanged captopril in blood is about 2 hours. Greater than 95% of the absorbed dose is eliminated in the urine within 24 hours; 40-50% is unchanged drug and the remainder are inactive disulphide metabolites (captopril disulphide and captopril cysteine disulphide). Impaired renal function could result in drug accumulation. Studies in animals indicate that captopril does not cross the blood-brain barrier to any significant extent.

Oral absorption of hydrochlorothiazide is relatively rapid. The mean plasma half-life in fasted individuals has been reported to be 5 to 15 hours. Hydrochlorothiazide is eliminated rapidly by the kidney, and excreted unchanged (> 95%) in the urine.

5.3 Preclinical safety data

Animal studies performed during organogenesis with captopril and/or hydrochlorothiazide have not shown any teratogenic effect but captopril has produced foetal toxicity in several species, including foetal mortality during late pregnancy, growth retardation and postnatal mortality in the rat. Preclinical data reveal no other specific hazard for human based on conventional studies of safety pharmacology, repeated dose toxicology, genotoxicity and carcinogenicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

[To be implemented locally]

6.2 Incompatibilities

[To be implemented locally]

6.3 Shelf life

[To be implemented locally]

6.4 Special precautions for storage

[To be implemented locally]

6.5 Nature and contents of container

[To be implemented locally]

6.6 Instructions for use and handling

[To be implemented locally]

7. MARKETING AUTHORISATION HOLDER

- 8. MARKETING AUTHORISATION NUMBER(S)**

- 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

- 10. DATE OF REVISION OF THE TEXT**