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BIFRIL® 30 mg film-coated tablets

108202

Zofenopril Calcium

COMPOSITION
Each film-coated tablet of BIFRIL 30 mg film-coated tablets contains:
Active ingredient: 28.7 mg zofenopril equal to 30 mg calcium zofenopril
Other ingredients:
Core: microcrystalline cellulose, monohydrate lactose, corn starch, magnesium stearate, anhydrous precipitated silica.
Coating: hypromellose, titanium dioxide (E 171), macrogol 400, macrogol 6000.

PHARMACEUTICAL FORM
White oblong film coated tablets with a breakline

THERAPEUTIC INDICATIONS
Hypertension
BIFRIL is indicated for the treatment of mild to moderate essential hypertension.
Acute Myocardial Infarction
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.

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MANUFACTURER
A. Menarini Manufacturing Logistics and Services s.r.l. - Campo di Pile - L'Aquila - Italy.

CONTRA-INDICATIONS
- Hypersensitivity to zofenopril calcium, any other ACE inhibitor or any of the excipients.
- 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.

SPECIAL PRECAUTIONS FOR USE
Hypotension:
As with other ACE inhibitors, 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 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 BIFRIL must not be initiated in acute myocardial infarction patients if there is a risk of additional serious haemodynamic depression following treatment with a vasodilator. These are patients with a systolic blood pressure of <100mmHg or with cardiogenic shock. Treatment with 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), BIFRIL should be discontinued. In patients with severe heart failure following an acute myocardial infarction BIFRIL should only be administered if the patient is haemodynamically stable.
Myocardial infarction patients with impaired hepatic function:
The efficacy and safety of BIFRIL in myocardial infarction patients with hepatic impairment has not been established. Therefore, it should not be used in these patients
Elderly:
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 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 BIFRIL is initiated and renal function be closely monitored during the first few weeks of therapy.
Patients with renal insufficiency:
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 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 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 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 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 BIFRIL a dry and non-productive cough may occur which disappears after discontinuation of 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.

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. May 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.

SPECIAL WARNINGS

Use in pregnancy
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, BIFRIL should not be used in nursing mothers.
Effects on ability to drive and use machines:
There are no studies on the effect of BIFRIL on the ability to drive. When driving vehicles or operating machines it should be remembered that occasionally drowsiness, dizziness or weariness may occur.

POSOLOGY AND METHOD OF ADMINISTRATION

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 precaution 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 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 BIFRIL; the once-daily dosage regimen does not require modification.

The starting dose and the dosage regimen of 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 "Special 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:

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

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

Dosage in hepatic impairment:

In hypertensive patients with mild to moderate hepatic impairment, the starting dose of BIFRIL is half of the dose for patients with normal hepatic function.

In hypertensive patients with severe liver impairment BIFRIL is contraindicated.

Children:

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

Acute myocardial infarction

Treatment with 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), 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:

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 BIFRIL in myocardial infarction patients with renal impairment or who are undergoing dialysis has not been established. Therefore, BIFRIL should not be used in these patients.

Dosage in patients with hepatic impairment:

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

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.

UNDESIRABLE EFFECTS

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

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)

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

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, 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.

SPECIAL PRECAUTIONS FOR STORAGE

No particular precautions for storage are required.
Caution: do not use the medicine after the expiration date indicated on the package.
It is important to always have information on the medicine available, so please keep the box and patient information leaflet.
Keep out the reach of children.