Package leaflet: Information for the user

Bifril Plus 30 mg /12.5 mg film-coated tablets
(zofenopril calcium / hydrochlorothiazide)

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Bifril Plus is and what it is used for

Bifril Plus contains zofenopril calcium 30 mg and hydrochlorothiazide 12.5 mg as the active ingredients.
- Zofenopril calcium is a cardiovascular drug which belongs to a group of blood pressure lowering medicines called angiotensin converting enzyme (ACE) inhibitors.
- Hydrochlorothiazide is a diuretic, that acts by increasing the amount of urine you produce.

Bifril Plus is used to treat mild to moderate high blood pressure (hypertension), when this is not adequately controlled by taking zofenopril alone.

2. What you need to know before you take Bifril Plus

Do not take Bifril Plus if you:
- are more than 3 months pregnant (It is also better to avoid Bifril Plus in early pregnancy - see "pregnancy section").
- are allergic to zofenopril calcium or to hydrochlorothiazide or to any of the other ingredients of this medicine (listed in section 6)
- are allergic to other sulphonamide-derived substances (like hydrochlorothiazide, which is a sulphonamide-derived drug)
- have had any previous allergic reaction to any other ACE inhibitor such as captopril or enalapril
- have a history of severe swelling and itching around the face, nose and throat (angioneurotic oedema) associated with previous ACE inhibitor therapy, or if you suffer from hereditary/idiopathic angioneurotic oedema (rapid swelling of the skin, tissues, digestive tract and other organs)
- have taken or are currently taking sacubitril/valsartan, a medicine used to treat a type of long-term (chronic) heart failure in adults, as the risk of angioedema (rapid swelling under the skin in an area such as the throat) is increased
- suffer from severe liver or kidney problems
- suffer from narrowing of the arteries to the kidneys
- have diabetes or impaired kidney function and you are treated with a blood pressure lowering medicine containing aliskiren

Warnings and precautions
Talk to your doctor before taking Bifril Plus.

Tell your doctor if you:

- have **liver** or **kidney problems**
- have high blood pressure that is caused by a kidney problem or by narrowing of the artery leading to the kidney (renovascular hypertension)
- have recently had a **kidney transplant**
- are undergoing **dialysis**
- are on **LDL apheresis** (a procedure similar to kidney dialysis that clears your blood of harmful cholesterol)
- have **abnormally high levels** of the hormone **aldosterone** in your blood (primary aldosteronism) or **decreased levels** of the hormone **aldosterone** in your blood (hypoaldosteronism)
- have a **narrowing of the heart valve** (aortic stenosis) or **thickening of the heart walls** (hypertrophic cardiomyopathy)
- suffer or have suffered from **psoriasis** (skin disease characterised by scaly pink patches)
- are receiving **desensitization** treatment ('allergy injections') for insect stings
- have **lupus erythematosus** (a disorder of the immune system, your body's defence system)
- if you tend to have **low blood potassium**, and especially if you suffer from prolonged QT syndrome (a kind of ECG abnormality) or you are taking digitalis (to help your heart pump)
- have **diabetes**
- if you have angina or disorders affecting the brain, since low blood pressure can lead to a heart attack or stroke.
- are taking any of the following medicines used to treat high blood pressure:
  - an "angiotensin II receptor blocker" (ARBs) (also known as sartans - for example valsartan, telmisartan, irbesartan, etc.), in particular if you have diabetes-related kidney problems.
  - aliskiren
- are taking any of the following medicines, the risk of angioedema (rapid swelling under the skin in area such as the throat) may be increased:
  - racecadotril, (a medicine used to treat diarrhoea)
  - medicines used to prevent organ transplant rejection and for cancer (e.g., temsirolimus, sirolimus, everolimus)
  - vildagliptin, (a medicine used to treat diabetes).
- if you have had skin cancer or if you develop an unexpected skin lesion during the treatment. Treatment with hydrochlorothiazide, particularly long term use with high doses, may increase the risk of some types of skin and lip cancer (non-melanoma skin cancer). Protect your skin from sun exposure and UV rays while taking Bifril Plus.

Your doctor may check your kidney function, blood pressure, and the amount of electrolytes (e.g. potassium) in your blood at regular intervals.

See also information under the heading "Do not take Bifril Plus''

The hydrochlorothiazide in Bifril Plus may cause your skin to be oversensitive to sunlight or artificial UV light. Stop taking Bifril Plus and tell your doctor if you get a rash, itchy spots or sensitive skin during treatment (see also section 4).

Anti-dope test: **Bifril Plus could cause a positive anti-dope test.**

Your **blood pressure may get too low** with Bifril Plus, especially after the first dose (this is more likely if you have also been taking diuretics, are dehydrated or a low-salt diet, or if you have sickness or diarrhea). If this happens, tell your doctor **immediately** and then lie down on your back (see also section 4).

If you are having an **operation, tell your anaesthetist** that you are taking Bifril Plus before being anaesthetised. This will help him/her to control your blood pressure and heart rate during the procedure.

You must tell your doctor if you think you are (or might become) pregnant. Bifril Plus is not recommended in early pregnancy, and must not be taken if you are more than 3 months pregnant, as it may cause serious harm to your baby if used at that stage (see pregnancy section)

Children and adolescents
Do not give this medicine to children and adolescents under the age of 18 years because it is unlikely to be safe.

Other medicines and Bifril Plus
Tell your doctor if you are taking, have recently taken or might take any other medicines.
In particular, tell your doctor if you are taking:

- potassium supplements (including salt substitutes), potassium-sparing diuretics and other medicines that can increase the amount of potassium in your blood (e.g. trimethoprim and co-trimoxazole for infections caused by bacteria; cyclosporin, an immunosuppressant medicine used to prevent organ transplant rejection; and heparin used to thin blood to prevent clots)
- other medicines that affect the levels of blood chemicals (AdrenoCorticoTropic Hormone - ACTH - used to stimulate the production of some hormones by the body, amphotericin B injections, carbenoxolone, stimulant laxatives)
- lithium (used to treat mood disorders)
- anaesthetics
- narcotic drugs (such as morphine)
- antipsychotic drugs (used to treat schizophrenia and similar illnesses)
- antidepressants of the tricyclic type, e.g. amitriptyline and clomipramine
- barbiturates (used to treat anxiety, insomnia, and seizure disorders)
- other high blood pressure medicines and vasodilators (including, beta-blockers alpha-blockers and diuretics, such as hydrochlorothiazide, furosemide, torasemide).
- Your doctor may need to change your dose and/or to take other precautions:
  If you are taking an angiotensin II receptor blocker (ARB) or aliskiren (see also information under the headings 'Do not take Bifril Plus' and 'Warnings and precautions')
- nitroglycerine and other nitrates used for chest pain (angina)
- antacids including cimetidine (used to treat heartburn and stomach ulcers)
- cyclosporin (used after organ transplants) and other immunosuppressant drugs (medicines that suppress your body's immune defences)
- medicines for gout (e.g. probenecid, sulfinpyrazone and allopurinol)
- insulin or oral anti-diabetic medicines
- cytostatic agents (used to treat cancer or diseases which affect the body's immune defences)
- corticosteroids (powerful anti-inflammatory drugs)
- procainamide (used to control an irregular heart beat)
- nonsteroidal anti-inflammatory drugs (NSAIDs, such as aspirin or ibuprofen)
- sympathomimetic drugs (medicines that act on the nervous system, including some used to treat asthma or hay fever and pressor amines, e.g. adrenalin)
- calcium salts
- digitalis (used to help the heart pump)
- cholestyramine and colestipol resins (used to lower cholesterol)
- medicines used to relax muscles (e.g. tubocurarine)
- amantadine (an antiviral medicine).
- racecadotril (a medicine used to treat diarrhoea), medicines used to prevent organ transplant rejection and for cancer (e.g. temsirolimus, sirolimus, everolimus) and vildagliptin (a medicine used to treat diabetes). The risk of angioedema may be increased.

Bifril Plus with food, drink and alcohol
Bifril Plus can be taken with food or on an empty stomach, but always with some water.

Alcohol increases the hypotensive (lowering of blood pressure) effect of Bifril Plus; ask your doctor for further advice on drinking alcohol whilst on this medication.

Pregnancy and breast-feeding
Pregnancy
If you are pregnant, you think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine. Your doctor will normally advise you to stop taking Bifril Plus before you become pregnant or as soon as you know you are pregnant and will advise you to take another medicine instead of Bifril Plus.
Bifril Plus is not recommended in early pregnancy, and must not be taken when more than 3 months pregnant, as it may cause serious harm to your baby if used after the third month of pregnancy.

Breast-feeding
If you are breast-feeding or about to start breast-feeding ask your doctor for advice before taking this medicine. Bifril Plus is not recommended for mothers who are breast-feeding, and your doctor may choose another treatment for you if you wish to breast-feed, especially if your baby is newborn, or was born prematurely.

Driving and using machines
This medicine may cause dizziness or tiredness. If this happens to you, do not drive or operate machinery.

Bifril Plus contains lactose
This product contains **lactose**. If you know you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. How to take Bifril Plus

Always take Bifril Plus exactly as your doctor has told you. Check with your doctor if you are not sure.

The recommended dose of Bifril Plus is one tablet per day.
Bifril Plus may be taken with food or on an empty stomach. The tablet is best taken with some water.
The score line is only there to help you break the tablet if you have difficulty swallowing it whole.

If you are over 65 and suffer from an impaired kidney function, Bifril Plus may not be suitable for you (see also section 2 'Warnings and precautions')

Use in children and adolescents
This medicine is not recommended for use in children and adolescents under the age of 18 years.

If you take more Bifril Plus than you should
If you accidentally take too many tablets, contact your doctor or nearest hospital immediately (taking any remaining tablets, the carton or this leaflet with you if possible).
The most frequent symptoms and signs of an overdose are low blood pressure with fainting (hypotension), very slow heart beat (bradycardia), changes in blood chemicals (electrolytes), kidney dysfunction, excessive urination with consequent dehydration, nausea and somnolence, muscle spasms, heart rhythm disturbances (especially if you are also taking digitalis or medicines for heart rhythm problems).

If you forget to take Bifril Plus
If you miss a dose, take the next dose as soon as you remember. However if your next dose is nearly due, skip the forgotten dose and take the next scheduled normal dose at the usual time. Do not take a double dose to make up for a forgotten tablet.

If you stop taking Bifril Plus
Always consult your doctor before stopping Bifril Plus treatment.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, Bifril Plus can cause side effects, although not everybody gets them.

The following side effects have been reported in clinical trials with Bifril Plus:

Common side effects (may affect up to 1 in 10 people):
- dizziness
- headache
- cough.

Uncommon side effects (may affect up to 1 in 100 people):
- rapid-onset swelling, especially of the lips, cheeks, eyelids, tongue, palate, voice box (larynx), with possible sudden difficulty breathing (angioneurotic edema). If you have any of these, it means that you have a serious allergy for Bifril Plus. You may require urgent medical intervention, or you may need to be hospitalized
- infection
- bronchitis
- sore throat
- increase in blood cholesterol and/or other lipids, increased blood glucose, potassium, uric acid, creatinine and liver enzymes
- decrease in blood potassium
- insomnia
- somnolence, fainting, muscle tightness (hypertonia)
- angina, heart attack, atrial fibrillation, palpitations
- flushing, low blood pressure, high blood pressure
- nausea, indigestion, gastritis, inflammation of the gums, dry mouth, stomach pain
- skin disease characterised by scaly pink patches (psoriasis), acne, dry skin, itching, hives
- back pain
- increased urine (polyuria)
- general weakness (asthenia), flu like symptoms, peripheral swelling (usually around the ankles)
- impotence

The following side effects were not reported in clinical trials with Bifril Plus, but they have been reported with **zofenopril calcium and/or other ACE inhibitors**, so they may also occur with the use of Bifril Plus:

- Tiredness (fatigue). Severe low blood pressure at the start of treatment or when the dosage is increased, with dizziness, impaired vision, fainting; low blood pressure on standing.
- Chest pain, muscle aches and/or cramps.
- Impaired consciousness, sudden dizziness, suddenly impaired vision or weakness and/or loss of sense of touch on one side of the body (transient ischaemic attack or stroke).
- Reduced kidney function, changes in the amount of daily urine, presence of proteins in the urine (proteinuria).
- Vomiting, diarrhoea, constipation.
- Allergic skin reaction with peeling, redness, loosening and blistering of the skin (toxic epidermal necrolysis), worsening of psoriasis, hair loss (alopecia).
- Increased sweating.
- Mood changes, depression, sleep disorders.
- Altered skin sensations such as burning, prickling, or tingling (paraesthesia).
- Disorders of balance, confusion, ringing in the ears (tinnitus), taste disturbances, blurred vision.

- Difficulty in breathing, narrowing of the airways in the lung (bronchospasm), sinusitis, runny or stuffy nose (rhinitis), inflammation of the tongue (glossitis).
- Yellowing of the skin (jaundice), inflammation of the liver or pancreas (hepatitis, pancreatitis), bowel obstruction (ileus).
- Changes in blood tests, such as red blood cell, white blood cell or platelet count or a reduction in all kinds of blood cells (pancytopenia): **Contact your doctor if you find that you bruise easily or develop an unexplained sore throat or fever.**
- Increased blood levels of bilirubin, increased blood urea.
- Anaemia due to rupture of red blood cells (haemolytic anaemia), which may occur if you suffer from G6PD (glucose-6-phosphate dehydrogenase) deficiency.

The following side effects were not reported in clinical trials with Bifril Plus, but they have been reported with **hydrochlorothiazide**, so they may also occur with the use of Bifril Plus:

- Impaired production of new blood cells by the bone marrow (bone marrow failure).
- Fever, whole-body allergic reaction (anaphylactic reaction).
- Altered levels of body fluids (dehydration) and blood chemicals (electrolytes), gout, diabetes, metabolic alkalosis.
- Apathy, nervousness, restlessness.
- Convulsions, depressed level of consciousness, coma, paresis.
- Yellow vision (xanthopsia), worsening of myopia, decreased lacrimation.
- Vertigo (spinning sensation).
- Heart rhythm disturbances (arrhythmias), changes in the electrocardiogram.
- Formation of blood clots in veins (thrombosis) and embolism, circulatory collapse (shock).
- Respiratory distress, lung inflammation (pneumonitis), formation of fibrous tissue in the lungs (interstitial lung disease), fluid accumulation in the lung (pulmonary oedema).
- Thirst, lack of appetite (anorexia), absence of bowel movements (ileus paralytic), excessive gas in the stomach, inflammation of the glands that produce saliva (sialoadenitis), increased blood amylase (a pancreatic enzyme, hyperamylasaemia), inflammation of the gall bladder (cholecystitis).
- Purple spots/blotches on the skin (purpura), increased sensitivity of your skin to sunlight, rash (especially facial) and/or patchy redness that can cause scarring (cutaneous lupus erythematosus), inflammation of blood vessels with consequent death of tissue (vasculitis necrotising).
- Acute kidney failure (with reduced urine production and build-up of fluid and wastes in your body), inflammation of the connective tissue within the kidneys (interstitial nephritis), sugar in the urine.
- Frequency ‘not known’: Skin and lip cancer (Non-melanoma skin cancer).

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Bifril Plus

Keep this medicine out of the sight and reach of children.
Do not store above 30°C
Do not use this medicine after the expiry date which is stated on the box and blister pack after ‘EXP’. The expiry date refers to the last day of that month
Always keep the tablets in their original packaging.
Do not throw away any medicines via wastewater. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6 . Content of the pack and other information

What Bifril Plus contains
The **active substances** are zofenopril calcium 30 mg and hydrochlorothiazide 12.5 mg.
The **other ingredients** are the following:

- **Tablet Core:** Microcrystalline cellulose, lactose monohydrate, maize starch, hypromellose, silica colloidal anhydrous, magnesium stearate
- **Film Coat:** Opadry Pink 02B24436 (hypromellose, titanium dioxide (E 171), macrogol 400, iron oxide red (E 172), macrogol 6000

(see section 2 'Bifril Plus contains lactose').

What Bifril Plus looks like and contents of the pack
Bifril Plus 30mg/12.5 mg tablets are pastel-red, round, slightly bi-convex film-coated tablets with a score line on one side. The score line is to facilitate breaking for ease of swallowing and not to divide into equal doses. The tablets are available in packs of 14, 28, 30, 50, 56, 90 or 100 tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder
Menarini International Operations Luxembourg S.A.
1, Avenue de la Gare L-1611, Luxembourg.

Manufacturer
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This medicinal product is authorised in the Member States of the EEA under the following names:
Austria: Bifril Plus
Belgium: Zopranol Plus
France: Coteoula
Greece: Zopranol-Plus
Ireland: Bifril Plus
Italy: Zoprazide
Iceland: Bifril Comp
Luxembourg: Zopranol Plus
Portugal: Zopranol Plus
The Netherlands: Zopranol HCTZ
United Kingdom: Zofenico

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