Professional information for ZOFARIL CO 30 mg/12,5 mg

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

ZOFARIL CO 30 mg/12,5 mg film coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains 30 mg zofenopril calcium and 12,5 mg hydrochlorothiazide.

Excipients with known effect:

Each film coated tablet contains 56,2 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film coated tablets.

Pastel-red, round, slightly biconvex tablets with a score line on one side.

The score line is to facilitate breaking for ease of swallowing and not to divide into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of mild to moderate essential hypertension.

This fixed dose combination is indicated in patients whose blood pressure is not adequately controlled on zofenopril alone.

4.2 Posology and method of administration

Posology

Adults (18 to 65 years)

Dose titration with the individual components (i.e. zofenopril and hydrochlorothiazide) is

recommended before changing to the fixed dose combination. When clinically appropriate direct change from monotherapy to the fixed combination may be considered.

Patients without volume or salt depletion

The usual effective dose is one tablet once daily.

Patients suspected to have volume or salt depletion

The use of ZOFARIL CO is not recommended.

Elderly patients (over 65 years)

In the elderly with normal creatinine clearance no dose adjustment is necessary.

In the elderly with reduced creatinine clearance (less than 45 mL/min) the use of ZOFARIL CO is not recommended.

Creatinine clearance may be estimated from serum creatinine by the following Cockroft-Gault formula:

$$\text{CrCl (mL/min)} = \frac{(140 - \text{age}) \times \text{mass (kg)} \times 0{,}85 \text{ (if female)}}{\text{serum Cr (µmol/L)}}$$

Paediatric population

ZOFARIL CO should not be given to children under the age of 18 years as safety and efficacy of ZOFARIL CO have not been established.

Patients with renal impairment and dialysis

In hypertensive patients with mild impairment (creatinine clearance > 45 mL/min) the same dose level and once-daily regimen of ZOFARIL CO can be employed as for patients with normal renal function.

In patients with moderate to severe impairment (creatinine clearance < 45 mL/min) its use is not recommended (see section 4.4).

In patients with severe renal impairment (creatinine clearance < 30 mL/min) ZOFARIL CO is

contraindicated (see section 4.3).

In hypertensive patients maintained on dialysis the use of ZOFARIL CO is not recommended.

Patients with hepatic impairment

In hypertensive patients with mild to moderate hepatic impairment (Child-Pugh A and B), where the 30 mg dose of zofenopril alone has been achieved, the same dose regimen can be employed as for patients with normal hepatic function. In hypertensive patients with severe liver impairment (Child-Pugh C) ZOFARIL CO is contraindicated.

Method of administration

ZOFARIL CO should be used once daily, with or without food.

To ease swallowing, tablets may be broken in two parts and swallowed one half after the other, at the prescribed time of administration.

4.3 Contraindications

- Hypersensitivity to zofenopril or any other angiotensin-converting enzyme (ACE) inhibitor.
- Hypersensitivity to hydrochlorothiazide or other sulphonamide-derived substances.
- Hypersensitivity to any of the excipients (see section 6.1).
- History of angioedema associated with previous ACE inhibitors or angiotensin receptor blockers (ARBs): These patients must never again be given these medicines.
- Pregnancy and lactation (see sections 4.4 and 4.6).
- Concomitant use with sacubitril/valsartan therapy. ZOFARIL CO must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan (see sections 4.4 and 4.5).
- Hereditary/idiopathic angioedema.
- Hypertrophic obstructive cardiomyopathy (HOCM).
- Severe hepatic impairment.
- Severe renal impairment (creatinine clearance < 30 mL/min).
- Bilateral renal artery stenosis or unilateral renal artery stenosis in cases of a single kidney.

- Aortic stenosis.
- The concomitant use of ZOFARIL CO with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 mL/min/1,73 m^2) (see sections 4.5).
- Concomitant therapy with potassium sparing diuretics such as spironolactone, triamterene, amiloride (see section 4.5).
- Porphyria.
- Lithium therapy: Concomitant administration with ZOFARIL CO may lead to toxic blood concentrations of lithium (see section 4.5).
- Patients with a history of previous and/or current basal cell carcinomas and/or squamous cell carcinomas of the skin and lip.
- Concomitant use of fluoroquinolones with ZOFARIL CO is contraindicated in patients with moderate to severe renal impairment (creatinine clearance ≤ 30 mL/min) and in elderly patients.

4.4 Special warnings and precautions for use

ZOFENOPRIL

Hypotension:

As with other angiotensin-converting enzyme (ACE) inhibitors and diuretics, ZOFARIL CO may cause a profound fall in blood pressure especially after the first dose, although symptomatic hypotension is seen rarely in uncomplicated hypertensive patients. It is more likely to occur in patients who have been volume and electrolyte depleted by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting, or who have severe renin-dependent hypertension (see section 4.5 and section 4.8).

In patients with heart failure, with or without associated renal insufficiency, symptomatic hypotension has been observed. This is more 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 patients at increased risk of symptomatic hypotension, treatment

should be started under close medical supervision preferably in the hospital, with low doses and careful dose titration. If possible, diuretic treatment should be discontinued temporarily when therapy with ZOFARIL CO is initiated.

Such considerations apply also to patients with angina pectoris or cerebrovascular disease in whom an excessive fall in blood pressure could result in myocardial infarction or cerebrovascular incident.

If hypotension develops, the patient should be placed in a supine position. Volume repletion with intravenous normal saline may be required. The appearance of hypotension after the initial dose does not preclude subsequent careful dose titration with medicine after effective management.

Patients with renovascular hypertension:

There is an increased risk of severe 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, as in ZOFARIL CO. Treatment with diuretics may be a contributory factor. Loss of renal function may occur with only mild changes in serum creatinine even in patients with unilateral renal artery stenosis. In these patients, therapy should be initiated under close medical supervision with low dose, careful titration and monitoring of renal function.

Patients with renal insufficiency:

Close monitoring of renal function during therapy should be performed as deemed appropriate. Renal failure has been reported in association with ZOFARIL CO, mainly in patients with severe heart failure or underlying renal disease, including renal artery stenosis. Some patients, with no apparent pre-existing renal disease have developed increases in blood urea and creatinine concentrations, particularly when a diuretic is given concomitantly. Dosage reduction of the individual components may be required. It is recommended that the renal function be monitored closely during the first few weeks of therapy.

Patients who are dialysed:

Patients who are dialysed using high-flux polyacrylonitrile membranes (e.g. AN 69) and treated with ACE inhibitors, as in ZOFARIL CO are likely to experience anaphylactoid reactions such as facial swelling, flushing, hypotension and dyspnoea within a few minutes of commencing haemodialysis. It is recommended to use an alternative membrane or an alternative antihypertensive medicine. The efficacy and safety of zofenopril in myocardial infarction patients undergoing haemodialysis have not been established. Therefore, it should not be used in these patients.

Patients on LDL apheresis:

Patients treated with an ACE inhibitor, as in ZOFARIL CO undergoing LDL apheresis with dextrane sulphate may experience anaphylactoid reactions similar to those seen in patients undergoing haemodialysis with high-flux membranes (see above). It is recommended that a medicine from another class of antihypertensive medicines is used in these patients.

Anaphylactic reactions during desensitisation or after insect bites/stings:

Patients receiving ACE inhibitors, as in ZOFARIL CO during desensitisation treatment (e.g. hymenoptera venom) or after insect bites have experienced life-threatening anaphylactoid reactions. In the same patients, these reactions have been avoided when ACE inhibitors were temporarily withheld but they have reappeared upon inadvertent re-administration of the medicine. Therefore, caution should be used in patients treated with ZOFARIL CO undergoing such desensitisation procedures.

Kidney transplantation:

There is no experience regarding the administration of ZOFARIL CO in patients with a recent kidney transplantation. Its use in transplant recipients is therefore not recommended.

Primary aldosteronism:

Patients with primary aldosteronism generally will not respond to antihypertensive medicines acting through inhibition of the renin-angiotensin system. Therefore the use of ZOFARIL CO is not recommended.

Hypersensitivity/Angioedema:

Angioedema of the face, extremities, lips, mucous membranes, tongue, glottis and/or larynx may occur in patients treated with ZOFARIL CO, which occurs most frequently during the first weeks of treatment. However, in rare cases severe angioedema may develop after long-term treatment with an angiotensin-converting enzyme inhibitor. Treatment with ZOFARIL CO should promptly be discontinued and replaced by an agent belonging to another class of antihypertensive medicines. Angioedema involving the tongue, glottis or larynx may be fatal. Emergency therapy should be given including, but not necessarily limited to, immediate subcutaneous epinephrine (adrenaline) solution 1:1 000 (0,3 to 0,5 mL) or slow intravenous epinephrine (adrenaline) 1 mg/mL (which should be diluted as instructed) with close monitoring of ECG and blood pressure. 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.

Even in such instances where swelling of only the tongue is involved, without respiratory distress, patients may require observation since treatment with antihistamines and corticosteroids may not be sufficient.

Angiotensin-converting enzyme inhibitors cause a higher rate of angioedema in black patients than in non-black patients.

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

Concomitant use of ZOFARIL CO with sacubitril/valsartan is contraindicated due to the increased risk of angioedema. Treatment with sacubitril/valsartan must not be initiated earlier than 36 hours after the last dose of ZOFARIL CO. Treatment with ZOFARIL CO must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan (see sections 4.3 and 4.5).

Concomitant use of ZOFARIL CO with racecadotril, mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and vildagliptin may lead to an increased risk of angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment) (see section 4.5). Caution should be used when starting racecadotril, mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and vildagliptin in a patient already taking ZOFARIL CO.

Cough:

During treatment with ZOFARIL CO a dry and non-productive cough may occur which disappears after discontinuation of ZOFARIL CO. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

Hepatic failure:

ACE inhibitors, as in ZOFARIL CO 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 ZOFARIL CO who develop jaundice or marked elevations of hepatic enzymes should discontinue ZOFARIL CO and receive appropriate medical follow-up.

Serum potassium:

ACE inhibitors, as in ZOFARIL CO can cause hyperkalaemia because they inhibit the release of aldosterone. The effect is usually not significant in patients with normal renal function. However, in patients with impaired renal function and/or in patients taking potassium supplements (including salt substitutes), potassium-sparing diuretics, heparin, trimethoprim or co-trimoxazole also known as trimethoprim/sulfamethoxazole and especially aldosterone antagonists or angiotensin receptor blockers, hyperkalaemia can occur.

Potassium-sparing diuretics and angiotensin-receptor blockers should be used with caution in patients receiving ZOFARIL CO, and serum potassium and renal function should be monitored (see section 4.5).

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

There is evidence that the concomitant use of ACE inhibitors (like ZOFARIL CO), 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 (like ZOFARIL CO), angiotensin II receptor blockers or aliskiren is therefore not recommended (see sections 4.5).

If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure.

ZOFARIL CO and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

Surgery/anaesthesia:

ZOFARIL CO may cause hypotension or even hypotensive shock in patients undergoing major surgery or during anaesthesia, since they may block angiotensin II formation secondary to compensatory renin release. If it is not possible to withhold ZOFARIL CO, intravascular and plasma volumes should be carefully monitored.

Aortic and mitral valve stenosis/hypertrophic cardiomyopathy:

ZOFARIL CO should be used with caution in patients with mitral valve stenosis and left ventricular outflow tract obstruction and avoided in cases of cardiogenic shock and haemodynamically significant obstruction.

Neutropenia/agranulocytosis:

Neutropenia/agranulocytosis, thrombocytopenia and anaemia have been reported in patients receiving ZOFARIL CO. The risk of neutropenia appears to be dose- and type-related and is dependent on the patient's clinical status. It is rarely seen in uncomplicated patients but may occur

in patients with some degree of renal impairment, especially when it is associated with collagen vascular disease e.g. systemic lupus erythematosus, scleroderma and therapy with immunosuppressive medicines, treatment with allopurinol or procainamide or a combination of these complicating factors. Some of these patients developed serious infections which in a few instances did not respond to intensive antibiotic therapy.
If ZOFARIL CO 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 ZOFARIL CO 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. ZOFARIL CO and other concomitant medication (see section 4.5) should be withdrawn if neutropenia (neutrophils less than 1 000/mm^3) is detected or suspected. It is reversible after discontinuation of ZOFARIL CO.

Psoriasis:

ZOFARIL CO should be used with caution in patients with psoriasis.

Proteinuria:

Proteinuria may occur particularly in patients with existing renal function impairment or on relatively high doses of ZOFARIL CO. Patients with prior renal disease should have urinary protein estimation (dip-stick on first morning urine) prior to treatment, and periodically thereafter.

Diabetic patients:

The glycaemia levels should be closely monitored in diabetic patients previously treated with oral antidiabetic medicines or insulin, during the first month of treatment with ZOFARIL CO (see section 4.5).

Lithium:

The combination of lithium and ZOFARIL CO is generally not recommended (see section 4.5).

Fluoroquinolones:

Concomitant use of fluoroquinolones and ZOFARIL CO may precipitate acute kidney injury in patients, especially those with moderate to severe renal impairment and elderly patients (see section 4.3). Renal function should be assessed before initiating treatment and monitored during treatment with fluoroquinolones or ZOFARIL CO whether used separately and/or concomitantly.

Ethnic differences:

ZOFARIL CO may be less effective in lowering blood pressure in black people than in non-blacks. Angiotensin-converting enzyme inhibitors cause a higher rate of angioedema in black patients than in non-black patients.

Pregnancy:

ZOFARIL CO should not be used during pregnancy (see sections 4.3 and 4.6).

HYDROCHLOROTHIAZIDE

Renal impairment:

In patients with renal disease, thiazides as in ZOFARIL CO may increase azotaemia. Cumulative effects of this active substance 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.

Hepatic impairment:

ZOFARIL CO 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.

Metabolic and endocrine effects:

ZOFARIL CO may impair glucose tolerance. Dosage adjustments of insulin or oral hypoglycaemics

may be required (see section 4.5). Latent diabetes mellitus may become manifest during treatment with ZOFARIL CO.

Increases in cholesterol and triglyceride levels have been associated with treatment with ZOFARIL CO.

ZOFARIL CO may precipitate hyperuricaemia and/or gout in certain patients.

Electrolyte imbalance:

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

Hydrochlorothiazide, as in ZOFARIL CO 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 zofenopril 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.

ZOFARIL CO may decrease urinary calcium excretion and may 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. ZOFARIL CO should be discontinued before carrying out tests for parathyroid function. ZOFARIL CO have been shown to increase the urinary excretion of magnesium, which may result in hypomagnesaemia.

Lupus erythematosus:

Exacerbation or activation of systemic lupus erythematosus has been reported with the use of ZOFARIL CO.

Non-melanoma skin cancer:

An increased risk of non-melanoma skin cancer (NMSC) [basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)] with increasing cumulative dose of hydrochlorothiazide (HCTZ) exposure has been observed in two epidemiological studies. Photosensitising actions of HCTZ could act as a possible mechanism for NMSC. Patients taking ZOFARIL CO should be informed of the risk of NMSC and advised to regularly check their skin for any new lesions and promptly report any suspicious skin lesions. Possible preventive measures such as limited exposure to sunlight and UV rays and, in case of exposure, adequate protection should be advised to the patients in order to minimize the risk of skin cancer. Suspicious skin lesions should be promptly examined potentially including histological examinations of biopsies. ZOFARIL CO should not be used by patients who have had previous and/or current basal cell carcinomas and/or squamous cell carcinomas of the skin and/or lip (see section 4.3).

Anti-doping test:

Hydrochlorothiazide as in ZOFARIL CO 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. Cases of photosensitivity reactions have been reported with thiazide diuretics, as in ZOFARIL CO (see section 4.8). If photosensitivity reaction occurs during treatment, it is recommended to stop the treatment. If re-administration of the diuretic is deemed necessary, it is recommended to protect the areas exposed to the sun or artificial UVA.

ZOFENOPRIL AND HYDROCHLOROTHIAZIDE

In addition to the warnings related to the mono-components, the following should be observed:

Pregnancy:

ZOFARIL CO should not be used during pregnancy (see section 4.3 and 4.6).

Patients with renal insufficiency:

Considering the effect of zofenopril and hydrochlorothiazide in patients with impaired renal function, ZOFARIL CO should not be administered to patients with moderate to severe renal insufficiency (creatinine clearance < 45 mL/min).

Risk of hypokalaemia:

The combination of an ACE inhibitor with a thiazide diuretic, as in ZOFARIL CO does not rule out the occurrence of hypokalaemia. Regular monitoring of serum potassium should be performed.

Lactose warning:

Patients with rare hereditary problems of galactose intolerance, total lactose deficiency or glucose-galactose malabsorption should not take ZOFARIL CO.

4.5 Interaction with other medicines and other forms of interaction

ZOFENOPRIL

Medicines increasing the risk of angioedema:

Concomitant use of ZOFARIL CO with sacubitril/valsartan is contraindicated as this increases the risk of angioedema (see section 4.3 and 4.4).

Concomitant use of ZOFARIL CO with racecadotril, mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and vildagliptin may lead to an increased risk for angioedema (see section 4.4).

Concomitant use not recommended

Potassium sparing diuretics, potassium supplements, potassium-containing salt substitutes or other agents that increase serum potassium

Although serum potassium usually remains within normal limits, hyperkalaemia may occur in some patients treated with ZOFARIL CO. Potassium sparing diuretics (e.g. spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Care should also be taken when ZOFARIL CO is co-administered with other medicines that increase serum potassium, such as trimethoprim and cotrimoxazole (trimethoprim/sulfamethoxazole) as trimethoprim is known to act as a potassium-sparing diuretic like amiloride. Therefore, the combination of ZOFARIL CO with the above-mentioned medicines is not recommended. If concomitant use is indicated, they should be used with caution and with frequent monitoring of serum potassium.

ACE inhibitors, angiotensin II receptor blockers or aliskiren:

Clinical trial data has shown that dual blockade of the renin-angiotensin-aldosterone system (RAAS) through the combined use of ACE inhibitors (as in ZOFARIL CO), angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent (see sections 4.3 and 4.4).

Fluoroquinolones:

Concomitant use of fluoroquinolones and ZOFARIL CO may precipitate acute kidney injury. The mechanism of the possible interaction between the different classes of medicines, over and above different mechanisms of kidney damage, is unknown (see section 4.3).

Concomitant use requiring caution

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 ZOFARIL CO (see section 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 ZOFARIL CO.

Anaesthetics:

ZOFARIL CO may enhance the hypotensive effects of certain anaesthetics.

Narcotics/tricyclic antidepressants/antipsychotics/barbiturates:

Postural hypotension may occur.

Other antihypertensive substances (e.g. beta-blockers, alpha-blockers or calcium antagonists):

There may be additive hypotensive effect or potentiation. Treatment with nitroglycerin and other nitrates, or other vasodilators, should be used with caution.

Cimetidine:

May enhance the risk of hypotensive effect.

Ciclosporin:

Hyperkalaemia may occur during concomitant use of ZOFARIL CO with cyclosporin. Monitoring of serum potassium is recommended.

Heparin:

Hyperkalaemia may occur during concomitant use of ZOFARIL CO with heparin. Monitoring of serum potassium is recommended.

Allopurinol, procainamide, systemic corticosteroids, cytostatics or immunosuppressives:

Increased risk of hypersensitivity reactions when ZOFARIL CO is used concurrently. Data from other ACE inhibitors indicate an increased risk of leucopenia when used concurrently.

Antidiabetics:

ZOFARIL CO can potentiate the blood glucose-reducing effects of insulin and oral antidiabetics like sulphonylurea, in diabetics. In such cases it may be necessary to reduce the dose of the antidiabetic during simultaneous treatment with ZOFARIL CO.

Haemodialysis with high-flux dialysis membranes:

Increased risk of anaphylactoid reactions when ZOFARIL CO is used concurrently.

Sympathomimetics:

May reduce the antihypertensive effects of ZOFARIL CO; patients should be carefully monitored to confirm that the desired effect is being obtained.

Antacids:

Reduce the bioavailability of ZOFARIL CO.

Food:

May reduce the rate but not the extent of absorption of zofenopril, as in ZOFARIL CO.

Gold:

Nitritoid reactions (symptoms of vasodilatation including flushing, nausea, dizziness and hypotension, which can be very severe) following injectable gold (for example, sodium aurothiomalate) have been reported more frequently in patients receiving therapy with ZOFARIL CO.

Additional information:

CYP enzymes

Direct clinical data on the interaction of zofenopril, as in ZOFARIL CO with other active substances which are metabolised by CYP enzymes are not available. However, *in vitro* metabolic studies with

zofenopril, as in ZOFARIL CO demonstrated no potential interaction with active substances that are metabolised by CYP enzymes.

HYDROCHLOROTHIAZIDE

Concomitant use requiring caution

Colestyramine and colestipol resins:

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

Sulphonamide diuretics should be taken at least 1 hour before, or 4 – 6 hours after these medicines.

Corticosteroids, ACTH, amphotericin B (parenteral), carbenoxolone, stimulant laxatives:

There may be intensified electrolyte depletion, particularly hypokalaemia, when administered concomitantly with ZOFARIL CO.

Calcium salts:

Increased serum calcium levels due to decreased excretion may occur when administered concurrently with ZOFARIL CO.

Cardiac glycosides:

Thiazide-induced hypokalaemia or hypomagnesaemia favours the occurrence of digitalis-induced cardiac dysrhythmia.

Medicines associated with torsades de pointes:

Because of the risk of hypokalaemia, caution should be used when ZOFARIL CO is co-administered with medicines associated with torsades de pointes, e.g. some antidysrhythmics,

some antipsychotics, and other medicines known to induce torsades de pointes.

Pressor amines (e.g. adrenaline):

Possible decreased response to pressor amines, but not sufficient to preclude their use with ZOFARIL CO.

Skeletal muscle relaxants, non-depolarising (e.g. tubocurarine):

Possible increased responsiveness to the muscle relaxant when used with ZOFARIL CO.

Amantadine:

ZOFARIL CO may increase the risk of undesirable effects caused by amantadine.

Medicines used in the treatment of gout (probenecid, sulfinpyrazone, allopurinol):

Dosage adjustment of uricosuric medicines may be necessary as ZOFARIL CO may raise the level of serum uric acid. Increase of dosage of probenecid or sulfinpyrazone may be necessary.
Co-administration of ZOFARIL CO may increase the incidence of hypersensitivity reactions to allopurinol.

Additional information:

Laboratory test interactions

Because of their effects on calcium metabolism, ZOFARIL CO may interfere with tests for parathyroid function.

ZOFENOPRIL AND HYDROCHLOROTHIAZIDE

In addition to the interactions related to the mono-components, the following should be observed:

Concomitant use not recommended

Lithium:

Concomitant use of thiazide diuretics may increase the risk of lithium toxicity and enhance the already increased risk of lithium toxicity with ACE inhibitors. Therefore, ZOFARIL CO is not recommended in association with lithium and careful monitoring of serum lithium levels should be performed if the combination proves necessary (see section 4.3).

Clinical chemistry:

Thiazides, as in ZOFARIL CO may decrease serum PBI (protein bound iodine) levels without signs of thyroid disturbance.

Concomitant use requiring caution

Nonsteroidal anti-inflammatory medicine (including ASA ≥ 3 g/day):

The administration of nonsteroidal anti-inflammatory medicine may reduce the antihypertensive effect of ZOFARIL CO. Furthermore, it has been described that NSAIDs and ACE inhibitors, as in ZOFARIL CO exert an additive effect on the increase in serum potassium whereas renal function may decrease. These effects are in principle reversible and occur especially in patients with impaired renal function. Acute renal failure may occur, particularly in patients with compromised renal function such as elderly or dehydrated patients.

Alcohol:

Enhances the hypotensive effect of ZOFARIL CO.

Trimethoprim:

Concomitant administration of ZOFARIL CO with trimethoprim increases the risk of hypercalcaemia.

4.6 Fertility, pregnancy and lactation

Pregnancy

ZOFARIL CO should not be used in pregnancy.

Women of childbearing age should ensure effective contraception if on ZOFARIL CO treatment.

The use of ZOFARIL CO is not recommended during the first trimester of pregnancy (see section 4.4). The use of ZOFARIL CO is contraindicated during the second and third trimester of pregnancy (see sections 4.3 and 4.4).
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 ZOFARIL CO should be stopped immediately, and, if appropriate, alternative therapy should be started.

Breastfeeding

ZOFARIL CO should not be used while breastfeeding.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive a vehicle and use machines have been performed. When driving vehicles or operating machines it should be remembered that occasionally drowsiness, dizziness or tiredness may occur.

4.8 Undesirable effects

In controlled clinical trials involving 597 patients randomised to receive ZOFARIL CO, no adverse reactions peculiar to this combination product have been observed. Adverse reactions have been limited to those that were reported previously with zofenopril calcium or hydrochlorothiazide. The incidence of undesirable effects showed no correlation with gender or age of the patients.

The table below shows all the adverse reactions that have been reported during clinical trials as at least probably-possibly related to treatment with ZOFARIL CO. They are listed by body-system and ranked under headings of frequency using the following convention: very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1 000, ≤ 1/100); rare (≥ 1/10 000, ≤ 1/1 000); very rare

(≤ 1/10 000).

Infections and infestations	
Uncommon:	infection, bronchitis, pharyngitis
Metabolism and nutrition disorders	
Uncommon:	hypercholesterolaemia, hyperglycaemia, hyperlipidaemia, hypokalaemia, hyperkalaemia, hyperuricaemia
Psychiatric disorders	
Uncommon:	insomnia
Nervous system disorders	
Common:	dizziness, headache
Uncommon:	somnolence, syncope, hypertonia
Cardiac disorders	
Uncommon:	angina pectoris, atrial fibrillation, myocardial infarction, palpitations
Vascular disorders	
Uncommon:	flushing, hypotension, hypertension
Respiratory, thoracic and mediastinal disorders	
Common:	cough
Uncommon:	dyspnoea
Gastrointestinal disorders	
Uncommon:	nausea, dyspepsia, gastritis, gingivitis, dry mouth, abdominal pain
Skin and subcutaneous tissue disorders	
Uncommon:	angioedema, psoriasis, acne, dry skin, pruritus, urticaria
Musculoskeletal and connective tissue disorders	
Uncommon:	back pain
Renal and urinary disorders	
Uncommon:	polyuria
Reproductive system and breast disorders	

Uncommon:	erectile dysfunction
General disorders and administration site conditions	
Uncommon:	asthenia, influenza-like illness, peripheral oedema
Investigations	
Uncommon:	creatinine increase, abnormal liver function test

Additional information on individual component:

Adverse reactions known to occur with each component given as monotherapy may occur during treatment with ZOFARIL CO:

ZOFENOPRIL

The most common undesirable effects typical of ACE inhibitors that occurred in clinical trials in patients treated with zofenopril were the following:

Nervous system disorders	
Common:	dizziness, headache
Respiratory, thoracic and mediastinal disorders	
Common:	cough
Gastrointestinal disorders	
Common:	nausea/vomiting
Skin and subcutaneous tissue disorders	
Uncommon:	rash
Rare:	angioedema
Musculoskeletal and connective tissue disorders	
Uncommon:	muscle spasms
General disorders and administration site conditions	
Common:	fatigue
Uncommon:	asthenia

The following adverse reactions have been observed associated with ACE inhibitor therapy:

Blood and lymphatic system disorders

In a few patients, agranulocytosis and pancytopenia may occur.

There were reports of haemolytic anaemia in patients with glucose 6-phosphate dehydrogenase deficiency.

Endocrine disorders

Not known, inappropriate antidiuretic hormone secretion.

Metabolism and nutrition disorders

Very rare, hypoglycaemia.

Psychiatric disorders

Rarely, depression, altered mood, sleep disorders, confusional state.

Nervous system disorders

Occasionally paraesthesia, dysgeusia, balance disorder.

Eye disorders

Rarely, blurred vision.

Ear and labyrinth disorders

Rarely, tinnitus.

Cardiac disorders

Individual cases of tachycardia, palpitations, dysrhythmias, angina pectoris, and myocardial infarction have been reported for ACE inhibitors in association with hypotension.

Vascular disorders

Severe hypotension has occurred after initiation or increase of therapy. This occurs especially in certain risk groups (see section 4.4). In association with hypotension, symptoms like dizziness, feeling of weakness, impaired vision, rarely with disturbance of consciousness (syncope) have been reported.

Rarely, flushing.

Respiratory, thoracic and mediastinal disorders

Rarely, dyspnoea, sinusitis, rhinitis, glossitis, bronchitis and bronchospasm have been reported.

ACE inhibitors have been associated with the onset of angioneurotic oedema in a small subset of patients, involving the face and oropharyngeal tissues. In isolated cases angioneurotic oedema involving the upper airways has caused fatal airway obstruction.

Gastrointestinal disorders

Occasionally, abdominal pain, diarrhoea, constipation and dry mouth can occur. Individual cases of pancreatitis and ileus have been described in association with ACE inhibitors.

Very rare, small bowel angioedema.

Hepato-biliary disorders

Individual cases of cholestatic jaundice and hepatitis have been described in association with ACE inhibitors.

Skin and subcutaneous tissue disorders

Occasionally allergic and hypersensitivity reactions can occur like pruritus, urticaria, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, psoriasis-like efflorescences, alopecia. This can be accompanied by fever, myalgia, arthralgia, eosinophilia and/or increased ANA-titres.

Rarely, hyperhidrosis.

Musculoskeletal and connective tissue disorders

Occasionally, myalgia can occur.

Renal and urinary disorders

Renal insufficiency may occur or be intensified. Acute renal failure has been reported (see section 4.4).

Rarely, micturition disorders.

Reproductive system and breast disorders

Rarely, erectile dysfunction.

General disorders and administration site conditions

Very rare, peripheral oedema and chest pain.

Investigations

Increases in blood urea and creatinine, reversible on discontinuation may occur, especially in the presence of renal insufficiency, severe heart failure and renovascular hypertension. In a few patients, decreases in haemoglobin, haematocrit, platelets and white cell count have been reported. Increases in serum levels of hepatic enzymes and bilirubin have also been reported.

HYDROCHLOROTHIAZIDE

The adverse events that have been reported with the use of hydrochlorothiazide alone include the following:

Neoplasms benign, malignant and unspecified (including cysts and polyps)

Not known, non-melanoma skin cancer (NMSC) (basal cell carcinoma and squamous cell carcinoma). Based on available data from epidemiological studies, cumulative dose-dependent

association between HCTZ and NMSC has been observed (see also sections 4.4).

Blood and lymphatic system disorders

Leucopenia, neutropenia, agranulocytosis, thrombocytopenia, aplastic anaemia, haemolytic anaemia, bone marrow failure.

Immune system disorders

Anaphylactic reaction.

Metabolism and nutrition disorders

Anorexia, dehydration, gout, diabetes mellitus, metabolic alkalosis, hyperuricaemia, electrolyte imbalance (including hyponatraemia, hypokalaemia, hypomagnesaemia, hypochloraemia, hypercalcaemia), hyperglycaemia, hyperamylasaemia.

Psychiatric disorders

Apathy, confusional state, depression, nervousness, restlessness, sleep disorder.

Nervous system disorders

Convulsions, depressed level of consciousness, coma, headache, dizziness, paraesthesia, paresis.

Eye disorders

Xanthopsia, blurred vision, myopia (aggravated), decreased lacrimation.

Ear and labyrinth disorders

Vertigo.

Cardiac disorders

Cardiac dysrhythmias, palpitations.

Vascular disorders

Orthostatic hypotension, thrombosis, embolism, shock.

Respiratory, thoracic and mediastinal disorders

Pneumonitis, interstitial lung disease, pulmonary oedema.

Gastrointestinal disorders

Dry mouth, nausea, vomiting, stomach discomfort, diarrhoea, constipation, abdominal pain, paralytic ileus, flatulence, sialadenitis, pancreatitis.

Hepato-biliary disorders

Cholestatic jaundice, cholecystitis.

Skin and subcutaneous tissue disorders

Pruritus, purpura, urticaria, photosensitivity reactions, rash, cutaneous lupus erythematosus, necrotising vasculitis, toxic epidermal necrolysis.

Musculoskeletal and connective tissue disorders

Muscle spasm, myalgia.

Renal and urinary disorders

Renal impairment, acute renal failure, interstitial nephritis, glycosuria.

Reproductive system and breast disorders

Erectile dysfunction.

General disorders and administration site conditions

Asthenia, pyrexia, fatigue, thirst.

Investigations

Electrocardiogram change, increased blood cholesterol, increased blood triglycerides.

Reporting of suspected adverse reactions

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

4.9 Overdose

Symptoms of overdosage are severe hypotension, shock, stupor, bradycardia, electrolyte disturbances and renal failure.

Treatment is symptomatic and supportive. After ingestion of an overdose, the patient should be kept under close supervision, preferably in an intensive care unit. Serum electrolytes and creatinine should be monitored frequently. Therapeutic measures depend on the nature and severity of the symptoms. If the ingestion is recent, measures to prevent absorption such as administration of adsorbents and sodium sulphate may be implemented. If hypotension occurs, the patient should be placed in shock position and the judicious use of volume expanders and/or treatment with angiotensin II should be considered. Bradycardia or extensive vagal reactions should be treated by administering atropine. The use of a pacemaker may be considered. ACE inhibitors may be removed from the circulation by haemodialysis. The use of high-flux polyacrylonitrile membranes should be avoided.

Overdosage with hydrochlorothiazide is associated with electrolyte depletion (hypokalaemia,

hypochloraemia) and dehydration resulting from excessive diuresis. The most common signs and symptoms of overdosage are nausea and somnolence. Hypokalaemia may result in muscle spasm and/or accentuate cardiac dysrhythmias associated with the concomitant use of digitalis glycosides or certain antidysrhythmic medicines.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 7.1.3 Other hypotensives

Pharmacotherapeutic group: ACE inhibitors and diuretics, ATC code: C09BA15

ZOFENOPRIL AND HYDROCHLOROTHIAZIDE COMBINATION

ZOFARIL CO is a fixed dose combination product containing zofenopril, an inhibitor of angiotensin-converting enzyme (ACE) and hydrochlorothiazide, a thiazide diuretic. Both components have complementary modes of action and exert an additive antihypertensive effect.

Zofenopril is a sulfhydryl ACE inhibitor able to block the enzyme that catalyses the conversion of angiotensin I to the vasoconstrictor peptide angiotensin II, which leads to decreased vasopressor activity and to reduced aldosterone secretion. This latter decrease may result in an increase in serum potassium concentration, along with sodium and fluid loss. The cessation of the negative feedback of angiotensin II on the renin secretion results in an increase of the plasma renin activity. The mechanism through which zofenopril lowers blood pressure is believed to be primarily suppression of the renin-angiotensin-aldosterone system. ACE is identical to kininase II, an enzyme that degrades bradykinin, a potent vasodilatory peptide, that seems to play a role in the therapeutic effect of ACE inhibitors.

Hydrochlorothiazide is a diuretic and antihypertensive agent. It affects the distal renal tubular mechanism of electrolyte reabsorption. Hydrochlorothiazide increases excretion of sodium and chloride in approximately equivalent amounts. Natriuresis may be accompanied by some loss of potassium and bicarbonate. Presumably through blockade of the renin-angiotensin-aldosterone system, co-administration of zofenopril tends to reverse the potassium lost associated with these

diuretics. With hydrochlorothiazide, diuresis begins within 2 hours, peaks in about 4 hours and lasts about 6 to 12 hours.

5.2 Pharmacokinetic properties

Concomitant administration of zofenopril and hydrochlorothiazide has little or no effect on the bioavailability of either active substance. The combination tablet is bioequivalent to concomitant administration of the separate entities.

ZOFENOPRIL

Zofenopril is a prodrug, since the active inhibitor is the free sulfhydryl compound, zofenoprilat, resulting from thio-ester hydrolysis.

Absorption

Zofenopril is rapidly and completely absorbed by the oral route and undergoes nearly complete conversion to zofenoprilat, which reaches peak blood levels after 1,5 hours following an oral dose of ZOFARIL CO. Single dose kinetics are linear over a dose-range of 10 – 80 mg of zofenopril calcium and no accumulation occurs after the administration of 15 – 60 mg of zofenopril for 3 weeks. The presence of food in the gastrointestinal tract reduces the rate but not the extent of absorption and the AUCs of zofenoprilat are nearly identical in the fasted or fed state.

Distribution

Approximately 88 % of the circulating radioactivity measured *ex vivo* following a radiolabelled dose of zofenopril is bound to plasma protein and the steady state volume of distribution is 96 litres.

Biotransformation

Eight metabolites, accounting for 76 % of the urinary radioactivity, were identified in human urine following a radiolabelled dose of zofenopril. The main metabolite is zofenoprilat (22 %), which is then metabolised through several pathways, including glucuronide conjugation (17 %), cyclisation

and glucuronide conjugation (13 %), cysteine conjugation (9 %) and S-methylation of the thiol group (8 %).

Elimination

Radiolabelled zofenoprilat administered intravenously is eliminated in urine (76 %) and faeces (16 %), while following an oral dose of radiolabelled zofenopril calcium, 69 % and 26 % of the radioactivity is recovered in urine and faeces respectively, indicating a dual route of elimination (kidney and liver). Half-life of zofenoprilat is 5,5 hours and its total body clearance is 1 300 mL/min following orally administrated zofenopril.

Pharmacokinetics in special populations

Pharmacokinetics in elderly patients

In elderly patients, no dose adjustment is required when the renal function is normal.

Pharmacokinetics in renal dysfunction

Based on comparison of key pharmacokinetic parameters of zofenoprilat measured after oral administration of radiolabelled zofenopril, patients with mild renal impairment (creatinine clearance > 45 and < 90 mL/min) eliminate zofenopril from the body at the same rate as subjects with normal renal function (creatinine clearance > 90 mL/min). In patients with moderate to severe renal impairment (7 – 44 mL/min), the rate of elimination is reduced to about 50 % of normal. In patients with end-stage renal disease on haemodialysis and peritoneal dialysis, the rate of elimination is reduced to 25 % of normal.

Pharmacokinetics in hepatic dysfunction

In patients with mild to moderate hepatic dysfunction given single doses of radiolabelled zofenopril, the C_{max} and T_{max} values for zofenoprilat were similar to those in subjects with normal hepatic function. However, AUC values in cirrhotic patients were about twice those obtained for normal subjects, indicating that the initial dose of ZOFARIL CO for patients with mild to moderate hepatic

dysfunction should be half of that for patients with normal hepatic function. There are no pharmacokinetic data of zofenopril and zofenoprilat in patients with severe hepatic dysfunction, therefore zofenopril is contraindicated in these patients.

HYDROCHLOROTHIAZIDE

Absorption

Hydrochlorothiazide is well absorbed (65 – 75 %) following oral administration. Plasma concentrations are linearly related to the administered dose. The absorption of hydrochlorothiazide is dependent on intestinal transit time, being increased when the intestinal transit time is slow, for example when given with food. When plasma levels have been followed for at least 24 hours, the plasma half-life has been observed to vary between 5,6 and 14,8 hours and peak plasma levels were observed within 1 and 5 hours after dosing.

Distribution

The thiazides are widely distributed in body fluids and are extensively (92 %) bound to plasma proteins, particularly so to albumin, the substituted molecules being the most highly bound. This results in a lower renal clearance than the earlier compounds and in a more prolonged duration of action. No relationship has been demonstrated between hydrochlorothiazide plasma levels and the degree of reduction of blood pressure.

Elimination

Hydrochlorothiazide is eliminated primarily by renal pathway. Most of the thiazide is excreted in the urine unchanged and more than 95 % of hydrochlorothiazide appears unchanged in the urine within 3 – 6 hours after an oral dose. In patients with renal disease, plasma concentrations of hydrochlorothiazide are increased, and elimination half-life is prolonged. Hydrochlorothiazide crosses the placental but not the blood-brain barrier.

5.3 Preclinical safety data

The fixed combination zofenopril/hydrochlorothiazide revealed no special risks for human use, based on acute toxicity, repeated dose toxicity and genotoxicity studies. Reproductive toxicity of the combination has been studied in rats and rabbits and zofenopril and hydrochlorothiazide did not show to be teratogenic. However, in pregnant rats and rabbits the combination markedly increased the maternal toxicity induced by zofenopril alone. Carcinogenicity studies were not performed with the combination zofenopril/ hydrochlorothiazide. Carcinogenicity studies conducted in mice and rats with zofenopril alone revealed no evidence of carcinogenicity. Preclinical data of hydrochlorothiazide reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Hypromellose

Lactose monohydrate

Magnesium stearate

Maize starch

Microcrystalline cellulose

Silica, colloidal anhydrous

Tablet coating

Opadry Pink 02B24436:

Hypromellose

Titanium dioxide (E171)

Macrogol 400

Iron oxide red (E172)

Macrogol 6000

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

Store at or below 30 °C.

6.4 Special precautions for storage

Keep blister strips in outer carton until required for use.

6.5 Nature and contents of container

Transparent PVC/PVDC/silver aluminium blister strips packed into a cardboard carton.

Pack size: 28 tablets.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

LeBasi Pharmaceuticals (Pty) Ltd

San Domenico Building, Unit 6, Ground Floor

10 Church Street

Durbanville

7551

8. REGISTRATION NUMBER

55/7.1.3/0019.018

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

14 February 2023

10. DATE OF REVISION OF THE TEXT