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

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CPMP/2011/00

COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP) SUMMARY INFORMATION ON A Referral OPINION FOLLOWING AN ARBITRATION ACCORDING TO ARTICLE 7(5) OF COMMISSION REGULATION (EC) No 541/95 AS AMENDED, FOR

Zofenil/Zopranol/Bifril

International Nonproprietary Name (INN): **zofenopril**

BACKGROUND INFORMATION

Zofenil/Zopranol/Bifril is supplied in film-coated tablet containing 4.5, 15, 30 or 60 mg of the active substance zofenopril, which is an angiotensin converting enzyme inhibitor. The indication when first authorised in all Member States following a Mutual Recognition Procedure was the treatment of mild to moderate essential hypertension.

In October 1999, Menarini International Operations Luxembourg SA submitted applications for a Type II variation in the Mutual Recognition procedure, with the United Kingdom as Reference Member State, for Zofenil/Zopranol/Bifril. The scope of the variation was to extend the indication to include the treatment of acute myocardial infarction and to update the SPC. The Mutual Recognition Variation procedure started on 29 November 1999. The Concerned Member States were Belgium, Denmark, Germany, Greece, Spain, Finland, France, Ireland, Italy, Luxembourg, The Netherlands, Austria, Portugal, and Sweden. The Concerned Member State, Germany, not agreeing with the Reference Member State's Final Variation Assessment Report referred the reasons for disagreement to the EMEA on 5 June 2000, with a request to initiate an arbitration procedure in order to clarify the matter.
The objections raised by Germany were related to grant an indication in patients with an acute myocardial infarction of any site and in patients who received thrombolytic therapy.

The arbitration procedure started on 30 June 2000.
The CPMP, having considered the points of disagreement, the proposed Summary of Product Characteristics by the (Co-)Rapporteurs and the written comments provided by the Marketing Authorisation Holders, was of the opinion by consensus that the objections raised by Germany should not prevent the approval of the variation applied for.
The CPMP therefore adopted a positive opinion on 27 July 2000 CPMP recommending the granting of the variation of the Marketing Authorisation for Zofenil/Zopranol/Bifril, and the amendment of the Summary of Product Characteristics.
An overall summary of the scientific evaluation is provided, together with the amended SPC.

A Decision was issued by the European Commission on 29 November 2000.

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 86 13
E-mail: mail@emea.eudra.org http://www.eudra.org/emea.html

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF Zofenil/Zopranol/Bifril

- Efficacy issues

The CPMP considered that a restrictive indication in the acute anterior myocardial infarction does not seem appropriate as it is essentially one disease and it will be difficult and unusual for the prescriber to choose the medicinal product depending of the topography of the acute myocardial infarction.
Apart from this point, the indication should reflect the population studied, i.e. haemodynamically stable patients, who have not received thrombolytic therapy.
The pharmacodynamic section of the SPC (section 5.1) should summarise the supporting data of this indication mentioning that they were obtained from patients with anterior myocardial infarction who had not received thrombolytic therapy.

Thus, the CPMP considered that the data suggest that early treatment with zofenopril initiated within the first 24 hours in patients with acute myocardial infarction with or without signs and symptoms of heart failure, who are haemodynamically stable, and have not received thrombolytic therapy, is safe and offers benefits in term of;

- reducing severe heart failure and/or death at short-term,
- and improving survival at one year.

GROUNDS FOR AMENDMENT OF THE SUMMARIES OF PRODUCT CHARACTERISTICS

Whereas

- The indication should not be limited to a specific topographic site of acute myocardial infarction,

- Apart from the above, the indication should reflect the data available which should be summarised in section 5.1 of the SPC.

the CPMP has recommended the amendment of the Summaries of Product Characteristics for which the Summary of Product Characteristic (of the 7.5 mg strength as relevant example) is set out in the Annex to this summary.

ANNEX

AMENDED SUMMARY OF PRODUCT CHARACTERISTICS
OF THE REFERENCE MEMBER STATE

1. NAME OF THE MEDICINAL PRODUCT

ZOFENIL/ZOPRANOL/BIFRIL 7.5 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ZOFENIL/ZOPRANOL/BIFRIL 7.5 mg tablet contains 7.2 mg of zofenopril as 7.5 mg of zofenopril calcium.

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets
ZOFENIL/ZOPRANOL/BIFRIL 7.5 mg:
White round film coated tablets with convex faces

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Hypertension

ZOFENIL/ZOPRANOL/BIFRIL is indicated for the treatment of mild to moderate essential hypertension.

Acute Myocardial Infarction

ZOFENIL/ZOPRANOL/BIFRIL 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

ZOFENIL/ZOPRANOL/BIFRIL can be taken before, during or after meals. Dosage must be titrated according to the therapeutic response of the patient.

Hypertension

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 per day administered in a single or two divided doses.

In case of inadequate response, other antihypertensive agents such as diuretics may be added.

Patients suspected of volume or 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.

Dosage in patients with 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/ZOPRANOL/BIFRIL 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/ZOPRANOL/BIFRIL; the once-daily dosage regimen does not require modification.

The starting dose and the dosage regimen of ZOFENIL/ZOPRANOL/BIFRIL 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»).

Dosage in the elderly:
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:

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

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

Dosage in hepatic impairment:
In hypertensive patients with mild to moderate hepatic impairment, the starting dose of ZOFENIL/ZOPRANOL/BIFRIL is half of the dose for patients with normal hepatic function.
In hypertensive patients with severe liver impairment ZOFENIL/ZOPRANOL/BIFRIL is contraindicated

Children:
The safe or effective use of ZOFENIL/ZOPRANOL/BIFRIL in children has not been established. Therefore, it should not be used in children.

Acute myocardial infarction

Treatment with ZOFENIL/ZOPRANOL/BIFRIL 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/ZOPRANOL/BIFRIL 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 β-blockers.

Dosage in the elderly:
ZOFENIL/ZOPRANOL/BIFRIL should be used with caution in myocardial infarction patients who are more than 75 years of age.

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

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

4.3. Contra-indications

- Hypersensitivity to zofenopril calcium or any other ACE inhibitor.
- History of angioneurotic oedema associated with previous ACE inhibitor therapy.
- Hereditary/idiopathic angioneurotic oedema.
- Severe hepatic impairment.
- Pregnancy.
- Lactation period.
- 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.

4.4. Special warnings and special precautions for use

Hypotension:
As with other ACE inhibitors, ZOFENIL/ZOPRANOL/BIFRIL may cause a profound fall in blood pressure especially after the first dose. Symptomatic hypotension is rare in uncomplicated hypertensive patients.

It is more likely to occur in patients who have been volume depleted by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting. It has been reported mainly in patients with severe heart failure with or without associated renal insufficiency. This is more likely in patients on high doses of loop diuretics, or those with hyponatraemia or functional renal impairment. In these patients 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/ZOPRANOL/BIFRIL is initiated. Such considerations apply also to patients with angina pectoris or cerebrovascular disease in whom excessive hypotension could result in a 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.

Hypotension in acute myocardial infarction:
Treatment with ZOFENIL/ZOPRANOL/BIFRIL 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/ZOPRANOL/BIFRIL 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/ZOPRANOL/BIFRIL should be discontinued. In patients with severe heart failure following an acute myocardial infarction ZOFENIL/ZOPRANOL/BIFRIL should only be administered if the patient is haemodynamically stable.

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

Elderly:
ZOFENIL/ZOPRANOL/BIFRIL 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/ZOPRANOL/BIFRIL 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/ZOPRANOL/BIFRIL is initiated and renal function be closely monitored during the first few weeks of therapy.

Patients with renal insufficiency:
ZOFENIL/ZOPRANOL/BIFRIL 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/ZOPRANOL/BIFRIL 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/ZOPRANOL/BIFRIL should not be used.

Patients who are dialysed:
Patients who are dialysed using high-flux polyacrylonitrile membranes 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/ZOPRANOL/BIFRIL 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 or after insect bites have experienced life-threatening anaphylactoid reactions. These reactions are avoided by temporarily withholding ACE inhibitor therapy prior to each desensitisation.

Kidney transplantation:
There is no experience regarding the administration of ZOFENIL/ZOPRANOL/BIFRIL 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.

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.

Cough:
During treatment with ZOFENIL/ZOPRANOL/BIFRIL a dry and non-productive cough may occur which disappears after discontinuation of ZOFENIL/ZOPRANOL/BIFRIL.
Hyperkalaemia:

Hyperkalaemia may occur during treatment with an ACE inhibitor, especially in the presence of renal insufficiency and/or heart failure. Potassium supplements or potassium sparing diuretics are generally not recommended, since they may lead to significant increases in plasma potassium. If concomitant use of the above mentioned agents is deemed appropriate, they should be used with frequent monitoring of serum potassium.

Surgery/Anaesthesia:
ACE inhibitors may cause hypotension or even hypotensive shock in patients undergoing major surgery or during anaesthesia. If it is not possible to withhold the ACE inhibitor, intravascular and plasma volumes should be carefully monitored.

Aortic stenosis/Hypertrophic cardiomyopathy:
ACE inhibitors should be used with caution in patients with left ventricular outflow tract obstruction.

Neutropenia/Agranulocytosis:
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. 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.

4.5. Interactions with other medicinal products and other forms of interaction

Not recommended association

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

Precaution for use

Diuretics. Patients on diuretics and especially those who are volume and/or salt depleted, may experience an excessive reduction of blood pressure after initiation of therapy with an ACE inhibitor. The possibility of hypotensive effects can be reduced by initiation of therapy with lower doses of the ACE inhibitor.
Further increases in dosage should be with caution.

Lithium. The concomitant administration of ACE inhibitors with lithium may reduce the excretion of lithium. Serum lithium levels should be monitored frequently.

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

Narcotic drugs/Antipsychotics. Postural hypotension may occur.

Antihypertensive agents. β-blockers, α-blockers and diuretics may increase the hypotensive effect of ACE inhibitors.

Cimetidine. May enhance the risk of hypotensive effect.

Cyclosporin. Increased risk of renal dysfunction when ACE inhibitors are used concurrently.

Allopurinol. Increased risk of hypersensitivity reactions when ACE inhibitors are used concurrently. Data from other ACE inhibitors indicate an increased risk of leucopenia when used concurrently.

Insulin or oral hypoglycaemic agents. Increased risk of hypoglycaemia when ACE inhibitors are used concurrently.

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

Cytostatic or immunosuppressive agents, systemic corticosteroids or procainamide. Concomitant administration with ACE inhibitors may lead to an increased risk of leucopenia.

Take into account

Non-Steroidal Anti-inflammatory medicinal products. 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.

Antacids. Reduce the bioavailability of ACE inhibitors.

Sympathomimetics. May reduce the antihypertensive effects of ACE inhibitors.

Alcohol. Enhances the hypotensive effect.

*Food. M*ay reduce the rate but not the extent of absorption of zofenopril calcium.

Other Drug Interactions

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. Pregnancy and lactation

ZOFENIL/ZOPRANOL/BIFRIL is contraindicated in pregnancy and should not be used in women of child bearing potential unless protected by effective contraception.

Foetal exposure to ACE inhibitors during the second and third trimesters has been associated with neonatal hypotension, renal failure, face or skull deformities and/or death. Maternal oligohydramnios has also been reported reflecting decreasing renal function in the foetus. Limb contractures, craniofacial deformities, hypoplastic lung development and intrauterine growth retardation have been reported in association with

oligohydramnios. Infants exposed in utero to ACE inhibitors should be closely observed for hypotension, oliguria and hyperkalemia. Oliguria should be treated with support of blood pressure and renal perfusion.

It is not known whether exposure limited to the first trimester can adversely affect foetal outcome. Women who become pregnant while receiving an ACE inhibitor should be informed of the potential hazard to the foetus.

Use during lactation.
Because zofenopril calcium is excreted in breast milk, ZOFENIL/ZOPRANOL/BIFRIL should not be used in nursing mothers.

4.7. Effects on ability to drive and use machines

There are no studies on the effect of ZOFENIL/ZOPRANOL/BIFRIL 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

The most commonly undesirable effects typical of ACE inhibitors occurred in clinical trials in patients treated with ZOFENIL/ZOPRANOL/BIFRIL were the following:

Common:
dizziness 3.9%, fatigue 2.6%, headache 2.4%, cough 1.2%, nausea/vomiting 1.2%,

Uncommon:
rash 0.8%, muscle cramp 0.8%, weakness 0.5%.

The following adverse reactions have been observed associated with ACE inhibitors therapy.
Cardiovascular system. Severe hypotension has occurred after initiation or increase of therapy. This occurs especially in certain risk groups (see Special warnings and precautions for use). Symptoms like dizziness, feeling of weakness, impaired vision, rarely with disturbance of consciousness (syncope) can occur.

Individual cases of tachycardia, palpitations, arrhythmias, angina pectoris, myocardial infarction, transient ischemic attacks and cerebral haemorrhage have been reported for ACE inhibitors in association with hypotension.

Very rarely, peripheral oedema, orthostatic hypotension and chest pain have been reported.

Musculoskeletal system. Occasionally, myalgia and muscle cramps can occur.

Renal system. Renal insufficiency may occur or be intensified. Acute renal failure has been reported (see Special warnings and precautions for use).

Respiratory system. ACE inhibitors have been documented to induce cough in a substantial number of patients. 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 tract. Occasionally nausea, abdominal pain, indigestion, vomiting, diarrhoea, constipation and dry mouth can occur.

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

Skin, and appendages. Occasionally allergic and hypersensitivity reactions can occur like rash, pruritus, urticaria, 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.

Nervous system. Occasionally headaches, dizziness, weariness; rarely, depression, mood changes, sleep disorders, paraesthesias, impotence, disorders of balance, confusion, tinnitus, blurred vision and taste disturbances.

Laboratory parameters. Increases in blood urea and plasma 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. This includes agranulocytosis and pancytopenia. There are reports of haemolytic anaemia in patients with glucose-6-phosphate dehydrogenase deficiency. Increases in serum levels of hepatic enzymes and bilirubin have also been reported

General. Rarely, increased sweating, flushing and abnormal micturition occur.

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

ATC code: C09AA.

The beneficial effects of ZOFENIL/ZOPRANOL/BIFRIL in hypertension and acute myocardial infarction appear 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% and 74.4% at 24 hours after administration of single oral doses of 30 mg and 60 mg zofenopril calcium respectively.

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/ZOPRANOL/BIFRIL 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/ZOPRANOL/BIFRIL 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/ZOPRANOL/BIFRIL 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/ZOPRANOL/BIFRIL 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 Zofenil 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/ZOPRANOL/BIFRIL. 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.

Metabolism:
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.

Excretion:
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 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/ZOPRANOL/BIFRIL.

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/ZOPRANOL/BIFRIL.

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/ZOPRANOL/BIFRIL 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 feetal 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, maize starch, magnesium stearate, colloidal anhydrous silica
Coat: hydroxypropylmethyl cellulose (hypromellose), titanium dioxide (E171), macrogol 400, macrogol 6000

6.2. Incompatibilities

None stated

6.3. Shelf life

3 years

6.4. Special precautions for storage

No special precautions for storage

6.5. Nature and contents of container

6.6. Instruction for use and handling, and disposal

No special requirements

7. MARKETING AUTHORISATION HOLDER

8. MARKETING AUTHORISATION NUMBER

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

10. DATE OF REVISION OF THE TEXT