Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

ZOFENIL 30 mg film-coated tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ZOFENIL 30 mg tablet contains 30 mg of zofenopril calcium as 28.7 mg of zofenopril.

Excipients with known effect:
Each ZOFENIL 30 mg film-coated tablet contains 69.4 mg of lactose monohydrate

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet
ZOFENIL 7.5 mg:
White round film-coated tablets with convex faces
ZOFENIL 30 mg:
White oblong film coated tablets with a break line. The tablet can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypertension
ZOFENILis indicated for the treatment of mild to moderate essential hypertension.

Acute Myocardial Infarction
ZOFENIL is indicated for the treatment initiated within the first 24 hours of patients with acute myocardial infarction with or without signs and symptoms of heart failure, who are haemodynamically stable and have not received thrombolytic therapy.

4.2 Posology and method of administration

Posology

Hypertension

Adults

The need for dosage titration should be determined by measurement of blood pressure just before the next dose. The dose should be increased at an interval of four weeks.

Patients without volume or salt depletion:
Treatment should be started with 15 mg once daily and titrated upwards to achieve optimal blood pressure control.

The usual effective dose is 30 mg once daily.

The maximum dose is 60 mg once daily.

In case of inadequate response, other antihypertensive agents such as diuretics may be added (see Sections 4.3, 4.4, 4.5 and 5.1).

Patients suspected of volumeor salt depletion
First-dose hypotension may occur in high risk patients (see Special warnings and precautions for use). Initiation of therapy with ACE inhibitors requires correction of salt and/or volume deficiencies, discontinuation of an existing diuretic therapy for

two to three days before ACE inhibition and a starting dose of 15 mg daily. If this is not possible, the initial dose should be 7.5 mg daily.

Patients at high risk for severe acute hypotension should be monitored closely preferably in hospital, for as long as the maximal effect is expected after administration of the first dose and whenever the dose of ACE inhibitor and/or diuretic is increased. This also applies to patients with angina pectoris or cerebrovascular disease in whom excessive hypotension could result in a myocardial infarction or cerebrovascular accident.

Renal impairment and dialysis
In hypertensive patients with mild renal impairment (creatinine clearance > 45 ml/min.) the same dose level and once-daily regimen for ZOFENIL can be employed as for patients with normal renal function. Patients with moderate to severe impairment (creatinine clearance < 45 ml/min.) should be given one-half the therapeutic dose of ZOFENIL; the once-daily dosage regimen does not require modification.

The starting dose and the dosage regimen of ZOFENIL for hypertensive patients maintained on dialysis should be one-quarter the dose used for patients with normal renal function.

Recent clinical observations have shown a high incidence of anaphylactoid-like reactions in patients on ACE inhibitors during haemodialysis with high-flux dialysis membranes or during LDL apheresis (see section 4.4 Special warnings and precaution for use).

Elderly (over 65 years)
In the elderly with normal creatinine clearance no adjustment is necessary.

In the elderly with reduced creatinine clearance (less than 45 ml/min) half of the daily dose is recommended.
Creatinine clearance may be estimated from serum creatinine by the following formula:

$$\text{Clearance Creatinine (ml/min)} = \frac{(140\text{-age}) \text{ X weight (Kg)}}{\text{Serum Cr. (mg/dl) X } 72}$$

The above method provides creatinine clearance in males. For females the value obtained should be multiplied by 0.85.

Hepatic impairment
In hypertensive patients with mild to moderate hepatic impairment, the starting dose of ZOFENIL is half of the dose for patients with normal hepatic function.
In hypertensive patients with severe liver impairment ZOFENIL is contraindicated

Paediatric population
The safety and efficacy of ZOFENIL in children and adolescents below 18 years has not been established. Therefore its use is not recommended.

Acute myocardial infarction

Adults
Treatment with ZOFENIL should begin within 24 hours after the onset of symptoms of acute myocardial infarction and continued for six weeks.

The posology should be as follows:
1st and 2nd day: 7.5 mg every 12 hours
3rd and 4th day: 15 mg every 12 hours
from 5th day and onwards: 30 mg every 12 hours

In the event of low systolic blood pressure (£120mmHg) at the start of treatment or during the first three days following myocardial infarction, the daily dose should not be increased. In the event of hypotension (£100mmHg), the treatment can be continued with the dose that was previously tolerated. In the event of severe hypotension (systolic blood pressure lower than 90mmHg in two consecutive measurement at least one hour apart), ZOFENIL should be discontinued.

After 6 weeks treatment patients must be re-evaluated and the treatment should be discontinued in patients without signs of left ventricular dysfunction or cardiac failure. If these signs are present, treatment might be continued long term.

Patients should also receive, as appropriate, the standard treatment such as nitrates, aspirin or b-blockers.

Elderly (over 65 years)
ZOFENIL should be used with caution in myocardial infarction patients who are more than 75 years of age.

Renal impairment and dialysis
The efficacy and safety of ZOFENIL in myocardial infarction patients with renal impairment or who are undergoing dialysis has not been established. Therefore, ZOFENIL should not be used in these patients.

Hepatic impairment
The efficacy and safety of ZOFENIL in myocardial infarction patients with hepatic impairment has not been established. Therefore, it should not be used in these patients.

Method of administration
Zofenil can be taken before, during or after meals. Dosage must be titrated according to the therapeutic response of the patient.

4.3 Contraindications

Hypersensitivity to zofenopril calcium, any other ACE inhibitor or any of the excipients listed in section 6.1.
History of angioneurotic oedema associated with previous ACE inhibitor therapy.
Concomitant use with sacubitril/valsartan therapy. Zofenil must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan (see also sections 4.4 and 4.5).
Hereditary/idiopathic angioneurotic oedema.
Severe hepatic impairment.
Second and third trimesters of pregnancy (see sections 4.4 and 4.6).
Women of child-bearing potential unless protected by effective contraception.
Bilateral renal artery stenosis or unilateral renal artery stenosis in cases of a solitary single kidney.
The concomitant use of ZOFENIL with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m2) (see Sections 4.5 and 5.1).

4.4 Special warnings and precautions for use

Hypotension:
As with other ACE inhibitors, ZOFENIL 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 ZOFENIL 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 accident.

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 drug after effective management.

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

Hypotension in acute myocardial infarction:
Treatment with ZOFENIL must not be initiated in acute myocardial infarction patients if there is a risk of additional serious heamodynamic depression following treatment with a vasodilator. These are patients with a systolic blood pressure of <100mmHg or with cardiogenic shock. Treatment with ZOFENIL in acute myocardial infarction patients may lead to severe hypotension. In the case of persistent hypotension (systolic blood pressure <90mmHg for more than one hour), ZOFENIL should be discontinued. In patients with severe heart failure following an acute myocardial infarction ZOFENIL should only be administered if the patient is haemodynamically stable.

Myocardial infarction patients with impaired hepatic function:
The efficacy and safety of ZOFENIL in myocardial infarction patients with hepatic impairment has not been established. Therefore, it should not be used in these patients

Elderly:
ZOFENIL should be used with caution in myocardial infarction patients ≥75 years of age

Patients with renovascular hypertension:
There is an increased risk of severe hypotension and renal insufficiency when patients with renovascular hypertension and pre-existing bilateral renal artery stenosis or stenosis of the artery to a solitary kidney are treated with ACE inhibitors. 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. If considered absolutely necessary, treatment with ZOFENIL should be started in hospital under close medical supervision with low doses and careful dose titration. Diuretic treatment should be discontinued temporarily when therapy with ZOFENIL is initiated and renal function be closely monitored during the first few weeks of therapy.

Patients with renal insufficiency:
ZOFENIL should be used with caution in patients with renal insufficiency as they require reduced doses. Close monitoring of renal function during therapy should be performed as deemed appropriate. Renal failure has been reported in association with ACE inhibitors, 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 ACE inhibitor and/or discontinuation of the diuretic may be required. It is recommended that the renal function be monitored closely during the first few weeks of therapy.

The efficacy and safety of ZOFENIL in myocardial infarction patients with renal impairment has not been established. Therefore, in presence of renal impairment (serum creatinine ≥ 2.1 mg/dl and proteinuria ≥500 mg/day) and myocardial infarction ZOFENIL should not be used.

Patients who are dialysed:
Patients who are dialysed using high-flux polyacrylonitrile membranes (e.g. AN 69) and treated with ACE inhibitors 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 medicinal product.

The efficacy and safety of ZOFENIL in myocardial infarction patients undergoing haemodialysis has not been established. Therefore, it should not be used in these patients.

Patients on LDL apheresis:
Patients treated with an ACE inhibitor 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 an agent from another class of antihypertensive drugs is used in these patients.

Anaphylactic reactions during desensitisation or after insect bites:
Rarely, patients receiving ACE inhibitors 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 medicinal product. Therefore, caution should be used in patients treated with ACE inhibitors undergoing such desensitisation procedures.

Kidney transplantation:
There is no experience regarding the administration of ZOFENIL in patients with a recent kidney transplantation.

Primary aldosteronism:
Patients with primary aldosteronism generally will not respond to antihypertensive drugs acting through inhibition of the renin-angiotensin system. Therefore the use of this product is not recommended.

Hypersensitivity/Angioedema:
Angioedema of the face, extremities, lips, mucous membranes, tongue, glottis and/or larynx may occur in patients treated with ACE inhibitors 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 ACE inhibitors should promptly be discontinued and replaced by an agent belonging to another class of drugs.

Angioedema involving the tongue, glottis or larynx may be fatal. Emergency therapy should be given including, but not necessarily limited to, immediate subcutaneous adrenaline solution 1:1000 (0.3 to 0.5 ml) or slow intravenous 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 an ACE inhibitor (see 4.3 Contraindication).
Concomitant use of ACE inhibitors 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 Zofenil. Treatment with Zofenil 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 ACE inhibitors 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 an ACE inhibitor.

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

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

Serum potassium:
ACE inhibitors 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 ACE inhibitors, 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, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended (see Section 4.5 and 5.1).
If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure.
ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

Surgery/Anaesthesia:

ACE inhibitors 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 the ACE inhibitor, intravascular and plasma volumes should be carefully monitored.

Aortic and mitral valve stenosis/Hypertrophic cardiomyopathy:
ACE inhibitors should be used with caution in patients with mitral valve stenosis and obstruction in the outflow of the left ventricule.

Neutropenia/Agranulocytosis:
Neutropenia/agranulocytosis, thrombocytopenia and anaemia have been reported in patients receiving ACE inhibitors. The risk of neutropenia appears to be dose- and type-related and is dependent on 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 agents, 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 zofenopril 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 zofenopril 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. Zofenopril and other concomitant medication (see section 4.5) should be withdrawn if neutropenia (neutrophils less than 1000/mm3) is detected or suspected.

It is reversible after discontinuation of the ACE inhibitor.

Psoriasis:
ACE inhibitors 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 ACE inhibitors. 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 patientspreviously treated with oral antidiabeticproductsor insulin, during the first month of treatment with an ACE inhibitor (see section 4.5).

Lithium:
The combination of Lithium and ZOFENIL is generally not recommended (see section 4.5).

Ethnic differences
As with other angiotensin converting enzyme inhibitors, zofenopril 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:
ACE inhibitors should not be initiated during pregnancy. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

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

4.5 Interaction with other medicinal products and other forms of interaction

Medicines increasing the risk of angioedema
Concomitant use of ACE inhibitors with sacubitril/valsartan is contraindicated as this increases the risk of angioedema (see section 4.3 and 4.4).

Concomitant use of ACE inhibitors 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 substitutesor other agents that increase serum potassium
Although serum potassium usually remains within normal limits, hyperkalaemia may occur in some patients treated with zofenopril. 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 zofenopril is co-administered with other agents 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 zofenopril with the above-mentioned drugs 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, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent (see Sections 4.3, 4.4 and 5.1).

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 zofenopril (see 4.4). The hypotensive effects can be reduced by discontinuation of the diuretic, by increasing volume or salt intake or by initiating therapy with a low dose of zofenopril.

Lithium
Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors. Concomitant use of thiazide diuretics may increase the risk of lithium toxicity and enhance the already increased risk of lithium toxicity with ACE inhibitors.

Therefore, Zofenil is not recommended in association with lithium and careful monitoring of serum lithium levels should be performed if the concomitant use proves necessary.

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 ACE inhibitor therapy.

Anaesthetic medicinal products
ACE inhibitors may enhance the hypotensive effects of certain anaesthetic medicinal products.

Narcotic drugs/Tricyclic antidepressants/Antipsychotics/Barbiturates
Postural hypotension may occur.

Other antihypertensive substances (e.g. Beta-blockers, alpha-blockers, calcium antagonists)
There may be additive hypotensive effect or potentiation. Treatment with nitroglycerine and other nitrates, or other vasodilators, should be used with caution.

Cimetidine
May enhance the risk of hypotensive effect.

Cyclosporin
Hyperkalaemia may occur during concomitant use of ACE inhibitors with cyclosporin.
Monitoring of serum potassium is recommended.

Heparin

Hyperkalaemia may occur during concomitant use of ACE inhibitors with heparin. Monitoring of serum potassium is recommended.

Allopurinol, cytostatic or immunosuppressive agents, systemic corticosteroids or procainamide
Increased risk of hypersensitivity reactions when ACE inhibitors are used concurrently. Concomitant administration with ACE inhibitors may lead to an increased risk of leukopenia.

Antidiabetics.
Rarely ACE inhibitors 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 ACE inhibitors.

Haemodialysis with high-flux dialysis membranes. Increased risk of anaphylactoid reactions when ACE inhibitors are used concurrently.

To be taken into account with concomitant use
Non-Steroidal Anti-inflammatory medicinal products (including ASA ≥ 3g/day)
The administration of non-steroidal anti-inflammatory agents may reduce the antihypertensive effect of an ACE inhibitor. Furthermore, it has been described that NSAIDS and ACE inhibitors exert an additive effect on the increase in serum potassium whereas renal function may decrease. These effects are in principle reversible, and occur especially in patients with compromised renal function. Rarely, acute renal failure may occur, particularly in patients with compromised renal function such as the elderly or dehydrated.

Antacids
Reduce the bioavailability of ACE inhibitors.

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

Food
May reduce the rate but not the extent of absorption of zofenopril calcium.

Additional information
Direct clinical data on the interaction of zofenopril with other drugs which are metabolised by CYP enzymes are not available. However, in vitro metabolic studies with zofenopril demonstrated no potential interaction with drug that are metabolised by CYP enzymes.

4.6 Fertility, pregnancy and lactation

Pregnancy
The use of ACE inhibitors is not recommended during the first trimester of pregnancy (see section 4.4). The use of ACE inhibitors is contraindicated during the second and third trimester of pregnancy (see sections 4.3 and 4.4).
Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started.

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

Breast-feeding
Because no information is available regarding the use of ZOFENIL during breastfeeding, ZOFENIL is not recommended and alternative treatments with better established safety profiles during breastfeeding are preferable, especially while nursing a newborn or preterm infant.

4.7 Effects on ability to drive and use machines

There are no studies on the effect of ZOFENIL on the ability to drive. When driving vehicles or operating machines it should be remembered that occasionally drowsiness, dizziness or weariness may occur.

4.8 Undesirable effects

Tabulated list of adverse reactions

The table below shows all the adverse reactions that have been reported during clinical practice in patients treated with ZOFENIL. 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)

MedDRA System Organ Class	Adverse reactions	Frequency
Nervous system disorders	Dizziness	Common
	Headache	Common
Cardiac disorders	Palpitations	Rare
Vascular disorders	Hypotension (see section 4.4)	Rare
	Syncope	Rare
Respiratory, thoracic and mediastinal disorders	Cough	Common
Gastrointestinal disorders	Nausea	Common
	Vomiting	Common
Skin and subcutaneous tissue disorders	Rash	Uncommon
	Angioedema	Rare
	Pruritus	Rare
	Urticaria	Rare
Musculoskeletal and connective tissue disorders	Muscle cramp	Uncommon
General disorders and administration site conditions	Fatigue	Common
	Asthenia	Uncommon
Metabolism and nutrition disorders	Hyperkalaemia (see section 4.4, 4.5)	Rare

The following adverse reactions have been observed associated with ACE inhibitors therapy.

Blood and lymphatic system disorders
In a few patients agranulocytosis and pancytopenia may occur.

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

Metabolism and nutrition disorders
Very rare hypoglycaemia

Endocrine disorders
Not known, inappropriate antidiuretic hormone secretion.

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

Nervous system disorders
Occasionally paraesthesia, dysgeusia, balance disorder.

Eye disorders
Rarely, vision blurred.

Ear and labyrinth disorders
Rarely, tinnitus.

Cardiac disorders
Individual cases of tachycardia, arrhythmias, angina pectoris, 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 Special warnings and precautions for use). In association with hypotension, symptoms like dizziness, feeling of weakness, impaired vision.
Rarely flushing occurs.

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.

Gastro-intestinal 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

Hepatobiliary 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 erythema multiforme, Stevens-Johnson syndrome, toxic epidermic necrolysis, psoriasis-like efflorescences, alopecia.
This can be accompanied by fever, myalgia, arthralgia, eosinophilia and/or increased ANA- titers.
Rarely hyperhidrosis occurs.

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 Special warnings and precautions for use).
Rarely micturition disorders occur.

Reproductive system and breast disorders
Rarely, erectile dysfunction.

General disorders and administration site conditions.
Very rarely oedema peripheral 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.

Reporting of suspected adverse reactions:
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, website: www.hpra.ie.

4.9 Overdose

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

After ingestion of an overdose, the patients 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 gastric lavage and 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 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 hemodialysis. The use of high-flux polyacrylonitrile membranes should be avoided.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ACE inhibitor, ATC code: C09AA15.

The beneficial effects of ZOFENIL in hypertension and acute myocardial infarctionappear to result primarily from the suppression of the plasma renin-angiotensin aldosterone system. Inhibition of ACE (Ki 0.4 nM in rabbit lung for arginine salt of zofenoprilat) results in decreased plasma angiotensin II, which leads to decreased vasopressor activity and to reduced aldosterone secretion. Although the latter decrease is small, small increases in serum potassium concentrations may occur, 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 plasma ACE activity is suppressed by 53.4% at 24 hours after administration of a single oral dose of 30 mg zofenopril calcium.

Inhibition of ACE results in an increased activity of circulating and local kallikrein-kinin-system, which contributes to peripheral vasodilatation by activating the prostaglandin system. It is possible that this mechanism is involved in the hypotensive effect of zofenopril calcium and is responsible for certain side effects.

In patients with hypertension, administration of ZOFENIL results in a reduction of supine and standing blood pressure to about the same extent, with no compensatory increase of the heart rate. Mean systemic vascular resistance tends to decline after ZOFENIL administration.

Achievement of optimal blood pressure reduction may require several weeks of therapy in some patients. The antihypertensive effects are maintained during long term therapy.

Abrupt withdrawal of therapy has not been associated with a rapid increase in blood pressure.Currently there are no data regarding the effects of ZOFENIL on morbidity and mortality in hypertensive patients.

Although antihypertensive effects have been found in all races studied, black hypertensive patients (usually a low-renin hypertensive population) has a smaller average response to ACE inhibitor monotherapy than non-black patients. This difference disappears when a diuretic is added.

The clinical effect resulting from the early use of ZOFENIL following myocardial infarction may be linked to many factors such as the reduction in plasma levels of angiotensin II (in this way limiting the process of ventricular remodelling which can negatively influence the quod vitam prognosis of the infarction patient), and the increase in plasma/tissue concentrations of vasodilator substances (prostaglandins-kinin system)

A randomised, placebo-controlled clinical trial of zofenopril was performed in 1,556 patients with anterior myocardial infarction who had not received thrombolytic therapy. Treatment was begun within 24 hours and continued for 6 weeks. The incidence of the primary combined endpoint (severe heart failure and/or death at 6 weeks) was reduced in zofenopril-treated patients (zofenopril 7.1%, placebo 10.6%). At one year, the survival rate was improved in the ZOFENILgroup.

<u>Other information:</u>

Two large randomised, controlled trials (ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial), VA NEPHRON-D (The Veterans Affairs Nephropathy in Diabetes) have examined the use of combination of an ACE-inhibitor with an angiotensin II receptor blocker.

ONTARGET was a study conducted in patients with a history of cardiovascular or cerebrovascular disease, or type 2 diabetes mellitus accompanied by evidence of end-organ damage. VA NEPHRON-D was a study in patients with type 2 diabetes mellitus and diabetic nephropathy.
These studies have shown no significant beneficial effect on renal and/or cardiovascular outcomes and mortality, while an increased risk of hyperkalaemia, acute kidney injury and/or hypotension as compared to monotherapy was observed.
Given their similar pharmacodynamic properties, these results are also relevant for other ACE- inhibitors and angiotensin II receptor blockers.
ACE-inhibitors and angiotensin II receptor blockers should therefore not be used concomitantly in patients with diabetic nephropathy.
ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints) was a study designed to test the benefit of adding aliskiren to a standard therapy of an ACE-inhibitor or an angiotensin II receptor blocker in patients with type 2 diabetes mellitus and chronic kidney disease, cardiovascular disease, or both. The study was terminated early because of an increased risk of adverse outcomes. CV death and stroke were both numerically more frequent in the aliskiren group than in the placebo group and adverse events and serious adverse events of interest (hyperkalaemia, hypotension and renal dysfunction) were more frequently reported in the aliskiren group than in the placebo group.

5.2 Pharmacokinetic properties

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

Absorption:
Zofenopril calcium is rapidly and completely absorbed by the oral route and undergoes nearly complete conversion to zofenoprilat, which reaches peak blood levels after 1.5 h following an oral dose of ZOFENIL. Single dose kinetics are linear over a dose-range of 10-80 mg of zofenopril calcium and no accumulation occurs after the administration of 15-60mg of zofenopril calcium 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 calcium 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 calcium. The main metabolite is zofenoprilat (22%), which is then metabolized through several pathways, including glucuronide conjugation (17%), cyclization and glucuronide conjugation (13%), cysteine conjugation (9%) and S-methylation of the thiol group (8%). Half-life of zofenoprilat is 5.5 h and its total body clearance is 1300 ml/min following oral zofenopril calcium.

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).

Pharmacokinetics in special populations
Pharmacokinetics in the elderly:
In the elderly, 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 calcium, patients with mild renal impairment (creatinine clearance >45 and <90 ml/min) eliminate zofenopril from the body at the same rate as normal subjects (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. This indicates that these patients should be given half the usual starting dose of ZOFENIL.

In patients with end stage renal disease on haemodialysis and peritoneal dialysis, the rate of elimination is reduced to 25% of normal. This indicates that these patients should be given a quarter of the usual starting dose of ZOFENIL.

Pharmacokinetics in hepatic dysfunction:
In patients with mild to moderate hepatic dysfunction given single doses of radiolabelled zofenopril calcium, the Cmax and Tmax values for zofenoprilat were similar to those in normal subjects. However, AUC values in cirrhotic patients were about twice those obtained for normal subjects, indicating that the initial dose of ZOFENIL 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.

5.3 Preclinical safety data

In repeat oral dose toxicity studies conducted in three mammalian species most of the treatment related effects where those usually reported for ACE inhibitors. These changes included a decrease in erythrocytic parameters, an increase in serum urea nitrogen, a decrease in heart weight and hyperplasia of the juxta-glomerular cells which occurred at dose levels much higher than the maximum recommended human dose. In a repeat dose oral toxicity study in the dog, species-specific immunologically-mediated blood dyscrasias occurred at high dose levels.

No significant changes in cytochrome P450 enzyme activities have been observed in a 1 year repeated oral toxicity study in the monkey.

In reproductive toxicity studies, zofenopril caused a dose related reduction in growth rate in offspring and also nephrotoxicity and reduced postnatal viability at dose levels of 90 and 270 mg/kg in the F1 generation. Treatment with zofenopril during pregnancy caused foetal and developmental toxicity in offspring in the rat and also embryo- and feto-toxicity in the rabbit but only at maternally toxic dose levels.

Genotoxicity studies showed that zofenopril was not mutagenic or clastogenic.

Carcinogenicity studies conducted in mice and rats revealed no evidence of carcinogenicity. An increased incidence of testicular atrophy occurred only in the mouse study, the clinical significance of which is unknown.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:
Microcrystalline cellulose
Lactose monohydrate
Croscarmellose sodium
Magnesium stearate
Colloidal anhydrous silica

Coat:
Hypromellose
Titanium dioxide (E171)
Macrogol 400
Macrogol 6000

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

No special precautions for storage

6.5 Nature and contents of container

Blister PVDC /PVC/aluminium or Aclar/Aluminium, packs of:
7, 14, 15, 28, 30, 50, 50 unit doses, 56, 56 unit doses, 90 or 100 film coated tablets
(Not all pack sizes may be marketed.)

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

Menarini International Operations Luxembourg S.A.
1, Avenue de la Gare
1611 Luxembourg
Luxembourg

8 MARKETING AUTHORISATION NUMBER

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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