Package leaflet: Information for the user

NEBILET PLUS 5 mg / 12.5 mg film-coated tablets

Nebivolol / Hydrochlorothiazide

Read all of this leaflet carefully before you start using 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 only. 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 or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

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

Nebilet Plus contains nebivolol and hydrochlorothiazide as the active ingredients.

- Nebivolol is a cardiovascular drug belonging to the group of selective beta-blocking agents (i.e. with a selective action on the cardiovascular system). It prevents increased heart rate and controls heart pumping strength. It also widens blood vessels, which helps to lower your blood pressure.
- Hydrochlorothiazide is a diuretic, that acts by increasing the amount of urine you produce.

Nebilet Plus is a one-tablet combination of nebivolol and hydrochlorothiazide and is used for the treatment of raised blood pressure (hypertension). It is used instead of the two separate products for those patients who are already taking them together.

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

Do not take Nebilet Plus
- if you are allergic to nebivolol or to hydrochlorothiazide or to any of the other ingredients of this medicine (listed in section 6).
- if you are allergic (hypersensitive) to other sulphonamide-derived substances (like hydrochlorothiazide, which is a sulphonamide-derived drug)
- if you have one or more of the following disorders:
  - very slow heartbeat (less than 60 beats per minute)
  - certain other serious heart rhythm problems (e.g. sick sinus syndrome, sino-atrial block, 2nd and 3rd degree atrioventricular block).
  - heart failure, which has just occurred or which has recently become worse, or you are receiving treatment for circulatory shock due to acute heart failure by intravenous drip feed to help your heart work
  - low blood pressure
  - serious circulation problems in the arms or legs
  - untreated phaeochromocytoma, a tumour located on top of the kidneys (in the adrenal glands)
  - severe kidney problems, complete absence of urine (anuria)
  - a metabolic disorder (metabolic acidosis), e.g., diabetic ketoacidosis.
  - asthma or wheezing (now or in the past)

– liver function disorder
– high blood calcium, low blood potassium, low blood sodium levels that are persistent and resistant to treatment
– high uric acid levels with gout symptoms

Warnings and precautions
Talk to your doctor or pharmacist before taking Nebilet Plus.

- Inform your doctor if you have or develop one of the following problems:
  - a type of chest pain due to spontaneously occurring heart cramp, called Prinzmetal angina
  - 1st degree heart block (a kind of mild heart conduction impairment that affects heart rhythm)
  - abnormally slow heartbeat
  - untreated chronic heart failure
  - lupus erythematosus (a disorder of the immune system, i.e. your body's defence system)
  - psoriasis (a skin disease characterised by scaly pink patches) or if you have ever had psoriasis
  - overactive thyroid gland: this medicine may mask the signs of an abnormally fast heart rate due to this condition
  - poor circulation in the arms or legs, e.g. Raynaud's disease or syndrome, cramp-like pains when walking
  - allergy: this medicine may intensify your reaction to pollen or other substances you are allergic to
  - prolonged breathing problems
  - diabetes: this medicine could conceal the warning signs of a low sugar level (e.g. palpitations, fast heartbeat); your doctor will also tell you to check your blood sugar more often while taking Nebilet Plus, as the dose of your antidiabetic drugs may need to be adjusted
  - kidney problems: your doctor will check your kidney function to make sure it does not get worse. If you have serious kidney problems do not take Nebilet Plus (see section 'Do not take Nebilet Plus')
  - 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); you are more likely to have low blood potassium if you suffer from liver cirrhosis, or have had too rapid a loss of water due to a strong diuretic treatment, of if your intake of potassium with food and drinks is inadequate
  - if you have to have surgery, always inform your anaesthetist that you are on Nebilet Plus before being anaesthetised.
  - 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 Nebilet Plus.

- Nebilet Plus may increase blood fat levels and uric acid. It may affect the levels of certain chemicals in your blood, called electrolytes: your doctor will check them from time to time via a blood test.

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

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

Children and adolescents
Because of the lack of data on the use of the product in children and adolescents, Nebilet Plus is **not** recommended for use in them.

Other medicines and Nebilet Plus
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Always tell your doctor if you are using or receiving any of the following medicines in addition to Nebilet Plus:
- Medicines that, as well as Nebilet Plus, may influence the blood pressure and/or heart function:
  - Medicines for controlling blood pressure or medicines for heart problems (such as amiodarone, amlodipine, cibenzoline, clonidine, digoxin, diltiazem, disopyramide, dofetilide, felodipine, flecainide, guanfacine,

hydroquinidine, ibutilide, lacidipine, lidocaine, mexiletine, methyldopa, moxonidine, nicardipine, nifedipine, nimodipine, nitrendipine, propafenone, quinidine, rilmenidine, sotalol, verapamil)
- Sedatives and therapies for psychosis (a mental illness) e.g. amisulpiride, barbiturates (also used for epilepsy), chlorpromazine, cyamemazine, droperidol, haloperidol, levomepromazine, narcotic drugs, phenothiazine (also used for vomiting and nausea), pimozide, sulpiride, sultopride, thioridazine, tiapride trifluoperazine
- Medicines for depression e.g. amitriptyline, fluoxetine, paroxetine
- Medicines used for anaesthesia during an operation
- Medicines for asthma, blocked nose or certain eye disorders such as glaucoma (increased pressure in the eye) or dilation (widening) of the pupil
- Baclofen (an antispasmodic drug)
- Amifostine (a protective medicine used during cancer treatment)

➢ Medicines whose effect or toxicity may be increased by Nebilet Plus:
- Lithium, used as a mood stabilizer
- Cisapride (used for digestive problems)
- Bepridil (used for angina)
- Diphemanil (used for excessive sweating)
- Medicines used for infections: erythromycin given by infusion or injection, pentamidine and sparfloxacin, amphotericin and penicillin G sodium, halofantrine (used for malaria)
- Vincamine (used for brain circulation problems)
- Mizolastine and terfenadine (used for allergy
- Diuretics and laxatives
- Medicines used to treat acute inflammation: steroids (e.g cortisone and prednisone), ACTH (adrenocorticotropic hormone) and medicines derived from salicylic acid (e.g. acetylsalicylic acid/aspirin and other salicylates)
- Carbenoxolone (used for heartburn and stomach ulcer)
- Calcium salts, used as supplements for bone health
- Medicines used to relax muscles (e.g. tubocurarine)
- Diaxozide, used to treat low blood sugar and high blood pressure
- Amantadine, an antiviral medicine
- Cyclosporine, used to suppress the body's immune response
- Iodinated contrast media, used for contrast in X-ray scans
- Anti-cancer medicines (e.g. cyclophosphamide, fluorouracil, methotrexate)

➢ Medicines whose effect may be decreased by Nebilet Plus:
- Blood sugar-lowering medicines (insulin and oral antidiabetic drugs, metformin)
- Medicines for gout (e.g. allopurinol, probenecid and sulfinpyrazone)
- Medicines like noradrenalin, used to treat low blood pressure or slow heart rate

➢ Medicines for pain and inflammation (non-steroidal anti-inflammatory drugs), as they may reduce the blood pressure lowering effect of Nebilet Plus

➢ Medicines for treating excessive stomach acid or ulcers (antacid): you should take Nebilet Plus during a meal and the antacid between meals.

Nebilet Plus with alcohol
Take care when drinking alcohol while you are taking Nebilet Plus, as you may feel faint or dizzy. If this happens to you, do not drink any alcohol, including wine, beer or alcopops.

Pregnancy and breast-feeding
You must tell your doctor if you are pregnant or if you think that you are. Usually, your doctor will advise you to take another medicine instead of Nebilet Plus, as Nebilet Plus is not recommended during pregnancy. This is because the active ingredient hydrochlorothiazide crosses the placenta. The use of Nebilet Plus during pregnancy may cause potentially harmful foetal and neonatal effects.

Tell your doctor if you are breast-feeding or about to start breast-feeding. Nebilet Plus is not recommended for mothers who are breast-feeding.

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines
This medicine may cause dizziness or fatigue. If affected, **do not** drive or operate machinery.

Nebilet Plus contains lactose and sodium
This product contains **lactose**. If you have been told by your doctor that you have an intolerance to some sugars, **contact your doctor before**taking this medicine.

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This medicine contains less than 1 mmol sodium (23 mg) per film-coated tablet, that is to say essentially 'sodium free'.

3. How to take Nebilet Plus

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

Take 1 tablet a day with some water, preferably at the same time of day.
Nebilet Plus may be taken before, during or after a meal, but you can take it independently of meals.

Use in children and adolescents
Do not give Nebilet Plus to children or adolescents.

The score line is only there to help you break the tablet if you have difficulty swallowing it whole.

If you take more Nebilet Plus than you should
If you accidentally take an overdose of this medicine, tell your doctor or pharmacist **immediately.** The most frequent symptoms and signs of overdose are very slow heart beat (bradycardia), low blood pressure with possible fainting, breathlessness such as in asthma, acute heart failure**,** 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 Nebilet Plus
If you forget a dose of Nebilet Plus, but remember a little later on that you should have taken it, take that day's dose as usual. However, if a long delay has occurred (e.g. several hours), so that the next due dose is near, skip the forgotten dose and take the next, scheduled, normal dose at the usual time. Do not take a double dose. Repeated skipping, however, should be avoided.

If you stop taking Nebilet Plus
Always consult your doctor before stopping Nebilet 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, this medicine can cause side effects, although not everybody gets them.

The following side effects have been reported with nebivolol:

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

- tiredness
- an unusual burning, pricking, tickling, or tingling sensation
- diarrhoea
- constipation
- nausea
- shortness of breath
- swollen hands or feet.

Uncommon side effects (may affect up to 1 in 100 people):
- slow heartbeat or other heart complaints
- low blood pressure
- cramp-like leg pains on walking
- abnormal vision
- impotence
- feelings of depression
- digestive difficulties, gas in stomach or bowel, vomiting
- skin rash, itchiness
- breathlessness such as in asthma, due to sudden cramps in the muscles around the airways (bronchospasm)
- nightmares.

Very rare side effects (may affect up to 1 in 10,000 people):
- fainting
- worsening of psoriasis (a skin disease characterised by scaly pink patches).

The following side effects have been reported only in some isolated cases:
- whole-body allergic reactions, with generalised skin eruption (hypersensitivity reactions);
- rapid-onset swelling, especially around the lips, eyes, or of the tongue with possible sudden difficulty breathing (angioedema);
- kind of skin rash notable for pale red, raised, itchy bumps of allergic or non allergic causes (urticaria).

The following side effects have been reported with hydrochlorothiazide:

Frequency 'not known': Skin and lip cancer (Non-melanoma skin cancer)

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Allergic reactions
- whole-body allergic reaction (anaphylactic reaction)

Heart and circulation
- heart rhythm disturbances, palpitations
- changes in the electrocardiogram
- sudden fainting when standing upright, formation of blood clots in veins (thrombosis) and embolism, circulatory collapse (shock)

Blood
- changes in the number of blood cells, such as: decreased white blood cells, decreased blood platelets, decreased red blood cells; impaired production of new blood cells by the bone marrow
- altered levels of body fluids (dehydration) and blood chemicals, in particular decreased potassium, decreased sodium, decreased magnesium, decreased chlorine and increased calcium
- increased uric acid levels, gout, increased blood glucose, diabetes, metabolic alkalosis (a disorder of metabolism), increased blood cholesterol and/or triglycerides

Stomach and gut
- lack of appetite, dry mouth, nausea, vomiting, stomach discomfort, abdominal pain, diarrhoea, fewer bowel movements (constipation), absence of bowel movements (ileus paralytic), flatulence
- inflammation of the glands that produce saliva, inflammation of the pancreas, increased blood amylase level (a pancreatic enzyme)
- yellowing of the skin (jaundice), inflammation of the gall bladder

Chest
- respiratory distress, lung inflammation (pneumonitis), formation of fibrous tissue in the lungs (interstitial lung disease), fluid accumulation in the lung (pulmonary oedema)

Nervous system
- vertigo (spinning sensation)
- convulsions, depressed level of consciousness, coma, headache, dizziness
- apathy, confusional state, depression, nervousness, restlessness, sleep disturbances
- unusual burning, pricking, tickling, or tingling skin sensations
- muscle weakness (paresis)

Skin and hair
- itchiness, purple spots/blotches on the skin (purpura), hives (urticaria), increased sensitivity of your skin to sunlight, rash, facial rash and/or patchy redness that can cause scarring (cutaneous lupus erythematosus), inflammation of blood vessels with consequent death of tissue (vasculitis necrotising), peeling, redness, loosening, and blistering of the skin (toxic epidermal necrolysis)

Eyes and ears
- yellow vision, blurred vision, worsening of myopia, decreased tear production

Joint and muscles
- muscle spasm, muscle pain

Urinary
- kidney dysfunction, acute kidney failure (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.

Sexual
- Erection disturbances

General/Other
- General weakness, tiredness, fever, thirst

Reporting of side effects
If you get any side effects talk to your doctor, pharmacist or nurse. 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 Nebilet Plus

Keep this medicine out of the sight and reach of children.
This medicinal product does not require any special storage condition.
Do not use this medicine after the expiry date which is stated on the box and on the blister pack after *'EXP'*. The expiry date refers to the last day of that month.
Do not throw away any medicine via wastewater or household waste.
Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Nebilet Plus contains
- The active substances are nebivolol and hydrochlorothiazide. Each tablet contains 5 mg nebivolol (as nebivolol hydrochloride) 2.5 mg of d-nebivolol and 2.5 mg of l-nebivolol) and 12.5 mg of hydrochlorothiazide

- The other ingredients are:
  - tablet core: lactose monohydrate, polysorbate 80 (E433), hypromellose (E464), maize starch, croscarmellose sodium (E468), cellulose microcrystalline (E460), silica colloidal anhydrous (E551), magnesium stearate (E572)
  - coating: macrogol 40 stearate Type I, titanium dioxide (E171), carmines (carminic acid aluminium lake, E120), hypromellose (E464), cellulose microcrystalline (E460).

What Nebilet Plus looks like and contents of the pack
Nebilet Plus is available as almost pink, round, slightly biconvex film-coated tablets with "5/12.5" embossed on one side and a score line on the other side in packs of 7, 14, 28, 30, 56, 90 film-coated tablets.

Tablets are provided in blisters (PP/COC/PP/Aluminium blister).
(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
Berlin-Chemie AG
Glienicker Weg 125, 12489 Berlin, Germany

or

Menarini – Von Heyden GmbH
Leipziger Strasse 7-13, 01097 – Dresden, Germany

or

A. Menarini Manufacturing Logistics and Services S.r.l.
Via Sette Santi 3, 50131 Florence, Italy

This medicinal product is authorised in the member states of the EEA under the following names

Austria: Nomexor plus HCT
Belgium: Hyporetic
France: CONEBILOX
Greece: Hypoloc-plus
Iceland: Nebilet Comp
Ireland: Nebilet Plus
Italy: Lobidiur
Luxembourg: Hyporetic
Portugal: Hypoloc Plus
Spain: Silostar Plus
The Netherlands: Hyporetic
United Kingdom: Nebizide

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