PROFESSIONAL INFORMATION

SCHEDULING STATUS:

S3

1. NAME OF THE MEDICINE

Enpresil Co 20/12,5 mg (tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains enalapril maleate 20 mg and hydrochlorothiazide 12,5 mg.

Excipients with known effect

Enpresil Co contains sugar (lactose monohydrate 130,10 mg/tablet)

Enpresil Co contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Pale yellow colour, circular, biconvex uncoated tablets with breakline on one side & plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Enpresil Co is indicated for the treatment of hypertension in patients where fixed combination treatment is considered more appropriate than monotreatment.

4.2 Posology and method of administration

Posology

Hypertension

The usual dosage is 1 tablet, administered once daily. If necessary, the dosage may be

increased to a maximum of 2 tablets, administered once daily

Special populations

Renal insufficiency

Thiazides may not be appropriate diuretics for use in patients with renal impairment and are ineffective at creatinine clearance values of 30 ml/min or below (i.e. moderate or severe renal insufficiency).

Enpresil Co is not be used as initial treatment in any patient with renal insufficiency.

In patients with creatinine clearance of >30 and <80 ml/min, Enpresil Co may be used but only after titration of the individual components.

Method of administration

For oral use.

4.3 Contraindications

- Hypersensitivity to enalapril maleate and hydrochlorothiazide, or to any of the ingredients listed in section 6.1.
- Severe renal impairment (creatinine clearance ≤ 30 ml/min).
- Anuria.
- History of angioneurotic oedema associated with previous ACE-inhibitor treatment or angiotensin receptor blockers (ARBs). These patients must never again be given these medicines.
- Hereditary or idiopathic angioedema.
- Hypertrophic obstructive cardiomyopathy (HOCM).
- Hypersensitivity to other sulfonamide-derived medicines.
- Pregnancy and breastfeeding.
- Severe hepatic impairment.
- Bilateral renal artery stenosis.

- Renal artery stenosis in patients with a single kidney.
- Aortic stenosis.
- Concomitant treatment with potassium sparing diuretics such as spironolactone, triamterene, amiloride.
- Porphyria.
- Lithium treatment; concomitant administration with Enpresil Co may lead to toxic blood concentrations of lithium.
- The concomitant use of Enpresil Co with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR <60 ml/min/1,73m^2) (see sections 4.5 and 5.1).
- Combination with sacubitril/valsartan due to the increased risk of angioedema. Do not administer Enpresil Co within 36 hours of switching to or from sacubitril/valsartan, a product containing a neprilysin inhibitor. (See sections 4.4 and 4.5).

4.4 Special warnings and precautions for use

Should a woman become pregnant while receiving Enpresil Co, the treatment must be stopped promptly and switched to a different class of antihypertensive medicines. Should a woman contemplate pregnancy, the doctor should institute alternative medications (see section 4.6).

Enalapril Maleate - Hydrochlorothiazide

Hypotension and Electrolyte Fluid Imbalance

Symptomatic hypotension is rarely seen in uncomplicated hypertensive patients.

In hypertensive patients receiving Enpresil Co, symptomatic hypotension is more likely to occur if the patient has been volume-depleted or salt-depleted, e.g., by diuretic treatment (which should be discontinued for 2 to 3 days prior to initiation of treatment with Enpresil Co), dietary salt restriction, diarrhoea or vomiting (see sections 4.5 and 4.8). In such patients, regular determination of serum electrolytes should be performed at pertinent intervals.

In hypertensive 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, hyponatraemia or functional renal impairment. In these patients, treatment should be started under medical supervision and the patients should be followed closely whenever the dose of Enpresil Co and/or diuretic is adjusted.
Similar deliberations may apply to patients with ischaemic 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 contra-indication 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, further lowering of systemic blood pressure may occur with Enpresil Co. This effect is foreseen, 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 Enpresil Co may be necessary.

Renal Function Impairment
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 on time and treated appropriately, renal failure is usually reversible when associated with treatment with enalapril.

Enpresil Co should not be administered to patients with renal insufficiency (creatinine clearance < 80 ml/min and > 30 ml/min) until titration of enalapril has shown the necessity for the dose present in this formulation (see section 4.2).

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 (see Special warnings and precautions for use, Enalapril Maleate, Renal Function Impairment; Hydrochlorothiazide, Renal Function Impairment in section 4.4). If this occurs, treatment with Enpresil Co should be discontinued. This situation should raise the possibility of underlying renal artery stenosis (see Special warnings and precautions for use, Enalapril Maleate, Renovascular Hypertension in section 4.4).

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 sections 4.5 and 5.1). If dual blockade treatment 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.

Hyperkalaemia

The combination of enalapril and a low-dose diuretic cannot exclude the possibility of hyperkalaemia developing (see Special warnings and precautions for use, Enalapril Maleate, Hyperkalaemia in section 4.4).

Lithium

The combination of lithium with enalapril and diuretic medicines is generally not recommended (see section 4.5).

Elderly

In both elderly and younger hypertensive patients, the efficacy and tolerability were similar, when enalapril maleate and hydrochlorothiazide are administered concomitantly.

Enalapril Maleate

Aortic Stenosis/Hypertrophic Cardiomyopathy

As with all vasodilators, 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 haemodynamically significant obstruction.

Renal Function Impairment

In patients with severe heart failure or underlying renal disease (including renal artery stenosis) renal failure has been reported in association with enalapril. If recognized and treated appropriately, renal failure when associated with treatment with enalapril is usually reversible (see section 4.2 and Special warnings and precautions for use, Enalapril Maleate-Hydrochlorothiazide, Renal Function Impairment; Hydrochlorothiazide, Renal Function Impairment in section 4.4).

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, treatment should be initiated under close medical supervision with low doses, careful titration, and monitoring of renal function.

Haemodialysis Patients

The use of enalapril is not indicated in patients requiring dialysis for renal failure. 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 medicine.

Kidney Transplantation

Treatment with enalapril is not recommended in patients with recent kidney transplantation, as there is no experience regarding the administration of enalapril in these patients.

Hepatic failure

ACE inhibitors have rarely 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 (see Special warnings and precautions for use, Hydrochlorothiazide, Hepatic Disease in section 4.4).

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 treatment, 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 and in a few cases, patients did not respond to intensive antibiotic treatment. If enalapril is used in such patients, periodic monitoring of white blood cell counts is recommended and patients should be instructed to report any sign of infection.

Hyperkalaemia

Elevations in serum potassium have been noticed in some patients treated with ACE

inhibitors, including enalapril.

Risk factors for the development of hyperkalaemia include those with renal insufficiency, worsening of renal function, age (>70 years), diabetes mellitus, intercurrent events in particular dehydration, acute cardiac decompensation, metabolic acidosis and concomitant use of potassium-sparing diuretics (e.g., spironolactone, eplerenone, triamterene, or amiloride), potassium supplements or potassium-containing salt substitutes; or those patients taking other medicines associated with increases in serum potassium (e.g., heparin, trimethoprim-containing products such as co-trimoxazole).

The use of potassium supplements, potassium-sparing diuretics, potassium-containing salt substitutes, or other medicines that may increase serum potassium, particularly in patients with impaired renal function may lead to a significant increase in serum potassium. Hyperkalaemia can cause serious, sometimes fatal, dysrhythmia.

Hypoglycaemia

Diabetic patients treated with oral antidiabetic medicines or insulin starting an ACE inhibitor should be told to closely monitor for hypoglycaemia, especially during the first month of combined use (see Special warnings and precautions for use, Hydrochlorothiazide, Metabolic and Endocrine Effects in section 4.4 and section 4.5).

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 maleate. This may occur at any time during treatment.

In such cases, Enpresil Co should be discontinued promptly and appropriate monitoring should be initiated to ensure complete disappearance of symptoms prior to discharging the patient. 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.

Fatalities have been reported (very rarely) due to angioedema associated with laryngeal oedema or tongue oedema.

If the tongue, glottis or larynx is affected, patients are likely to experience airway obstruction, especially those with a history of airway surgery. To ensure a patent airway, appropriate treatment and/or measures (which may include subcutaneous epinephrine solution 1:1000 (0 3 ml to 0 5 ml) should be administered promptly.

Black patients receiving ACE inhibitors have been reported to have a higher incidence of angioedema compared to white patients. However, in general it appears that Black people have an increased risk for angioedema.

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

Patients receiving an ACE inhibitor concomitantly with an mTOR (mammalian target of rapamycin) inhibitor (e.g. temsirolimus, sirolimus, everolimus) treatment may be at increased risk for angioedema.

Patients receiving ACE inhibitor concomitantly with neprilysin inhibitor treatment (e.g., sacubitril, racecadotril) may be at increased risk for angioedema (see section 4.5). The combination of enalapril with sacubitril/valsartan is contraindicated due to the increased risk of angioedema (see section 4.3). Sacubitril/valsartan must not be initiated until 36 hours after taking the last dose of enalapril treatment. If treatment with sacubitril/valsartan is stopped, enalapril treatment must not be initiated until 36 hours after the last dose of sacubitril/valsartan (see sections 4.3 and 4.5).

Anaphylactoid Reactions during Hymenoptera Desensitisation

Patients receiving ACE inhibitors during desensitisation with hymenoptera venom have rarely experienced life threatening anaphylactoid reactions. These reactions can be prevented by temporarily withholding ACE inhibitor treatment prior to each desensitisation.

Anaphylactoid Reactions during LDL-Apheresis

Patients receiving ACE inhibitors during low density lipoprotein (LDL)-apheresis with dextran sulfate have experienced life-threatening anaphylactic reactions rarely. These reactions can be prevented by temporarily withholding ACE inhibitor treatment prior to each apheresis.

Cough

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

Surgery/Anaesthesia

Enalapril blocks angiotensin II formation and therefore impairs the ability of patients undergoing major surgery or anaesthesia with medicines that produce hypotension to compensate via the renin-angiotensin system. Hypotension which occurs due to this mechanism can be corrected by volume expansion (see section 4.5).

Pregnancy

ACE inhibitors should not be introduced during pregnancy. 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 treatment should be initiated (see sections 4.3 and 4.6).

Ethnic Differences

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

Hydrochlorothiazide

Renal Function Impairment

Thiazides may not be appropriate diuretics for use in patients with renal impairment and are ineffective at creatinine clearance values of 30 ml/min or below (i.e., moderate or severe renal insufficiency) (see section 4.2 and Special warnings and precautions for use, Enalapril Maleate-Hydrochlorothiazide, Renal Function Impairment; Enalapril Maleate, Renal Function Impairment in section 4.4).

Enpresil Co should not be administered to patients with renal insufficiency (creatinine clearance ≤ 80 ml/min) until titration of the individual components has shown the necessity for the doses present in the combination tablet.

Hepatic Disease

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 Special warnings and precautions for use, Enalapril Maleate, Hepatic Failure in section 4.4).

Metabolic and Endocrine Effects

Thiazide treatment may impair glucose tolerance. Dosage adjustment of antidiabetic medicines, including insulin, may be necessary (see Special warnings and precautions for use, Enalapril Maleate, Diabetic Patients in section 4.4). Thiazides may decrease serum sodium, magnesium and potassium levels.

Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic treatment; however, at the 12,5 mg dose of hydrochlorothiazide minimal or no effect has been reported.

In clinical studies with 6 mg of hydrochlorothiazide no clinically significant effect on glucose, cholesterol, triglycerides, sodium, magnesium or potassium was reported.

Thiazide treatment may decrease urinary calcium excretion and cause an intermittent and minor elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcaemia may be evidence of latent hyperparathyroidism. Thiazides should be discontinued before testing parathyroid function.

Thiazide treatment may precipitate hyperuricaemia and/or gout in certain patients. This effect on hyperuricemia appears to be dose-related. Furthermore, enalapril may increase urinary uric acid and thus may attenuate the hyperuricaemic effect of hydrochlorothiazide.
Periodic determination of serum electrolytes should be performed at appropriate intervals for any patient receiving diuretic treatment.

Thiazide treatment can cause fluid or electrolyte imbalance (hypokalaemia, hyponatraemia, and hypochloremic alkalosis). Warning signs of fluid or electrolyte imbalance are xerostomia, thirst, weakness, lethargy, somnolence, restlessness, muscle pain or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

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

Hyponatraemia may occur in patients with oedema, in hot weather. Chloride deficiency is generally mild and does not usually require treatment.

Thiazide treatment may increase the urinary excretion of magnesium, which may result in hypomagnesaemia.

Anti-doping test

Hydrochlorothiazide can produce a positive analytic result in an anti-doping test.

Hypersensitivity

In patients receiving thiazide treatment, sensitivity reactions may occur with or without a history of allergy and bronchial asthma.

Aggravation or activation of systemic lupus erythematosus has been reported with the use of thiazide treatment.

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 exposure has been observed in two epidemiological studies based on the Danish National Cancer Registry. Photosensitizing actions of hydrochlorothiazide could act as a likely mechanism for NMSC.

Patients taking hydrochlorothiazide should be informed of the risk of NMSC and be 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 hydrochlorothiazide may also need to be reconsidered in patients who have experienced previous NMSC (see also section 4.8).

Paediatric population

Safety and efficacy in children has not been established.

Lactose

Enpresil Co contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the total lactase deficiency or glucose-galactose malabsorption should

not take Enpresil Co.

Sodium

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicines and other forms of interaction

Enalapril Maleate-Hydrochlorothiazide

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)

In clinical studies, dual blockade of the renin-angiotensin-aldosterone-system (RAAS) through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren has been shown to be 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 medicine (see sections 4.3, 4.4 and 5.1).

Other Antihypertensive Medicines

Concomitant use of other antihypertensive medicines may increase the hypotensive effects of enalapril and hydrochlorothiazide.

Concomitant use with nitroglycerin and other nitrates, or other vasodilators, may further reduce blood pressure.

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 further increase lithium levels and enhance the risk of lithium toxicity with ACE inhibitors.

Use of Enpresil Co with lithium is not recommended (see section 4.4).

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) including selective cyclooxygenase-2 (COX-2) inhibitors

Non-steroidal anti-inflammatory drugs (NSAIDs) including selective cyclooxygenase-2 inhibitors (COX-2 inhibitors) may diminish the effect of diuretics and other antihypertensive medicines. Therefore, the antihypertensive effect of angiotensin II receptor antagonists, ACE inhibitors or diuretics may be attenuated by NSAIDs including selective COX-2 inhibitors.

The coadministration of NSAIDs (including COX-2 inhibitors) and angiotensin II receptor antagonists or ACE inhibitors exert an additive effect on the increase in serum potassium, and may result in a worsening of renal function. These effects are usually reversible. Acute renal failure may occur (rarely), especially in patients with compromised renal function (such as the elderly or patients who are volume-depleted, including those on diuretic treatment). Therefore, the combination should be administered with caution in patients with compromised renal function.

Enalapril Maleate

Other Antihypertensive Medicines

Ganglionic blocking medicines or adrenergic blocking medicines in combination with enalapril should only be administered to the patient under careful observation.

Potassium-sparing Diuretics, Potassium Supplements, or other medicines that may increase serum potassium

ACE inhibitors attenuate diuretic induced potassium loss. Potassium sparing diuretics (e.g., spironolactone, eplerenone, triamterene or amiloride), potassium supplements, potassium-containing salt substitutes, or other medicines that may increase serum potassium (e.g., heparin, trimethoprim-containing products such as co-trimoxazole) may lead to significant increases in serum potassium (particularly in patients with impaired renal function).

Diuretics (thiazide or loop diuretics)

Prior treatment with high dose diuretic treatment may result in volume depletion and a risk of hypotension when starting treatment with enalapril (see sections 4.2 and 4.4). The hypotensive effects can be reduced by discontinuation of the diuretic or by increasing volume

or salt intake.

Tricyclic Antidepressants/Antipsychotics/Anaesthetics

Concomitant use of certain anaesthetic medicines, tricyclic antidepressants and antipsychotics with ACE inhibitors may result in further lowering of blood pressure (see section 4.4).

Gold

Nitritoid reactions have been reported rarely in patients on treatment with injectable gold (sodium aurothiomalate) and concomitant ACE inhibitor treatment. Symptoms of Nitritoid reactions include facial flushing, nausea, vomiting and hypotension.

Mammalian Target of Rapamycin (mTOR) inhibitors

Patients taking concomitant mTOR inhibitor (e.g., temsirolimus, sirolimus, everolimus) treatment may be at increased risk for angioedema (see section 4.4).

Neprilysin Inhibitors

Patients taking concomitant ACE inhibitor and neprilysin inhibitor treatment (e.g., sacubitril, racecadotril) may be at increased risk for angioedema (see section 4.4). The concomitant use of enalapril with sacubitril/valsartan is contraindicated, as the concomitant inhibition of neprilysin and ACE may increase the risk of angioedema.

Sacubitril/valsartan must not be initiated until 36 hours after taking the last dose of enalapril. Enalapril treatment must not be started until 36 hours after the last dose of sacubitril/valsartan (see sections 4.3 and 4.4).

Sympathomimetics

Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors (see section 4.5).

Alcohol

Alcohol enhances the hypotensive effect of ACE inhibitors.

Antidiabetics

Epidemiological studies have put forward that concomitant administration of ACE inhibitors and antidiabetic medicines (insulins, oral hypoglycaemic medicines) may cause an increased blood-glucose-lowering effect with risk of hypoglycaemia. This phenomenon appeared to be more likely to occur during the first weeks of combined treatment and in patients with renal impairment (see sections 4.4 and 4.8).

Acetyl Salicylic Acid, Thrombolytics and β-blockers

Enalapril can be safely administered concomitantly with acetyl salicylic acid (at cardiologic doses), thrombolytics and β-blockers.

Hydrochlorothiazide

Non-depolarising Muscle Relaxants

Thiazides may increase the responsiveness to non-depolarising muscle relaxants such as tubocurarine.

Alcohol, Barbiturates, or Opioid Analgesics

Potentiation of orthostatic hypotension may occur.

Antidiabetic medicines (Oral Medicines and Insulin)

Dosage adjustment of the antidiabetic medicine may be required (see sections 4.4 and 4.8).

Cholestyramine and Colestipol Resins (*anionic exchange resins)*

Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastro-intestinal tract by up to 85 and 43 % respectively.

Increasing the QT Interval (e.g., quinidine, procainamide, amiodarone, sotalol)

Increased risk of torsades de pointes.

Digoxin

Hypokalaemia can sensitise or exaggerate the response of the heart to the toxic effects of digoxin (e.g., increased ventricular irritability).

Corticosteroids, ACTH

Intensified electrolyte depletion, particularly hypokalaemia.

Kaliuretic Diuretics (e.g., Furosemide), Carbenoxolone, or Laxative Abuse

Hydrochlorothiazide may increase the reduction of potassium and/or magnesium.

Pressor Amines (e.g., Noradrenaline)

The effect of pressor amines may be decreased (see section 4.5).

Cytostatics (e.g., Cyclophosphamide, Methotrexate)

Thiazide treatment may reduce the renal excretion of cytotoxic medicines and potentiate their myelosuppressive effects.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

ACE inhibitors:

The use of ACE inhibitors is contraindicated in pregnancy, as the safety in this group has not been established.

Enpresil Co can cause foetal morbidity and death. Enpresil Co crosses through the placenta

and can cause disturbance in foetal blood pressure regulatory mechanisms.

The use of Enpresil Co during the first trimester of pregnancy can be associated with an increased risk of birth defects, in particular of the cardiovascular and the central nervous system.

Exposure to ACE inhibitor treatment during the second and third trimesters is known to induce human foeto-toxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia). Prematurity and low birth mass can occur.

Maternal oligohydramnios, presumably representing decreased foetal renal function, can occur and may result in limb contractures, craniofacial deformations and hypoplastic lung development.

Ultrasound check of renal function and skull is recommended in patients where exposure to ACE inhibitors has occurred from the second trimester of pregnancy. Infants (whose mothers have taken ACE inhibitors) should be closely observed for hypotension, oliguria and hyperkalaemia.

Hydrochlorothiazide:

There is limited experience with hydrochlorothiazide during pregnancy, especially during the first trimester.

Thiazides cross the placental barrier and appear in cord blood. Hazards include foetal and neonatal jaundice, thrombocytopenia and possibly other adverse reactions which occur in the adult.

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 treatment should not be used for gestational oedema, gestational hypertension or preeclampsia due to the risk of decreased plasma volume and placental hypoperfusion. Hydrochlorothiazide treatment should not be used for essential hypertension in pregnant women except in rare situations where no other treatment could be used.

Breastfeeding

ACE inhibitors:

The use of ACE inhibitors is contraindicated in breastfeeding as the safety in lactation has not been established.

Enalapril:

Limited pharmacokinetic data demonstrate very low concentrations in breast milk. Although these concentrations seem to be clinically inconsequential the use of Enpresil Co 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.

Hydrochlorothiazide:

Hydrochlorothiazide is excreted in human milk in small amounts. Thiazides in high doses can cause intense diuresis and can inhibit the milk production. The use of Enpresil Co during breastfeeding is not recommended.

Both enalapril and thiazides appear in human milk. If use of Enpresil Co is deemed essential, the patient should stop breastfeeding their infants.

Fertility

No data available.

4.7 Effects on ability to drive and use machines

When driving vehicles or operating machines occasional dizziness or weariness may occur (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported side effects for this medicine are headache and cough.

Tabulated summary of adverse reactions

Enalapril maleate / Hydrochlorothiazide

System Organ Class	Frequency	Side effect
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Frequency unknown	Non-melanoma skin cancer (basal cell carcinoma and squamous cell carcinoma)
Blood and lymphatic system disorders	Less frequent	Decreases in haemoglobin, decreases in haematocrit, decrease in platelets and white cell count, anaemia (including aplastic and haemolytic), neutropaenia, thrombocytopenia, agranulocytosis, bone marrow depression, leukopenia, pancytopenia, lymphadenopathy, autoimmune diseases
Immune system disorders	Less frequent	Hypersensitivity, angioedema of the face, extremities, lips, tongue, glottis and/or larynx
Endocrine disorders	Frequency unknown	Syndrome of inappropriate antidiuretic hormone secretion (SAIDH)
Metabolism and nutrition disorders	Less frequent	Hyperglycaemia, hyperuricaemia, gout, hypokalaemia, increase of cholesterol, increase of triglycerides, increase in blood glucose, hypercalcaemia
Psychiatric disorders	Frequent	Depression
	Less frequent	Nervousness, confusion, dream abnormality
Nervous system disorders	Frequent	Dizziness, insomnia, paraethesia, headache, decreased libido, syncope, sleep disorders, paraesis (due to hypokalaemia)
	Less frequent	Somnolence, vertigo
Eye disorders	Frequent	Blurred vision
Ear and labyrinth disorders	Less frequent	Tinnitus
Cardiac disorders	Frequent	Angina pectoris

System Organ Class	Frequency	Side effect
	Less frequent	Chest pain, palpitations, tachycardia, myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients
Vascular disorders	Frequent	Orthostatic effects including hypotension, syncope, dizziness, orthostatic hypotension, rhythm disturbances, flushing
	Less frequent	Non-orthostatic hypotension, Raynaud's phenomenon
Respiratory, thoracic and mediastinal disorders	Frequent	Cough
	Less frequent	Dyspnoea, rhinorrhoea, sore throat and hoarseness, bronchospasm/asthma, pulmonary infiltrates, rhinitis, allergic alveolitis/eosinophilic pneumonia
Gastrointestinal disorders	Frequent	Nausea, diarrhea, vomiting
	Less frequent	Dyspepsia, abdominal pain, constipation, flatulence, dry mouth, pancreatitis, ileus, anorexia, gastric irritations, dry mouth, peptic ulcer, stomatitis/aphthous, ulcerations, glossitis, intestinal angioedema
Hepato-biliary disorders	Less frequent	Hepatic failure, hepatic necrosis (may be fatal), hepatitis – either hepatocellular or cholestatic, jaundice, cholecystitis (in particular in patients with pre-existing cholelithiasis)
Skin and subcutaneous tissue disorders	Frequent	Rash, diaphoresis
	Less frequent	Pruritus, Stevens-Johnson syndrome, DRESS (symptoms such as fever, serositis, vasculitis, myalgia/myositis, arthralgia/arthritis, a positive antinuclear antibody, elevated erythrocyte sedimentation rate, eosinophilia and leukocytosis), rash, photosensitivity and other dermatologic manifestations, pruritis, urticaria,

System Organ Class	Frequency	Side effect
		alopecia, Erythema multiforme, exfoliative dermatitis, toxic epidermal necrolysis, purpura, cutaneous lupus erythematosus, erythroderma, pemphigus
Musculoskeletal and connective tissue disorders	Frequent	Muscle cramps
	Less frequent	Arthralgia
Renal and urinary disorders	Less frequent	Renal dysfunction, renal failure, proteinurea, oliguria, interstitial nephritis
Reproductive system and breast disorders	Frequent	Impotence
	Less frequent	Gynaecomastia
General disorders and administration site conditions	Frequent	Fatigue, asthenia, chest pain, malaise, fever
Investigations	Less common	Increases in blood urea, increases in serum creatinine, elevations of liver enzymes, elevations of serum bilirubin, hyperkalaemia, hyponatraemia

Enalapril maleate

System Organ Class	Frequency	Side effect
Blood and lymphatic system disorders	Less frequent	Neutropenia, decreases in haemoglobin, decreases in haematocrit, thrombocytopenia, bone marrow depression
Immune system disorders	Less frequent	Hypersensitivity, angioedema of the face, extremities, lips, tongue, glottis and larynx
Psychiatric disorders	Frequent	Depression
	Less frequent	Confusion, nervousness, abnormal dreams
Nervous system disorders	Frequent	Headache
	Less frequent	Somnolence, insomnia, paraesthesia, vertigo
Eye disorders	Frequent	Blurred vision
Cardiac disorders	Frequent	Myocardial infarction or

System Organ Class	Frequency	Side effect
		cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients, chest pain, dysrhythmia, angina pectoris, tachycardia
	Less frequent	Palpitations
Vascular disorders	Frequent	Dizziness, hypotension (including orthostatic hypotension)
	Less frequent	Orthostatic hypotension, Raynaud's phenomenon
Respiratory, thoracic and mediastinal disorders	Frequent	Cough, dyspnoea
	Less frequent	Rhinorrhoea, sore throat, hoarseness, bronchospasm/asthma, pulmonary infiltrates
Gastrointestinal disorders	Frequent	Nausea, diarrhea, abdominal pain, taste alteration
	Less frequent	Ileus, pancreatitis, vomiting, dyspepsia, constipation, anorexia, dry mouth, stomatitis, glossitis, intestinal angioedema
Hepato-biliary disorders	Less frequent	Hepatic failure, hepatitis (either hepatocellular or cholestatic), hepatitis (including jaundice)
Skin and subcutaneous tissue disorders	Frequent	Rash
	Less frequent	Diaphoresis, pruritis, urticaria, alopecia, erythema multiforme, Stevens-Johnson syndrome, exfoliative dermatitis, toxic epidermal necrolysis, pemphigus, a symptom complex including some or all of the following: fever, serotosis, vasculitis, myalgia/myositis, arthralgia/arthritis, a positive antinuclear antibody, elevated erythrocyte sedimentation rate, eosinophilia and leukocytosis. Rash, photosensitivity and other dermatologic manifestations may occur
Renal and urinary disorders	Less frequent	Renal dysfunction, renal failure, oliguria

System Organ Class	Frequency	Side effect
Reproductive system and breast disorders	Less frequent	Impotence
General disorders and administration site conditions	Frequent	Asthenia, fatigue
	Less frequent	Muscle cramps, flushing, tinnitus
Investigations	Frequent	Hyperkalaemia, increases in serum creatinine
	Less frequent	Increases in blood urea, hyponatraemia, elevation of liver enzymes, elevations of serum bilirubin

Hydrochlorothiazide

System Organ Class	Frequency	Side effect
Infections and infestations	Frequency unknown	Sialodenitis
lood and lymphatic system disorders	Frequency unknown	Leukopenia, agranulocytosis, aplastic anaemia, haemolytic anaemia
Immune system disorders	Frequency unknown	Anaphylactic reactions
Metabolism and nutrition disorders	Frequency unknown	Electrolyte imbalance including hyponatraemia
Nervous system disorders	Frequency unknown	Restlessness
Eye disorders	Frequency unknown	Transient blurred vision, xanthopsia
Vascular disorders	Frequency unknown	Necrotising angitis (vasculitis)
Gastrointestinal disorders	Frequency unknown	Anorexia, gastric irritation
Hepato-biliary disorders	Frequency unknown	Jaundice (intrahepatic cholestatic jaundice)
Skin and subcutaneous tissue disorders	Frequency unknown	Toxic epidermal necrolysis, urticaria, purpura, photosensitivity
Musculoskeletal and connective tissue disorders	Frequency unknown	Muscle spasm
Renal and urinary	Frequency	Glycosuria, interstitial nephritis

System Organ Class	Frequency	Side effect
disorders	unknown	

Description of selected adverse reactions

Non-melanoma skin cancer: Based on available data from epidemiological studies, cumulative dose-dependent association between hydrochlorothiazide and NMSC has been observed (see also sections 4.4 and 5.1).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

Adverse reactions must also be reported to Unicorn Pharmaceuticals (Pty) Ltd to enquiries@unicornpharma.co.za.

4.9 Overdose

No precise information is available on the treatment of overdosage with Enpresil Co therefore treatment is symptomatic and supportive. Enpresil Co should be discontinued and the patient should be monitored closely. Measures such as induction of emesis, administration of activated charcoal, and administration of a laxative if ingestion is recent, and correction of dehydration, electrolyte imbalance and hypotension by established procedures, can be introduced within 2 hours after ingestion.

Enalapril Maleate

Symptoms and signs

The most evident symptoms and signs of overdosage are marked hypotension, which occurs approximately six hours after ingestion of tablets, concomitant with blockade of the renin-

angiotensin system, and stupor.

Management of overdose

The recommended treatment of overdosage is intravenous infusion of normal saline solution.

If hypotension occurs, the patient should be placed in the shock position.

If available, treatment with angiotensin II infusion, may also be considered. Enalapril may be removed from the general circulation by haemodialysis (see section 4.4).

Hydrochlorothiazide

Symptoms and signs

The most common signs and symptoms observed are those caused by electrolyte depletion (hypokalaemia, hypochloraemia, hyponatraemia) and dehydration resulting from excessive diuresis. If digoxin has also been administered, hypokalaemia may accentuate cardiac dysrhythmias.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A.7.1.3 Vascular medicines, other hypotensives

Pharmacotherapeutic group:

Enalapril and diuretics, ATC code C09 BA02.

Enalapril maleate and hydrochlorothiazide is a combination of an angiotensin-converting enzyme inhibitor (enalapril maleate) and a diuretic (hydrochlorothiazide), resulting in an additive antihypertensive effect. Enalapril is hydrolysed to the active metabolite enalaprilat.

5.2 Pharmacokinetic properties

Enalapril maleate

Oral enalapril maleate is rapidly absorbed, with peak serum concentrations of enalapril occurring within 1 hour. The absorption of oral enalapril maleate is not influenced by the presence of food in the gastrointestinal tract.

Enalapril is rapidly 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. Excretion of enalapril is primarily renal. In subjects with normal renal function, steady state serum concentrations of enalaprilat were achieved by the fourth day of administration of enalapril maleate.

Hydrochlorothiazide

The plasma half-life varies between 5,6 and 14,8 hours. Hydrochlorothiazide is eliminated rapidly by the kidney with atleast 61 % of the oral dose eliminated unchanged within 24 hours.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate, pregelatinized starch, maleic acid, iron oxide yellow (E172), dried maize starch, sodium stearyl fumarate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 25°C.

Store in the original container.

Do not use the tablets after the expiry date printed on the container.

Return all unused medicine to your pharmacist.

Do not dispose of unused medicine in drains or sewerage systems (e.g. toilets).

6.5 Nature and contents of container

Aluminium / Aluminium Blister pack and HDPE bottle pack

Pack size of 30 tablets

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Unicorn Pharmaceuticals (Pty) Ltd

Cnr. Searle & Pontac Streets

Cape Town

South Africa, 8001

8. REGISTRATION NUMBER(S)

A 55/7.1.3/0413

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23 May 2023

10. DATE OF REVISION OF THE TEXT

Not applicable.