SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Bifril Plus 30 mg/12.5 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 28.7 mg of zofenopril as 30 mg of zofenopril calcium and 12.5 mg of hydrochlorothiazide.

Excipients with known effect:
Each film-coated tablet contains 56.20 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Pastel-red, round, slightly bi-convex tablets of 9 mm with a score line on one side.
The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of mild to moderate essential hypertension.
This fixed dose combination is indicated in patients whose blood pressure is not adequately controlled on zofenopril alone.

4.2 Posology and method of administration

Posology

Adults
Dose titration with the individual components (i.e. zofenopril and hydrochlorothiazide) is recommended before changing to the fixed dose combination.
When clinically appropriate direct change from monotherapy to the fixed combination may be considered.

Patients without volume or salt depletion
The usual effective dose is one tablet once daily.

Patients suspected of volume or salt depletion
The use of Bifril Plus is not recommended.

Elderly (over 65 years)

In the elderly with normal creatinine clearance no dose adjustment is necessary.
In the elderly with reduced creatinine clearance (less than 45 mL/min) the use of Bifril Plus is not recommended.
Creatinine clearance may be estimated from serum creatinine by the following Cockroft-Gault formula:

$$\text{CrCl (mL/min)} = \frac{[(140 - \text{age}) * \text{weight (Kg)}]}{72 * \text{serum Cr (mg/dL)}}$$

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

Paediatric population

The safety and efficacy of Bifril Plus in children and adolescents below 18 years has not been established. Therefore, its use is not recommended.

Renal impairment and dialysis

In hypertensive patients with mild impairment (creatinine clearance > 45 mL/min) the same dose level and once-daily regimen of Bifril Plus can be employed as for patients with normal renal function.
In patients with moderate to severe impairment (creatinine clearance < 45 mL/min) its use is not recommended (see section 4.4).
In patients with severe renal impairment (creatinine clearance <30 ml/min) Bifril Plus is contraindicated (see section 4.3).
In hypertensive patients maintained on dialysis the use of Bifril Plus is not recommended.

Hepatic impairment

In hypertensive patients with mild to moderate hepatic impairment, where the 30 mg dose of zofenopril alone has been achieved, the same dose regimen can be employed as for patients with normal hepatic function.
In hypertensive patients with severe liver impairment Bifril Plus is contra-indicated.

Method of administration

Bifril Plus should be used once daily, with or without food.

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

4.3 Contraindications

Second and third trimester of pregnancy (see sections 4.4 and 4.6).

Hypersensitivity to zofenopril or any other ACE inhibitor.

Hypersensitivity to hydrochlorothiazide or other sulphonamide-derived substances.

Hypersensitivity to 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. Bifril Plus 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.

Severe renal impairment (creatinine clearance < 30 mL/min)

Bilateral renal artery stenosis or unilateral renal artery stenosis in cases of a solitary single kidney.

The concomitant use of Bifril Plus 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

ZOFENOPRIL

Hypotension :
As with other ACE inhibitors and diuretics, Bifril Plus 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 Bifril Plus 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 occurrence of hypotension after the initial
dose does not preclude subsequent careful dose titration with each component of the medicinal product after effective management.

Patients with renovascular hypertension:
There is an increased risk of severe hypotension and renal insufficiency when patients with bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney are treated with ACE inhibitors. Treatment with diuretics may be a contributory factor. Loss of renal function may occur with only mild changes in serum creatinine even in patients with unilateral renal artery stenosis.
In these patients, therapy should be initiated under close medical supervision with low dose, careful titration and monitoring of renal function.

Patients with renal insufficiency:
Close monitoring of renal function during therapy should be performed as deemed appropriate. Renal failure has been reported in association with 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 individual components may be required. It is recommended that the renal function be monitored closely during the first few weeks of therapy.

Patients who are dialysed:
Patients who are dialysed using high-flux polyacrylonitrile membranes (e.g. AN 69) and treated with ACE inhibitors 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 zofenopril 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 dextran 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 products 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 Bifril Plus in patients with a recent kidney transplantation. Its use in transplant recipients is therefore not recommended.

Primary aldosteronism:
Patients with primary aldosteronism generally will not respond to antihypertensive products acting through inhibition of the renin-angiotensin system. Therefore the use of zofenopril 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 antihypertensive products.
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 Bifril Plus. Treatment with Bifril Plus 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 any ACE inhibitor.

Cough:
During treatment with ACE-inhibitors a dry and non-productive cough may occur which disappears after discontinuation of therapy. 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 enzymes should 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 left ventricular outflow tract obstruction and avoided in cases of cardiogenic shock and haemodynamically significant obstruction.

Neutropenia/Agranulocytosis:
Neutropenia/agranulocytosis, thrombocytopenia and anaemia have been reported in patients receiving 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 $1000/mm^3$) 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 patients previously treated with oral antidiabetic products or insulin, during the first month of treatment with an ACE inhibitor (see section 4.5).

Lithium:
The combination of Lithium and Bifril Plus 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)

HYDROCHLOROTHIAZIDE

Renal impairment:
In patients with renal disease, thiazides may increase azotaemia. Cumulative effects of this active substance may develop in patients with impaired renal function. If progressive renal impairment becomes evident, as indicated by a rising non-protein nitrogen, careful reappraisal of therapy is necessary, with consideration given to discontinuing diuretic therapy.

Hepatic impairment:
Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Metabolic and endocrine effects:
Thiazide therapy may impair glucose tolerance. Dosage adjustments of insulin or oral hypoglycaemic agents may be required (see section 4.5). Latent diabetes mellitus may become manifest during thiazide therapy.

Increases in cholesterol and triglyceride levels have been associated with thiazide diuretic therapy. Thiazide therapy may precipitate hyperuricaemia and/or gout in certain patients.

Electrolyte imbalance:
As for any patient receiving diuretic therapy, periodic determination of serum electrolytes should be performed at appropriate intervals.
Thiazides, including hydrochlorothiazide, can cause fluid or electrolyte imbalance (hypokalaemia, hyponatraemia, and hypochloraemic alkalosis). Warning signs of fluid or electrolyte imbalance are dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pain or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea or vomiting.
Although hypokalaemia may develop with the use of thiazide diuretics, concurrent therapy with zofenopril may reduce diuretic-induced hypokalaemia. The risk of hypokalaemia is greatest in patients with cirrhosis of the liver, in patients experiencing brisk diuresis, in patients who are receiving inadequate oral intake of electrolytes and in patients receiving concomitant therapy with corticosteroids or ACTH (see section 4.5).
Dilutional hyponatraemia may occur in oedematous patients in hot weather. Chloride deficit is generally mild and usually does not require treatment.
Thiazides may decrease urinary calcium excretion and may cause an intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcaemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out test for parathyroid function.
Thiazides have been shown to increase the urinary excretion of magnesium, which may result in hypomagnesaemia.

Lupus erythematosus:
Exacerbation or activation of systemic lupus erythematosus has been reported with the use of thiazides.

Non-melanoma skin cancer:
An increased risk of non-melanoma skin cancer (NMSC) [basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)] with increasing cumulative dose of hydrochlorothiazide (HCTZ) exposure has been observed in two epidemiological studies based on the Danish National Cancer Registry. Photosensitizing actions of HCTZ could act as a possible mechanism for NMSC.
Patients taking HCTZ should be informed of the risk of NMSC and advised to regularly check their skin for any new lesions and promptly report any suspicious skin lesions. Possible preventive measures such as limited exposure to sunlight and UV rays and, in case of exposure, adequate protection should be advised to the patients in order to minimize the risk of skin cancer. Suspicious skin lesions should be promptly examined potentially including histological examinations of biopsies. The use of HCTZ may also need to be reconsidered in patients who have experienced previous NMSC (see also section 4.8).

Choroidal effusion, acute myopia and secondary angle-closure glaucoma:
Sulfonamide or sulfonamide derivative drugs can cause an idiosyncratic reaction resulting in choroidal effusion with visual field defect, transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue drug intake as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy.

Anti-doping test:
Hydrochlorothiazide contained in this medication could produce a positive analytic result in an anti-doping test.

Other:
Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma.

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

ZOFENOPRIL/HYDROCHLOROTHIAZIDE COMBINATION

In addition to the warnings related to the monocomponents, the following should be observed:

Pregnancy:
Bifril Plus is not recommended during the first trimester of pregnancy (see section 4.6).

Patients with renal insufficiency:
Considering the effect of zofenopril and hydrochlorothiazide in patients with impaired renal function, Bifril Plus should not be administered to patients with moderate to severe renal insufficiency (creatinine clearance < 45 ml/min).

Risk of hypokalaemia:
The combination of an ACE inhibitor with a thiazide diuretic does not rule out the occurrence of hypokalaemia. Regular monitoring of serum potassium should be performed.

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

4.5 Interactions with other medicinal products and other forms of interaction

ZOFENOPRIL

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 substitutes or 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.

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

Narcotics/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, procainamide, systemic corticosteroids, cytostatic or immunosuppressive agents
Increased risk of hypersensitivity reactions when ACE inhibitors are used concurrently. Data from other ACE inhibitors indicate an increased risk of leukopenia when used concurrently.

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.

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

Antacids
Reduce the bioavailability of ACE inhibitors.

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

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.

Additional information

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

HYDROCHLOROTHIAZIDE

Concomitant use requiring caution

Cholestyramine and colestipol resins
Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastro-intestinal tract by up to 85% and 43%, respectively.
Sulphonamid diuretics should be taken at least one hour before or four to six hours after these medications.

Corticosteroids, ACTH, amphotericin B (parenteral), carbenoxolone, stimulant laxatives
There may be intensified electrolyte depletion, particularly hypokalaemia when administered concomitantly with hydrochlorothiazide.

Calcium salts
Increased serum calcium levels due to decreased excretion may occur when administered concurrently with thiazide diuretics.

Cardiac glycosides
Thiazide induced hypokalaemia or hypomagnesaemia favours the occurrence of digitalis induced cardiac arrhythmia.

Medicinal products associated with torsade de pointes
Because of the risk of hypokalaemia, caution should be used when hydrochlorothiazide is coadministered with medicinal products associated with torsade de pointes, e.g. some antiarrhythmics, some antipsychotics, and other medicinal products known to induce torsade de pointes.

Pressor amines (e.g. adrenaline)
Possible decreased response to pressor amines, but not sufficient to preclude their use with hydrochlorothiazide.

Skeletal muscle relaxants, non-depolarising (e.g. tubocurarine)
Possible increased responsiveness to the muscle relaxant when used with hydrochlorothiazide.

Amantadine
Thiazide may increase the risk of undesirable effects caused by amantadine.

Medicinal products used in the treatment of gout (probenecid, sulfinpyrazone, allopurinol)

Dosage adjustment of uricosuric medicinal products may be necessary as hydrocholorothiazide may raise the level of serum uric acid. Increase of dosage of probenecid or sulfinpyrazone may be necessary. Co-administration of thiazide diuretics may increase the incidence of hypersensitivity reactions to allopurinol.

Additional information
Laboratory test interactions: because of their effects on calcium metabolism, thiazides may interfere with tests for parathyroid function.

ZOFENOPRIL/HYDROCHLOROTHIAZIDE COMBINATION
In addition to the interactions related to the monocomponents, the following should be observed:

Concomitant use not recommended

Lithium
Concomitant use of thiazide diuretics may increase the risk of lithium toxicity and enhance the already increased risk of lithium toxicity with ACE inhibitors.
Therefore, Bifril Plus is not recommended in association with lithium and careful monitoring of serum lithium levels should be performed if the combination proves necessary.

Clinical Chemistry
Thiazides may decrease serum PBI (Protein Bound Iodine) levels without signs of thyroid disturbance.

Concomitant use requiring caution

Non-Steroidal Anti-Inflammatory medicinal product (including ASA ≥ 3g/day)
The administration of non-steroidal anti-inflammatory agents may reduce the antihypertensive effect of ACE inhibitors and diuretics. 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 impaired renal function. Rarely, acute renal failure may occur, particularly in patients with compromised renal function such as the elderly or dehydrated.

Alcohol
Enhances the hypotensive effect of ACE and hydrochlorothiazide.

Trimethoprim
Concomitant administration of ACE-inhibitors and thiazides with trimethoprim increases the risk of hypercalaemia.

4.6 Fertility, pregnancy and lactation

Pregnancy

Zofenopril and hydrochlorothiazide
Given the effects of the individual components in this combination product on pregnancy, the use of Bifril Plus is not recommended during the first trimester of pregnancy (see section 4.4). The use of Bifril Plus is contra-indicated during the 2nd and 3rd trimester of pregnancy (see section 4.3 and 4.4)

Zofenopril
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 trimesters 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).

Hydrochlorothiazide
There is limited experience with hydrochlorothiazide during pregnancy, especially during the first trimester. Animal studies are insufficient.
Hydrochlorothiazide crosses the placenta. Based on the pharmacological mechanism of action of hydrochlorothiazide its use during the second and third trimester may compromise foeto-placental perfusion and may cause foetal and neonatal effects like icterus, disturbance of electrolyte balance and thrombocytopenia.
Hydrochlorothiazide should not be used for gestational oedema, gestational hypertension or preeclampsia due to the risk of decreased plasma volume and placental hypoperfusion, without a beneficial effect on the course of the disease.
Hydrochlorothiazide should not be used for essential hypertension in pregnant women except in rare situations where no other treatment could be used

Breast-feeding

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

Hydrochlorthiazide
Hydrochlorothiazide is excreted in human milk in small amounts. Thiazides in high doses causing intense diuresis can inhibit the milk production. The use of Bifril Plus during breast feeding is not recommended. If Bifril Plus is used during breast feeding, doses should be kept as low as possible.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

Tabulated list of adverse reactions

The table below shows all the adverse reactions that have been reported during clinical trials as at least probably-possibly related to treatment with zofenopril/hydrochlorothiazide 30/12.5 mg. 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
Infections and infestations	Infection	Uncommon
	Bronchitis	Uncommon
	Pharyngitis	Uncommon
Metabolism and nutrition disorders	Hypercholesterolaemia	Uncommon
	Hyperglycaemia	Uncommon
	Hyperlipidaemia	Uncommon
	Hypokalaemia,	Uncommon
	Hyperkalaemia	Uncommon
	Hyperuricaemia	Uncommon
Nervous system disorders	Dizziness	Common
	Headache	Common
	Somnolence	Uncommon
	Syncope	Uncommon
	Hypertonia	Uncommon
Psychiatric disorders	Insomnia	Uncommon
Cardiac disorders	Angina pectoris	Uncommon
	Atrial fibrillation,	Uncommon
	Myocardial infarction	Uncommon
	Palpitations	Uncommon
Vascular disorders	Flushing	Uncommon
	Hypotension	Uncommon
	Hypertension	Uncommon
Respiratory, thoracic and mediastinal disorders	Cough	Common
	Dyspnoea	Uncommon
Gastrointestinal disorders	Nausea	Uncommon
	Dyspepsia	Uncommon
	Gastritis	Uncommon
	Gingivitis	Uncommon
	Dry mouth	Uncommon
	Abdominal pain	Uncommon

Skin and subcutaneous tissue disorders	Angioedema	Uncommon
	Psoriasis	Uncommon
	Acne	Uncommon
	Dry skin	Uncommon
	Pruritus	Uncommon
	Urticaria	Uncommon
Musculoskeletal and connective tissue disorders	Back pain	Uncommon
Renal and urinary disorders	Polyuria	Uncommon
General disorders and administration site conditions	Asthenia	Uncommon
	Influenza like illness	Uncommon
	Oedema peripheral	Uncommon
Reproductive system and breast disorders	Erectile dysfunction	Uncommon
Investigations	Creatinine increase	Uncommon
	Liver Function test abnormal	Uncommon

Additional information on individual component
Adverse reactions known to occur with each component given as monotherapy may occur during treatment with Bifril Plus:

ZOFENOPRIL

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

MedDRA System Organ Class	Adverse reactions	Frequency
Nervous system disorders	Dizziness	Common
	Headache	Common
Respiratory, thoracic and mediastinal disorders	Cough	Common
Gastrointestinal disorders	Nausea	Common
	Vomiting	Common
Skin and subcutaneous tissue disorders	Rash	Uncommon
	Angioedema	Rare
Musculoskeletal and connective tissue disorders	Muscle cramp	Uncommon
General disorders and administration site conditions	Fatigue	Common
	Asthenia	Uncommon

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.

Endocrine disorders
Not known, inappropriate antidiuretic hormone secretion.

Metabolism and nutrition disorders
Very rare hypoglycaemia.

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, palpitations, 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 with disturbance of consciousness (syncope).
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 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.
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.

HYDROCHLOROTHIAZIDE

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

Neoplasms benign, malignant and unspecified (incl cysts and polyps)
Frequency 'not known': Non-melanoma skin cancer (Basal cell carcinoma and Squamous cell carcinoma)
Non-melanoma skin cancer: Based on available data from epidemiological studies, cumulative dose-dependent association between HCTZ and NMSC has been observed (see also sections 4.4 and 5.1).

Blood and lymphatic system disorders
Leukopenia, neutropenia, agranulocytosis, thrombocytopenia, aplastic anaemia, haemolytic anaemia, bone marrow failure.

Immune system disorders
Anaphylactic reaction.

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

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

Nervous system disorders

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

Eye disorders
Frequency 'not known': Choroidal effusion, acute myopia, acute angle-closure glaucoma.
Xanthopsia, blurred vision, myopia (aggravated), lacrimation decreased.

Ear and labyrinth disorders
Vertigo.

Cardiac disorders
Cardiac arrhythmias, palpitations.

Vascular disorders
Orthostatic hypotension, thrombosis, embolism, shock.

Respiratory thoracic and mediastinal disorders
Pneumonitis, interstitial lung disease, pulmonary oedema.

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

Hepato-biliary disorders
Jaundice cholestatic, cholecystitis.

Skin and subcutaneous tissue disorders
Pruritus, purpura, urticaria, photosensitivity reactions, rash, cutaneous lupus erythematosus, vasculitis necrotising, , toxic epidermal necrolysis.

Musculoskeletal and connective tissue disorders
Muscle spasm, myalgia.

Renal and urinary disorders
Renal impairment, renal failure acute, nephritis interstitial, glycosuria.

Reproductive system and breast disorders
Erectile dysfunction.

General disorders and administration site conditions
Asthenia, pyrexia, fatigue, thirst.

Investigations
Electrocardiogram change, blood cholesterol increased, blood triglycerides increased.

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.

4.9 Overdose

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

Treatment is symptomatic and supportive. After ingestion of an overdose, the 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.
Overdosage with hydrochlorothiazide is associated with electrolyte depletion (hypokalaemia, hypoclroraemia) and dehydration resulting from excessive diuresis. The most common signs and symptoms of overdosage are nausea and somnolence. Hypokalaemia may result in muscle spasm and/or accentuate cardiac arrhythmias associated with the concomitant use of digitalis glycosides or certain anti-arrhythmic medicinal products.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ACE-inhibitors and diuretics, ATC code: C09B A 15

ZOFENOPRIL/HYDROCHLOROTHIAZIDE COMBINATION

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

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

Hydrochlorothiazide is a diuretic and antihypertensive agent. It affects the distal renal tubular mechanism of electrolyte reabsorption. Hydrochlorothiazide increases excretion of sodium and chloride in approximately equivalent amounts. Natriuresis may be accompanied by some loss of potassium and bicarbonate. Presumably through blockade of the renin-angiotensin-aldosterone system, co-administration of zofenopril tends to reverse the potassium lost associated with these diuretics. With hydrochlorothiazide, diuresis begins within 2 hours, peaks in about 4 hours and lasts about 6 to 12 hours.

Other information:

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.

Non-melanoma skin cancer: Based on available data from epidemiological studies, cumulative dose-dependent association between HCTZ and NMSC has been observed. One study included a population comprised of 71,533 cases of BCC and of 8,629 cases of SCC matched to 1,430,833 and 172,462 population controls, respectively. High HCTZ use (≥50,000 mg cumulative) was associated with an adjusted OR of 1.29 (95% CI: 1.23-1.35) for BCC and 3.98 (95% CI: 3.68-4.31) for SCC. A clear cumulative dose response relationship was observed for both BCC and SCC. Another study showed a possible association between lip cancer (SCC) and exposure to HCTZ: 633 cases of lip-cancer were matched with 63,067 population controls, using a risk-set sampling strategy. A cumulative dose-response relationship was demonstrated with an adjusted OR 2.1 (95% CI: 1.7-2.6) increasing to OR 3.9 (3.0-4.9) for high use (~25,000 mg) and OR 7.7 (5.7-10.5) for the highest cumulative dose (~100,000 mg) (see also section 4.4).

5.2 Pharmacokinetic properties

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

ZOFENOPRIL

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

Absorption:
Zofenopril is rapidly and completely absorbed by the oral route and undergoes nearly complete conversion to zofenoprilat, which reaches peak blood levels after 1.5 h following an oral dose of zofenopril. Single dose kinetics are linear over a dose-range of 10-80 mg of zofenopril and no accumulation occurs after the administration of 15-60 mg of zofenopril for 3 weeks. The presence of food in the gastrointestinal tract reduces the rate but not the extent of absorption and the AUCs of zofenoprilat are nearly identical in the fasted or fed state.

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

Biotransformation:
Eight metabolites, accounting for 76% of the urinary radioactivity, were identified in human urine following a radiolabelled dose of zofenopril. The main metabolite is zofenoprilat (22%), which is the

metabolized through several pathways, including glucoronide conjugation (17%), cyclization and glucoronide conjugation (13%), cysteine conjugation (9%) and S-methylation of the thiol group (8%).

Elimination:
Radiolabelled zofenoprilat administered intravenously is eliminated in urine (76%) and faeces (16%) while following an oral dose of radiolabelled zofenopril, 69% and 26% of the radioactivity is recovered in urine and faeces respectively, indicating a dual route of elimination (kidney and liver). Half-life of zofenoprilat is 5.5 h and its total body clearance is 1300 ml/min following oral zofenopril.

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, 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.
In patients with end stage renal disease on haemodialysis and peritoneal dialysis, the rate of elimination is reduced to 25% of normal.

Pharmacokinetics in hepatic dysfunction
In patients with mild to moderate hepatic dysfunction given single doses of radiolabelled zofenopril, the 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 zofenopril for patients with mild to moderate hepatic dysfunction should be half of that for patients with normal hepatic function.
There are no pharmacokinetic data of zofenopril and zofenoprilat in patients with severe hepatic dysfunction, therefore zofenopril is contraindicated in these patients.

HYDROCHLOROTHIAZIDE

Absorption:
Hydrochlorothiazide is well absorbed (65 to 75 %) following oral administration. Plasma concentrations are linearly related to the administered dose. The absorption of hydrochlorothiazide is dependent on intestinal transit time, being increased when the intestinal transit time is slow for example when given with food. When plasma levels have been followed for at least 24 hours, the plasma half-life has been observed to vary between 5.6 and 14.8 hours and peak plasma levels were observed within 1 and 5 h after dosing.

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

Elimination:
Hydrochlorothiazide is eliminated primarily by renal pathway. Most of thiazide is excreted in the urine unchanged and more than 95 % of hydrochlorothiazide appears unchanged in the urine within 3-6 hours after an oral dose. In patients with renal disease, plasma concentrations of hydrochlorothiazide

are increased and elimination half-life is prolonged. Hydrochlorothiazide crosses the placental but not the blood-brain barrier.

5.3 Preclinical safety data

The fixed combination zofenopril/hydrochlorothiazide revealed no special risks for human use, based on acute toxicity, repeated dose toxicity and genotoxicity studies.
Reproductive toxicity of the combination has been studied in rats and rabbits and zofenopril and HCTZ did not show to be teratogenic. However in pregnant rats and rabbits the combination markedly increased the maternal toxicity induced by zofenopril alone.

Carcinogenicity studies were not performed with the combination zofenopril/ hydrochlorothiazide.
Carcinogenicity studies conducted in mice and rats with zofenopril alone revealed no evidence of carcinogenicity.

Preclinical data of HCTZ reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet Core:
Microcrystalline cellulose
Lactose, monohydrate
Maize Starch
Hypromellose
Silica, colloidal anhydrous
Magnesium stearate

Film Coat:
Opadry Pink 02B24436 composed by:
- Hypromellose
- Titanium dioxide (E 171)
- Macrogol 400
- Ironoxide Red (E 172)

Macrogol 6000

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 30° C

6.5 Nature and contents of container

PVDC coated PVC/Aluminium blisters.

14, 28, 30, 56, 50, 90 or 100 film coated tablets/pack

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.

8. MARKETING AUTHORISATION NUMBER

Rwanda FDA-HMP-MA-0543

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

Date of first authorization: 5 October 2023

10. DATE OF REVISION OF THE TEXT

07/2020