PATIENT PACKAGE INSERT IN ACCORDANCE WITH THE PHARMACISTS' REGULATIONS (PREPARATIONS) - 1986

The medicine is dispensed with a doctor's prescription only

Cilaril Plus

Tablets

Composition: Each tablet contains:
Cilazapril 5 mg
Hydrochlorothiazide 12.5 mg
For the list of inactive and allergenic ingredients in the preparation, see in section 2 "Important information about some of the ingredients of the medicine" and section 6 "Further information".

Read the leaflet carefully in its entirety before using the medicine. This leaflet contains concise information about the medicine. If you have further questions, refer to the doctor or pharmacist.

This medicine has been prescribed to treat you. Do not pass it on to others. It may harm them even if it seems to you that their medical condition is similar.

- **Do not use Cilaril Plus during pregnancy** (see in section 2 "Do not use the medicine if"), since angiotensin-converting enzyme (ACE) inhibitors, such as **Cilaril Plus**, can cause damage to, and even death of, the developing unborn baby.
- If you think you are pregnant, are planning a pregnancy, or become pregnant during the course of treatment, stop taking **Cilaril Plus** immediately and tell your doctor. Discuss with your doctor the risks associated with use of the medicine.
  Also, in order to reduce high blood pressure, switch to an alternative medicine with an established pregnancy safety profile.
- Do not combine **Cilaril Plus** with medicines that contain aliskiren, used to lower blood pressure, if you have diabetes or kidney problems.
- Do not combine **Cilaril Plus** with medicines containing a neprilysin inhibitor (e.g., sacubitril/valsartan), used to treat heart failure. Do not take **Cilaril Plus** within 36 hours before/after taking a medicine that inhibits neprilysin. Ask your doctor if you are uncertain about this.

1. WHAT IS THE MEDICINE INTENDED FOR?

The medicine is intended for the treatment of hypertension in patients who have been stabilized by the components of this preparation given in the same proportions.

Therapeutic group:

Cilazapril: angiotensin-converting enzyme (ACE) inhibitor.
Hydrochlorothiazide: a diuretic.

2. BEFORE USING THE MEDICINE

Do not use the medicine if:

- you are sensitive (allergic) to the active ingredients cilazapril, hydrochlorothiazide or to any of the additional ingredients contained in the medicine (see section 6 “Further information”).
- you are sensitive to medicines containing sulfonamide derivatives (sulfa medicines).
- you suffered in the past or have a family history of angioedema (an allergic reaction that causes swelling of the hands, feet, ankles, face, lips, tongue, throat or sudden difficulty breathing or swallowing). Report this to your doctor.
- you have difficulty passing urine or urinary retention.
- you suffer from ascites (fluids in the abdominal cavity).
- you are taking a medicine that inhibits neprilysin (e.g., sacubitril/valsartan) that treats heart failure, which may increase the risk of angioedema. Do not take **Cilaril Plus** for at least 36 hours before/after taking a neprilysin inhibitor (see in section 2 “Drug interactions” and “Special warnings regarding use of the medicine”).
- you are pregnant, planning to become pregnant or are of child-bearing age and are not using birth-control (see in section 2 “Pregnancy, breastfeeding and fertility” and section 4 “Side effects”).
- you are breastfeeding (see in section 2 “Pregnancy, breastfeeding and fertility”).
- you are sensitive to lactose or have one of the following hereditary problems: galactose intolerance, Lapp lactase deficiency, glucose-galactose malabsorption. **Cilaril Plus** contains lactose (see in section 2 “Special warnings regarding use of the medicine” and “Important information about some of the ingredients of the medicine”).
- you are taking medicines containing aliskiren, used to lower blood pressure, when you suffer from diabetes or kidney disease.

Special warnings regarding use of the medicine

Before treatment with Cilaril Plus, tell the doctor if:

- you are taking antihypertensives.
- you are sensitive (allergic) to penicillin. You recently received or are scheduled to receive an allergy shot after a bee or wasp sting.
- you have blood vessel or heart problems.
- you have liver problems.
- you have diabetes.
- you have kidney problems or are on dialysis.
- you have gout.
- you are at high risk of developing skin cancer. You may be at a higher risk if you have light-colored skin, have a personal or family history of skin cancer, get sunburned easily, or are taking medicines that weaken your immune system.
- you have a collagen vascular disease (a type of autoimmune disease in which the body’s immune system attacks the organs, skin and tissues). These diseases include lupus (e.g., systemic lupus erythematosus) or scleroderma (a condition leading to hardening or thickening of the skin).
- you are being treated with LDL apheresis with dextran sulfate (a treatment used to lower LDL levels in the blood).

- you are dehydrated or recently suffered from vomiting, diarrhea, or excessive sweating.
- you have experienced breathing difficulties or lung problems (e.g., fluid or inflammation in the lungs) after taking hydrochlorothiazide in the past.
  If you develop severe shortness of breath or breathing difficulties after taking **Cilaril Plus**, seek medical attention immediately.
- you are on a low-salt diet.
- you have hyponatremia (low sodium levels in the blood).
- you are at increased risk of developing hypotension.
- you are being treated with other vasodilators.
- you have a medical history of asthma.
- you have porphyria (build up of porphyrins in the body).
- you are planning to have surgery or a procedure that involves anesthesia.
- you have hypokalemia (low potassium levels in the blood).

Other warnings

Risk of developing skin cancer: Cilaril Plus contains hydrochlorothiazide, which increases the risk of developing non-melanoma skin cancer. The risk increases when you take **Cilaril Plus** for several years (more than 3 years) or are taking a high dosage. While taking **Cilaril Plus:**

- Regularly check if you have new skin lesions (e.g., swelling, lump/bump, sore, or patch). Particularly check areas that are more exposed to the sun, such as the face, ears, hands, shoulders, upper chest and back. Tell the doctor right away if you become more sensitive to the sun or UV rays, or if you develop a new skin lesion on your body during treatment with the medicine.
- Limit your time in the sun or in indoor tanning until you know how your skin reacts to them. Always use sunscreen (SPF-30 or higher) and wear long clothing that will protect the skin when going outside.

Eye problems: Cilaril Plus contains hydrochlorothiazide which can cause sudden eye disturbances:

- Myopia - sudden nearsightedness or blurred vision.
- Glaucoma - increased pressure in the eyes, eye pain, which, when untreated, may cause permanent vision loss.
- Choroidal effusion - liquid build-up in the eye that may result in vision changes.

If your vision changes, stop taking Cilaril Plus and seek immediate medical help. These vision disturbances may develop within hours to weeks of starting treatment with the medicine.

Children and adolescents

There is no information regarding the safety and effectiveness of use of this preparation in children and adolescents. Therefore, **Cilaril Plus** is not recommended for use in children and adolescents.

Tests and follow-up

You should be monitored by your doctor before starting treatment with the medicine, during and after the course of treatment with this medicine. The following tests should be performed: kidney function, liver function, blood pressure, blood tests, blood glucose levels (if you have diabetes) and blood electrolyte levels.

Drug interactions

If you are taking, or have recently taken, other medicines, including non-prescription medicines and nutritional supplements, tell the doctor or pharmacist, especially if you are taking:

- adrenocorticotropic hormone (ACTH) used to treat West Syndrome.
- medicines that may increase the levels of potassium in the blood (e.g., medicines that contain trimethoprim, co-trimoxazole also known as trimethoprim/sulfamethoxazole, cyclosporin, heparin, potassium supplements, potassium-sparing diuretics and salt substitutes that contain potassium).
- other antihypertensive medicines (guanethidine; methyldopa; beta-blockers; vasodilators; calcium channel blockers; angiotensin-converting enzyme (ACE) inhibitors; angiotensin receptor blockers (ARBs); direct renin inhibitors; diuretics (e.g., spironolactone, triamterene, amiloride, or eplerenone); ganglionic-blocking agents or adrenergic neuron-blocking agents; sympathomimetics; dual blockade of the renin-angiotensin-system (RAS).
- alcohol.
- barbiturates used to induce sleep.
- narcotic medicines used to relieve intense pain.
- amphotericin B used to treat fungal infections.
- antineoplastic medicines used to treat cancer (e.g., cyclophosphamide and methotrexate).
- antidepressants (SSRIs such as citalopram, escitalopram, sertraline; tricyclic antidepressants such as amitriptyline, clomipramine and imipramine).
- antidiabetic and hypoglycemic medicines to treat diabetes (e.g., insulin, alogliptin, linagliptin, saxagliptin, and sitagliptin).
- bile acid resins to lower cholesterol (cholestyramine and colestipol).
- calcium and vitamin D supplements.
- corticosteroids to treat joint pain and swelling.
- digoxin to treat certain heart conditions.
- medicines that slow down or speed up bowel activity (e.g., atropine, metoclopramide, and domperidone).
- anticonvulsants used to treat epilepsy (e.g., carbamazepine and topiramate).
- medicines that may cause abnormal heart rhythm, e.g., antiarrhythmics (e.g., quinidine, hydroquinidine, disopyramide, amiodarone, sotalol, dofetilide, and ibutilide); antipsychotics (e.g., thioridazine, chlorpromazine, trifluoperazine, sulpiride, tiapride, haloperidol, and droperidol); additional medicines, e.g., bepridil, cisapride, diphemanil, halofantrine, ketanserin, pentamidine, and terfenadine).
- medicines to treat gout (e.g., allopurinol, uricosurics, xanthine oxidase inhibitors, and probenecid).
- lithium to treat bipolar disorder.
- nonsteroidal anti-inflammatory medicines (NSAIDs) used to reduce pain and swelling. (e.g., aspirin, acetylsalicylic acid, ibuprofen, naproxen, and celecoxib).
- muscle relaxants used to relieve muscle spasms (e.g., tubocurarine).
- gold (sodium aurothiomalate) and gold salts used to treat autoimmune conditions such as rheumatoid arthritis and psoriatic arthritis.
- tetracycline antibiotics to treat bacterial infections.
- amantadine used to treat the flu and relieve symptoms of Parkinson’s disease.
- iodine-containing contrast agent.

- medicines to prevent transplant rejection (mTOR inhibitors), e.g., sirolimus, everolimus and temsirolimus.
- anesthetics used during surgery.
- amines that increase blood pressure, e.g., norepinephrine.

Use of the medicine and food

The medicine can be taken with or without food.

Use of the medicine and alcohol consumption

Worsening of orthostatic hypotension (when changing position or standing up quickly) can occur when consuming alcohol while using **Cilaril Plus**. Therefore, avoid drinking alcohol, especially at the beginning of treatment.

Driving and operating machinery

Use of this medicine may impair alertness, cause dizziness or loss of consciousness, especially at the beginning of treatment or when increasing the dosage. Therefore, caution should be exercised when driving a car, operating dangerous machinery, and when engaging in any activity that requires alertness.

Pregnancy, breastfeeding and fertility

Pregnancy and fertility

If you are pregnant, think you are pregnant, are planning a pregnancy, or are of child-bearing age and not using birth-control, do not take **Cilaril Plus**. Use of this medicine can cause severe damage to, and even death of, the unborn baby.

If you are taking **Cilaril Plus**, and discovered that you are pregnant, immediately stop taking the medicine and consult your doctor about changing the medical treatment to one that is suitable and safe during pregnancy.

If you are taking **Cilaril Plus** and you are planning to become pregnant, consult your doctor about changing the medical treatment.

Breastfeeding

Cilaril Plus is secreted into breast milk and is therefore not recommended during breastfeeding. If you are breastfeeding, refer to a doctor to change the medical treatment to one that is suitable and safe during breastfeeding.

Important information about some of the ingredients of the medicine

The medicine contains lactose. If you have been told by your doctor that you have an intolerance to certain sugars (such as lactose), contact your doctor before taking the medicine.

3. HOW SHOULD YOU USE THE MEDICINE?

Always use the preparation according to the doctor’s instructions. Check with the doctor or pharmacist if you are uncertain about the dosage and treatment regimen of the preparation.

The dosage and treatment regimen will be determined by the doctor only.

Do not exceed the recommended dosage.

Swallow the medicine with a bit of water, before or after a meal.

It is advisable to take the medicine at approximately the same time every day, preferably in the morning.

If necessary, the tablet can be halved for immediate use.

There is no information regarding crushing or chewing the tablet.

If you take a higher dosage of Cilaril Plus

If you took an overdose or if a child has accidentally swallowed the medicine, refer immediately to a doctor or proceed to a hospital emergency room and bring the package of the medicine with you.

If you forgot to take this medicine at the designated time, do not take a double dose. Take the next dose at the usual time and consult the doctor.

Adhere to the treatment regimen as recommended by the doctor. Even if there is an improvement in your health, do not stop treatment with the medicine without consulting the doctor.

Do not take medicines in the dark! Check the label and the dose each time you take medicine. Wear glasses if you need them.

If you have further questions regarding use of the medicine, consult the doctor or pharmacist.

4. SIDE EFFECTS

As with any medicine, use of **Cilaril Plus** may cause side effects in some users. Do not be alarmed by the list of side effects. You may not suffer from any of them.

Stop using the medicine and refer to a doctor immediately in the following situations:

Uncommon side effects (effects that occur in 1-10 in 1,000 patients):

- allergic reaction – swelling of the face, eyes, lips, tongue or pharynx. Difficulty swallowing or breathing, wheezing, rash, hives, itch, fever, abdominal cramps, chest discomfort or tightness.
- breathing problems – shortness of breath, difficulty breathing, chest tightness, cough or wheezing.
- myocardial infarction (heart attack) – pressure or pain between the shoulder blades, in the chest, in the jaw, in the left arm or upper abdomen, shortness of breath, dizziness, fatigue, clammy skin, sweating, indigestion, anxiety, feeling faint, palpitations (pounding heart, tremor), irregular heartbeats.

Rare side effects (effects that occur in 1-10 in 10,000 patients):

angioedema – swelling of the face, tongue, throat, abdomen, arms and legs.

Very rare side effects (effects that occur in less than one in 10,000 patients):

- acute respiratory distress syndrome (ARDS) – severe shortness of breath, fever, weakness or confusion.
- severe skin reactions (Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis) – itchy skin rash, redness, blisters and severe peeling of the skin and/or the inner part of the lips, eyes, mouth, nostrils, genitals, accompanied by fever, chills, headaches, cough, body aches or swollen glands, joint pains, yellowing of the skin or eyes or dark urine.

Side effects of unknown frequency (effects whose frequency have not yet been determined):

- myopia – sudden nearsightedness or blurred vision.
- glaucoma – increased pressure in the eyes, eye pain.
- choroidal effusion – blind spots in vision, eye pain or blurred vision.
- stroke (bleeding or blood clot in the brain) – weakness, blurred vision, trouble speaking, slurred speech, face drooping, dizziness or headache.

Refer to a doctor immediately in the following situations:

Common side effects (effects that occur in 1-10 in 100 patients):

- Changes in blood potassium levels – irregular heartbeats, muscle weakness and generally feeling unwell.
- Very low blood pressure – dizziness or loss of consciousness/fainting, especially when standing up from a sitting or lying position.

Uncommon side effects (effects that occur in 1-10 in 1,000 patients):

- angina (insufficient oxygen supply to the heart muscle) – chest pains, shortness of breath, dizziness, fatigue, upset stomach, vomiting, sweating, chest tightness or discomfort in the shoulder, arm, back, throat, jaw or teeth.
- blood electrolyte imbalance – weakness, drowsiness, muscle pains, cramps or irregular heartbeats.
- kidney problems – increase or decrease in urination, nausea, vomiting, swelling of extremities or fatigue.
- liver problems – yellowing of the skin or eyes, dark urine, abdominal pains, nausea, vomiting and loss of appetite.
- lupus (an autoimmune disease in which the immune system attacks the body organs and tissues) – fever, fatigue, joint and muscle pain or generally feeling unwell.
- tachycardia (faster than normal heart beats) – dizziness, shortness of breath, rapid heart rate.
- increased blood sugar levels – increased urination, thirst or hunger.

Rare side effects (effects that occur in 1-10 in 10,000 patients):

- decrease in blood platelets – manifested by bruises, bleeding, fatigue or weakness.
- decrease in white blood cells – manifested by inflammations, throat aches, fever, fatigue, aches or flu-like symptoms.

Side effects of unknown frequency (effects whose frequency have not yet been determined):

- anemia (reduced red blood cells) – fatigue, lack of energy, weakness, shortness of breath, irregular heartbeats or pallor.
- pancreatitis (inflammation of the pancreas) – upper abdominal pain which persists and worsens when switching to a lying position, nausea, vomiting, fever, rapid heartbeat or tender abdomen.
- non-melanoma skin cancer – growth or pale patch on the skin that does not pass after several weeks and slowly changes; cancerous growths are red/pink, firm and sometimes turn into ulcers; cancerous patches are usually flat and scaly.

Additional side effects

Common side effects (effects that occur in 1-10 in 100 patients):

headache, dizziness, fatigue, cough, sleepiness, nausea, increased urination frequency.

Uncommon side effects (effects that occur in 1-10 in 1,000 patients):

- palpitations, chest pain, tachycardia (rapid heartbeats), angina, low blood pressure, orthostatic hypotension (reduced blood pressure when standing up from a sitting or lying position), edemas, extrasystoles (excess heart contractions when the blood is being pumped), myocardial infarction (heart attack).
- abdominal pains, indigestion, diarrhea, flatulence, constipation.
- back pains, leg spasms, joint pains, muscle pains.

- nervous system disturbances – low sensitivity, stabbing and/or burning sensation in the body, vertigo, impotence, dry mouth, excessive sweating, depression, anxiety, nervousness, insomnia, confusion, reduced libido.
- rhinitis (nasal inflammation), inflammation in the upper respiratory tract, pharyngitis (throat inflammation), sinusitis (inflammation of the sinuses), bronchitis (bronchial inflammation), breathing difficulties or shortness of breath.
- rash, stinging of the skin.
- weakness, generally feeling unwell, hot flushes.

Rare side effects (effects that occur in 1-10 in 10,000 patients):

- atrial fibrillation, slow heart rate and pulse.
- anorexia, black stools as a result of internal bleeding, vomiting.
- increased libido, tendency to cry, nightmares and night terrors, depersonalization (self-detachment, feeling of derealization and detachment), neurosis.
- dermatitis, dry skin.
- pains, allergy, facial edema, fever, weight gain, chills, low body temperature, frequent urination, frequent night urination, flushing, peripheral ischemia (abnormal blood supply to an organ or certain part of the body), disturbed blood supply to the brain, vasodilation, vision changes, double vision, tinnitus, blocked ears, purpura (leakage of blood from small blood vessels under the skin), increased duration of bleeding, gout, thirst, vaginal discharge.

Additional side effects that were reported on use of cilazapril or hydrochlorothiazide taken separately, that do not occur on use of Cilaril Plus or which occur more frequently than with Cilaril Plus:

Cilazapril

Common side effects (effects that occur in 1-10 in 100 patients):

dry cough, rash, low blood pressure, dizziness, fatigue, headaches, nausea, indigestion.

Uncommon side effects (effects that occur in 1-10 in 1,000 patients):

- neutropenia (a low number of neutrophils), agranulocytosis (significant decrease in white blood cells, which may even cause death in severe cases), platelet deficiency, anemia.
- pancreatitis (in some cases, may cause death), liver function disorders, cholestatic hepatitis with or without necrosis.
- swelling of the face, lips, tongue, pharynx, larynx or esophagus (see in section 2 “Do not use the medicine if”), anaphylaxis (an acute allergic reaction; see in section 2 “Do not use the medicine if”), lupus-like syndrome.
- taste changes, transient ischemic attack (TIA), stroke.
- kidney failure, increased blood creatinine, increased blood urea, high blood potassium levels, low blood sodium levels.
- severe skin reactions (Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis), erythema, pemphigus (a skin disease), bullous pemphigoid (an autoimmune disease that manifests as a skin disease), skin inflammations, psoriasis, Lichen planus, vasculitis (inflammation of blood vessels), photosensitivity, balding, nail separation.
- low blood pressure.

Side effects of unknown frequency (effects whose frequency have not yet been determined):

A skin disease called pseudoporphyria.

Hydrochlorothiazide

Common side effects (effects that occur in 1-10 in 100 patients):
nausea, fatigue, dizziness.

Uncommon side effects (effects that occur in 1-10 in 1,000 patients):
thrombocytopenia (low blood platelet level), hemolytic anemia, granulocytopenia (low level of white blood cells); heart rate disorder; reduced tear secretion, vision problems; dry mouth, lack of appetite, salivary gland inflammation; cholestatic hepatitis; low blood levels of: potassium/sodium/chloride/magnesium/calcium; low levels of calcium in the urine, reduced blood volume, dehydration, metabolic alkalosis, high blood levels of: sugar/uric acid/cholesterol/triglycerides; sleep disorders, depression; muscle spasms; interstitial nephritis, kidney failure; sexual dysfunction; acute interstitial pneumonia, pulmonary edema, acute respiratory distress syndrome; rash, photosensitivity, cutaneous vasculitis, pseudoporphyria (a skin disease); low blood pressure.

If a side effect occurs, if one of the side effects worsens or if you suffer from a side effect not mentioned in the leaflet, consult with the doctor.

Reporting side effects

Side effects can be reported to the Ministry of Health by clicking on the link "Report Side Effects of Drug Treatment" found on the Ministry of Health homepage (www.health.gov.il) that directs you to the online form for reporting side effects, or by entering the link: https://sideeffects.health.gov.il/
In addition, you can report to "Unipharm Ltd.".

5. HOW SHOULD THE MEDICINE BE STORED?

- Avoid poisoning! This medicine and any other medicine should be kept in a safe place out of the reach and sight of children and/or infants in order to avoid poisoning. Do not induce vomiting unless explicitly instructed to do so by the doctor.
- Do not use the medicine after the expiry date (exp. date) that appears on the package. The expiry date refers to the last day of that month.
- Store the medicine below 25°C and in a place protected from light.

6. FURTHER INFORMATION

In addition to the active ingredients, the medicine also contains:

Lactose anhydrous, Maize starch, Hydroxypropyl methylcellulose, Sodium stearyl fumarate, Opadry brown OY-9375, Opadry white Y-1-7000.
Each **Cilaril Plus** tablet contains 173.4 mg lactose.

What the medicine looks like and the contents of the package:

Cilaril Plus is packaged in trays (blister) that is inserted into a carton package.
Each package contains 7, 10, 14, 15, 28 or 30 tablets.
Not all package sizes may be marketed.
Cilaril Plus tablets are film-coated, light brown, round and biconvex, with a score line on one side.
Registration holder and address: Unipharm Ltd., P.O.Box 21429, Tel Aviv, 6121301.
Manufacturer and address: Unipharm Ltd., "Mevo Carmel" Industrial Park.
Registration number of the medicine in the National Drug Registry of the Ministry of Health:
Cilaril Plus: 135 95 31365 00
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