Size : 560 x 210 mm

Front

TN49941

NEBUNTA 5

Nebivolol Tablets 5 mg

COMPOSITION

Each uncoated tablet contains:

Nebivolol Hydrochloride equivalent to Nebivolol	5 mg
Excipients (Contains Lactose)	q.s.

DOSAGE FORM

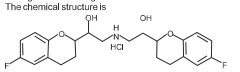
Tablets

DISTRIBUTION CATEGORY: Prescription only medicine or POM

DESCRIPTION

Nebivolol hydrochloride is a synthetic α,α'-[iminobis(methylene)]bis[6-fluoro-3,4-dihydro-2*H*-1-benzopyran-2-methanol] hydrochloride salt or (1*RS*,1'*RS*)-1,1'-[(2*RS*,2'*SR*)-Bis(6-fluorochroman-2-yl)]-2,2'-iminodiethanol hydrochloride with molecular formula $C_{22}H_{26}O_4NCl\ F_2$. Nebivolol hydrochloride having molecular weight of 441.9.

The chemical structure is



EXCIPIENT LIST

Nebunta 5(Nebivolol Tablets 5 mg), Pregelatinized Starch(1500 LM), Lactose monohydrate (Pharmatose 200M), croscarmellose sodium (Ac di sol type SD 711), Hypromellose (Methocel E15 Premium LV), Polysarbate 80 (Tween 80-LQ), Sodium Lauryl Sulfate (Kolliphore SLS Fine), Purified water, Microcrystalline cellulose (Avicel PH-102), Lake Pigment HT 6027 D&C Red #27 (Phloxine Aluminum Lake), Lake Pigment HT 5284 FD&C yellow #6 (Sunset yellow FCF Aluminum Lake), Lake Pigment HT 5624 FD&C Blue #2(Indigo Carmine Aluminum Lake), Magnesium Stearate.

CLINICAL PARTICULARS

Therapeutic Indications

Hypertension

Treatment of essential hypertension.

Chronic heart failure (CHF)

Treatment of stable mild and moderate chronic heart failure in addition to standard therapies in elderly patients 70 years old or above.

Notorious Effect of Excipients:

Nebunta 5 (Nebivolol Tablets 5mg) contains

Lactose: Adverse reactions to lactose are largely due to lactose intolerance, which occurs in individuals with a deficiency of the enzyme lactase. Recently, the presence of milk proteins in lactose-containing dry powder inhalers, which can cause anaphylaxis in cases of severe allergy to cow's milk, has been reported.[1]

References:

1. Rowe R, Sheskey P, Quinn M. Handbook of Pharmaceutical Excipients. 6th Ed. Lactose; 361-364.

Posology and Method of administration

Posology

Hypertension

Adults

The usual dose is one tablet (5 mg) daily, preferably taken at the same time of the day. Tablets may be taken with meals.

The blood pressure lowering effect may take up to 1-2 weeks of treatment to become evident. Occasionally, the optimal effect is only reached only after 4 weeks.

Beta-blockers can be used alone or concomitantly with other antihypertensive agents.

Patients with renal insufficiency

The recommended starting dose for patients with renal insufficiency is 2.5 mg daily. If needed, the daily dose may be increased to 5 mg.

Patients with hepatic insufficiency

Data in patients with hepatic insufficiency or impaired liver function are limited. Therefore, the use of Nebivolol in these patients is contraindicated.

Elderly

In patients over 65 years, the recommended starting dose is 2.5 mg daily. If needed, the daily dose may be increased to 5 mg. However, in view of the limited experience in patients above 75 years, caution must be exercised and these patients monitored closely.

Paediatric population

Nebivolol is not recommended for use in children and adolescents under the age of 18 years due to a lack of data on safety and efficacy.

Chronic Heart Failure (CHF)

The use of Nebivolol for treatment of stable chronic heart failure should involve a gradual increase of dosage until the optimal individual maintenance dose is reached.

Prior to starting treatment, patients should have stable chronic heart failure without acute failure during the past six weeks. It is recommended that the treating physician should be experienced in the management of chronic heart failure.

For those patients receiving cardiovascular drug therapy including diuretics and/or digoxin and/or ACE inhibitors and/or angiotensin II antagonists, these drugs should be maintained at a stable dose for the two weeks leading up to initiation of Nebivolol treatment.

The dose should be increased from the initial dose of 1.25 mg daily to 2.5 mg and then to 5 mg daily and then 10 mg daily at intervals of 1-2 weeks based on patient tolerability.

The maximum recommended dose is 10 mg Nebivolol once daily.

The initiation of therapy and all increases in dose should be carried out under the supervision of an experienced physician over a period of at least 2 hours to ensure that the clinical status (especially as regards blood pressure, heart rate, conduction disturbances, signs of worsening heart failure) remains stable.

The occurrence of adverse events may prevent patients being treated with the maximum recommended dose. If necessary, the dose reached can also be decreased step by step and reintroduced as appropriate.

During the initial dose increasing phase, in case of worsening of the heart failure or intolerance, it is recommended first to reduce the dose of Nebivolol, or to stop it immediately if necessary (in case of sever hypotension, worsening of heart failure with acute pulmonary oedema, cardiogenic shock, symptomatic bradycardia or AV block).

Treatment of stable chronic heart failure with Nebivolol is generally a long-term treatment.

The treatment with Nebivolol is not recommended to be stopped abruptly since this might lead to a transitory worsening of heart failure. If discontinuation is necessary, the dose should be decreased step-wise weekly.

Patients with renal insufficiency

No dose adjustment is required in mild to moderate renal insufficiency since up-titration to the maximum tolerated dose is individually adjusted. There is no experience in patients with severe renal insufficiency (serum creatinine ≥ 250 µmol/L). Therefore, the use of Nebivolol in these patients is not recommended.

Patients with hepatic insufficiency

Data in patients with hepatic insufficiency are limited. Therefore, the use of Nebivolol in these patients is contraindicated.

Elderly

No dose adjustment is required since up-titration to the maximum tolerated dose is individually adjusted.

Children and adolescents

Nebivolol is not recommended for use in children and adolescents under the age of 18 years due to a lack of data on safety and efficacy.

Method of administration

Oral use.

Tablets may be taken with meals.

Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Liver insufficiency or liver function impairment.
- Acute heart failure, cardiogenic shock or episodes of heart failure decompensation requiring I.V. inotropic therapy.

In addition, as with other beta-blocking agents, Nebivolol is contra-indicated in:

- Sick sinus syndrome, including sino-atrial block.
- Second and third degree heart block (without a pacemaker).
- History of bronchospasm and bronchial asthma.
- Untreated phaeochromocytoma
- Metabolic acidosis.
- Bradycardia (heart rate < 60bpm prior to start of therapy)
- Hypotension (systolic blood pressure <90 mmHg)
- Severe peripheral circulatory disturbances.

Special warnings and precaution for use

Anaesthesia

Continuation of beta blockade reduces the risk of arrhythmias during induction and intubation. If beta blockade is interrupted in preparation for surgery, the beta-adrenergic antagonist should be discontinued at least 24 hours beforehand.

Caution should be observed with certain anaesthetics that cause myocardial depression. The patient can be protected against vagal reactions by intravenous administration of atropine.

Cardiovascular

In general, beta-adrenergic antagonists should not be used in patients with untreated congestive heart failure (CHF), unless their condition has been stabilised.

In patients with ischaemic heart disease, treatment with a beta-adrenergic antagonist should be discontinued gradually, i.e. over 1-2 weeks. If necessary, replacement therapy should be initiated at the same time to prevent exacerbation of angina pectoris.

Beta-adrenergic antagonists may induce bradycardia. If the pulse rate drops below 50-55 bpm at rest and/or the patient experiences symptoms suggestive of bradycardia, the dosage should be reduced.

Beta-adrenergic antagonists should be used with caution in the following conditions:

- Peripheral circulatory disorders (Raynaud's disease or syndrome, intermittent claudication), as aggravation of these disorders may occur upon use of beta blockers.
- First degree heart block, because of the negative effect of beta-blockers on conduction time
- Prinzmetal's angina due to unopposed alpha-receptor mediated coronary artery vasoconstriction. Beta-adrenergic antagonists may increase the number and duration of anginal attacks.
- Concomitant treatment with calcium channel antagonists of the verapamil and diltiazem type, with Class I antiarrhythmic drugs, and with centrally acting antihypertensive drugs.

Metabolic/Endocrinological

Nebivolol does not affect glucose levels in diabetic patients. Care should be taken in diabetic patients however, as Nebivolol may mask certain symptoms of hypoglycaemia (tachycardia, palpitations).

Beta-adrenergic blocking agents may mask tachycardic symptoms in hyperthyroidism. Abrupt withdrawal may aggravate symptoms.

Respiratory

In patients with chronic obstructive pulmonary disorders, beta-adrenergic antagonists should be used with caution as airway constriction may be aggravated.

Other

This medicine contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Caution should be exercised when treating patients with a history of psoriasis with beta-adrenergic antagonists as they may increase the sensitivity to allergens and the severity of anaphylactic reactions.

The initiation of Chronic Heart Failure treatment with Nebivolol necessitates regular monitoring. Treatment discontinuation should not be done abruptly unless clearly indicated.

Interaction with other medicinal products

Pharmacodynamic interactions:

Combinations not recommended:

- Class I anti-arrhythmics (quinidine, hydroquinidine, cibenzoline, flecainide, disopyramide, lidocaine, mexiletine, propafenone) as the effect on atrio-ventricular conduction time may be potentiated and the negative inotropic effect increased.
- Calcium channel antagonists of verapamil/diltiazem the type due to a negative influence on contractility and atrio-ventricular conduction. Intravenous administration of verapamil in patients with β-blocker treatment may lead to profound hypotension and atrio-ventricular block.
- Centrally-acting antihypertensives (clonidine, guanfacin, moxonidine, methyldopa, rilmenidine). Concomitant use of centrally acting antihypertensive drugs may worsen heart failure by a decrease in the central sympathetic tonus (reduction of heart rate and cardiac output, vasodilation). Abrupt withdrawal, particularly if prior to beta-blocker discontinuation, may increase risk of hypertension.

Combinations to be used with caution:

- Class III anti-arrhythmic drugs (Amiodarone) as the effect on atrio-ventricular conduction time may be potentiated.

Volatile halogenated anaesthetics as concomitant use of beta-adrenergic antagonists and anaesthetics may attenuate reflex tachycardia and increase the risk of hypotension. Sudden withdrawal of beta-blocker treatment should be avoided if possible. The anaesthesiologist should be informed when the patient is receiving Nebivolol Tablets.

- Insulin and oral anti-diabetic drugs as, although Nebivolol does not affect glucose levels, concomitant use may mask symptoms of hypoglycaemia (palpitations, tachycardia).
- Baclofen (antispastic agent), Amifostine (antineoplastic adjunct): concomitant use with antihypertensives is likely to increase the fall in blood pressure, therefore the dosage of the antihypertensive medication should be adjusted accordingly.

Combinations to be used only after careful consideration:

- Digitalis glycosides as concomitant use may increase atrio-ventricular conduction time although clinical trials with Nebivolol have not shown any clinical evidence of an interaction. Nebivolol does not influence the kinetics of digoxin.
- Calcium antagonists of the Dihydropyridine type (Amlodipine, Felodipine, Lacidipine, Nifedipine, Nicardipine, Nimodipine, Nitrendipine) because concomitant use may increase the risk of hypotension, and cause an increase in the risk of a further deterioration of the ventricular pump function in patients with heart failure.
- Antipsychotics and Antidepressants (Tricyclics, Barbiturates and Phenothiazines). Concomitant use may enhance the hypotensive effect of the beta-blockers (additive effect).
- Non-steroidal anti-inflammatory drugs (NSAID) are thought to have no effect on the blood pressure lowering effect of Nebivolol.
- Sympathomimetic agents. Concomitant use may counteract the effect of beta-adrenergic antagonists. Beta-adrenergic agents may lead to unopposed alpha-adrenergic activity of sympathomimetic agents with both alpha- and beta-adrenergic effects causing increased risk of hypertension, severe bradycardia and heart block.

Pharmacokinetic interactions:

As Nebivolol metabolism involves the CYP2D6 isoenzyme, co-administration with substances inhibiting this enzyme, especially paroxetine, Fluoxetine, Thioridazine, Quinidine and Bupropion, Chloroquine, Levomepromazine, Dextrometorphan and Terbinafine may lead to increased plasma levels of Nebivolol associated with an increased risk of excessive bradycardia and adverse events.

Co-administration of Cimetidine increased the plasma levels of Nebivolol, without changing the clinical effect. Co-administration of Ranitidine did not affect the pharmacokinetics of Nebivolol. Provided Nebivolol is taken with the meal, and an antacid between meals, the two treatments can be co-prescribed.

Combining Nebivolol with Nicardipine slightly increased the plasma levels of both drugs, without changing the clinical effect. Co-administration of alcohol, Furosemide or Hydrochlorothiazide did not affect the pharmacokinetics of Nebivolol. Nebivolol does not affect the pharmacokinetics and pharmacodynamics of Warfarin.

Pregnancy & Lactation

Pregnancy

Nebivolol has pharmacological effects that may cause harmful effects on pregnancy and/or the foetus/new-born. In general, beta-blockers reduce placental profusion, which has been associated with growth retardation, intrauterine death, abortion or early labour. Adverse effects (e.g. hypoglycaemia and bradycardia) may occur in the foetus and new-born infant. If treatment with beta-adrenoreceptor blockers is necessary, beta-1-selective adrenoreceptor blockers are preferable.

Nebivolol should not be used during pregnancy unless clearly necessary. If treatment with Nebivolol is considered necessary, the uteroplacental blood flow and foetal growth should be monitored. In case of harmful effects on pregnancy or the foetus, alternative treatment should be considered. The new-born infant must be closely monitored. Symptoms of hypoglycaemia and bradycardia are generally to be expected in the first 3 days.

Breast-feeding

Animal studies have shown that Nebivolol is excreted in breast milk. It is not known whether this drug is excreted into human milk. Most beta-blockers, particularly lipophilic compounds like Nebivolol and its active metabolites, pass into breast milk although to a variable extent. Therefore, breast feeding in not recommended during administration of Nebivolol.

Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Pharmacodynamic studies have shown that Nebivolol does not affect psychomotor function. When driving vehicles or operating machines it should be taken into account that dizziness and fatigue may occasionally occur.

Undesirable effects

Adverse events are listed separately for hypertension and CHF because of differences in the background diseases.

Hypertension

The adverse reactions reported, which are in most of the cases of mild to moderate intensity are tabulated below, classified by system organ class and ordered by frequency:

Organ class	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1,000 to < 1/100)	Very rare (<1/10,000)	Not Known
Immune system disorders				angioneurotic oedema, hypersensitivity
Psychiatric disorders		nightmares, depression		
Nervous system disorders	headache, dizziness, paraesthesia		syncope	
Eye disorders		impaired vision		
Cardiac disorders		bradycardia, heart failure, slowed AV conduction/AV-block		
Vascular disorders		hypotension, (increase of) intermittent claudication		
Respiratory, thoracic and mediastinal disorders	dyspnoea	bronchospasm		
Gastrointestinal disorders	constipation, nausea, diarrhoea	dyspepsia, flatulence, vomiting		
Skin and subcutaneous tissue disorders		pruritus, rash erythematous	psoriasis aggravated	urticaria
Reproductive system and breast disorders		impotence		
General disorders and administration - site conditions	tiredness, oedema			

The following adverse reactions have also been reported with some beta adrenergic antagonists: hallucinations, psychoses, confusion, cold/cyanotic extremities, Raynaud phenomenon, dry eyes, and oculo-mucocutaneous toxicity of the practolol-type.

Chronic heart failure

Data on adverse reactions in CHF patients are available from one placebo-controlled clinical trial involving 1067 patients taking Nebivolol and 1061 patients taking placebo. In this study, a total of 449 Nebivolol patients (42.1%) reported at least possibly causally related adverse reactions compared to 334 placebo patients (31.5%). The most commonly reported adverse reactions in Nebivolol patients were bradycardia and dizziness, both occurring in approximately 11% of patients. The corresponding frequencies among placebo patients were 2% and 7%, respectively.

The following incidences were reported for adverse reactions (at least possibly drug-related) which are considered specifically relevant in the treatment of chronic heart failure:

Aggravation of cardiac failure occurred in 5.8% of Nebivolol patients compares to 5.2% of the placebo patients.

Orthostatic hypotension was reported in 2.1% of Nebivolol patients compared to 1.0% of placebo patients.

Drug intolerance occurred in 1.6% of the Nebivolol patients compared to 0.8% of the placebo patients.

First degree atrio-ventricular block occurred in 1.4% of Nebivolol patients compared to 0.9% of placebo patients.

Oedema of the lower limb were reported in 1.0% of Nebivolol patients compared to 0.2% of placebo patients.

Overdose

No data are available on overdosage with Nebivolol 5mg Tablets.

Symptoms of overdose with beta-adrenergic antagonists:

- Bradycardia
- Hypotension
- Bronchospasm
- Acute cardiac insufficiency.

Treatment

In case of overdose or hypersensitivity, the patient should be kept under close supervision and be treated in an intensive care ward. Blood glucose levels should be checked. Absorption of any drug residues still present in the gastro-intestinal tract can be prevented by gastric lavage and the administration of activated charcoal and a laxative. Artificial respiration may be required. Bradycardia or extensive vagal reactions should be treated by administering atropine or methylatropine. Hypotension and shock should be treated with plasma/plasma substitutes and, if necessary, catecholamines. The beta-blocking effect can be counteracted by slow intravenous administration of isoprenaline hydrochloride, starting with a dose of approximately 5 µg/minute, or dobutamine, starting with a dose of 2.5 µg/minute, until the required effect has been obtained. In refractory cases isoprenaline can be combined with dopamine. If this does not produce the desired effect either, intravenous administration of glucagon 50-100 µg/kg i.v. may be considered. If required, the injection should be repeated within one hour, to be followed - if required - by an i.v. infusion of glucagon 70 µg/kg/h. In extreme cases of treatment-resistant bradycardia, a pacemaker may be inserted.

Back

PHARMACOLOGICAL PROPERTIES
Pharmacodynamic properties
Nebivolol is a racemate of two enantiomers, SRRR-Nebivolol (or d-Nebivolol) and RSSS-Nebivolol (or l-Nebivolol). It is a competitive and selective beta-receptor antagonist, due to the SRRR-enantiomer (d-enantiomer), and also it has mild vasodilating properties due to an interaction with the L-arginine/nitric oxide pathway.
Single and repeated doses of Nebivolol reduce heart rate and blood pressure at rest and during exercise, both in normotensive subjects and in hypertensive patients. The antihypertensive effect is maintained during chronic treatment.
At therapeutic doses, Nebivolol is devoid of alpha-adrenergic antagonism.
During acute and chronic treatment with Nebivolol in hypertensive patients, systemic vascular resistance is decreased. Despite heart rate reduction, a reduction in cardiac output during rest and exercise may be limited due to an increase in stroke volume. The clinical relevance of these haemodynamic differences as compared to other beta-1 receptor antagonists has not been fully established.
In hypertensive patients, Nebivolol increases the Nitric Oxide-mediated vascular response to acetylcholine (ACh) which is reduced in patients with endothelial dysfunction.
In vitro and in vivo experiments in animals showed that Nebivolol has no intrinsic sympathomimetic activity.
In vitro and in vivo experiments in animals showed that at pharmacological doses Nebivolol has no membrane stabilising action.
In healthy volunteers, Nebivolol has no significant effect on maximal exercise capacity or endurance.
Available preclinical and clinical evidence in hypertensive patients has not shown that Nebivolol has a detrimental effect on erectile function.

Pharmacokinetic properties
Both Nebivolol enantiomers are rapidly absorbed after oral administration. The absorption of Nebivolol is not affected by food. It can be given with or without meals.
Nebivolol is extensively metabolised, partly to active hydroxy-metabolites. Nebivolol is metabolised via alicyclic and aromatic hydroxylation, N-dealkylation and glucuronidation. In addition, glucuronides of the hydroxy-metabolites are formed. The metabolism of Nebivolol by aromatic hydroxylation is subject to the CYP2D6 dependent genetic oxidative polymorphism. The oral bioavailability of Nebivolol averages 12% in fast metabolizing patients and is virtually complete in slow metabolisers. At steady state and at the same dose level, the peak plasma concentration of unchanged Nebivolol is about 23 times higher in poor metabolisers than in extensive metabolisers. When unchanged drug plus active metabolites are considered, the difference in peak plasma concentrations is 1.3 to 1.4 fold. Because of the variation in rates of metabolism, the dose of Nebivolol should always be adjusted to the individual requirements of the patient. Poor metabolisers therefore may require lower doses.
In fast metabolisers, elimination half-lives of the Nebivolol enantiomers average 10 hours. In slow metabolisers, they are 3-5 times longer. In fast metabolisers, plasma levels of the RSSS-enantiomer are slightly higher than for the SRRR-enantiomer. In slow metabolisers, this difference is larger. In fast metabolisers, elimination half-lives of the hydroxymetabolites of both enantiomers average 24 hours, and are about twice as long in slow metabolisers.
Steady-state plasma levels in most subjects (fast metabolisers) are reached within 24 hours for Nebivolol and within a few days for the hydroxy-metabolites.
Plasma concentrations are dose-proportional between 1 and 30 mg. The pharmacokinetics of Nebivolol are not affected by age.
In plasma, both Nebivolol enantiomers are predominantly bound to albumin.
Plasma protein binding is 98.1% for SRRR-Nebivolol and 97.9% for RSSS-Nebivolol.
One week after administration, 38% of the dose is excreted in the urine and 48% in the faeces. Urinary excretion of unchanged Nebivolol is less than 0.5% of the dose.

PRECLINICAL SAFETY DATA
No information available

PHARMACEUTICAL PARTICULARS
Incompatibilities
Not applicable.

Shelf life
24 months

Storage Condition
Store below 30°C.

Nature and Contents of Container
10 tablets in Alu-Alu blister pack, 3 such blister in a printed carton along with Pack Insert.

MANUFACTURING AUTHORISATON HOLDER AND MANUFACTURER

Manufacturing Authorisation Holder	Manufacturer
Ajanta Pharma Limited Ajanta House, Charkop Kandivli (West) Mumbai - 400 067 India. Tel : +91-22-6606 1000 Fax : (0091) 22-66061200/ 300 Email : info@ajantapharma.com	Ajanta Pharma Limited Z/103/A, Dahej Sez II, City: Bharuch – 392 130, Dist. Bharuch, Gujarat State, India. Tel : +91-22-6606 1000 Fax : (0091) 22-66061200/ 300 Email : info@ajantapharma.com

NEBUNTA 5
Nebivolol Tablets 5 mg

Read all of this leaflet carefully before you start taking this medicine
- 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.

Distribution Category: Prescription only medicine or POM

In this leaflet:

1. What Nebunta is and what it is used for?
2. What you need to know before you take Nebunta?
3. How to take Nebunta?
4. Possible side effects?
5. How to store Nebunta?
6. Contents of the pack and other information?

1. What Nebunta is and what it is used for?
Nebunta contains Nebivolol, 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, controls heart pumping strength. It also exerts a dilating action on blood vessels, which contributes as well to lower blood pressure.
It is used to treat raised blood pressure (hypertension).
Nebunta is also used to treat mild and moderate chronic heart failure in patients aged 70 or over, in addition to other therapies.

2. Before you take Nebunta tablets
Do not take this medicine and tell your doctor if:
- if you are allergic to Nebivolol or any of the other ingredients of this medicine.
- if you have one or more of the following disorders:
- low blood pressure
- serious circulation problems in the arms or legs
- very slow heartbeat (less than 60 beats per minute)
- certain other serious heart rhythm problems (e.g. 2nd and 3rd degree atrioventricular block, heart conduction disorders).
- 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
- asthma or wheezing (now or in the past)
- untreated phaeochromocytoma, a tumour located on top of the kidneys (in the adrenal glands)
- liver function disorder
- a metabolic disorder (metabolic acidosis), for example, diabetic ketoacidosis.

Warnings and Precautions
Talk to your doctor or pharmacist before taking Nebunta.
Inform your doctor if you have or develop one of the following problems:
- abnormally slow heartbeat
- a type of chest pain due to spontaneously occurring heart cramp called Prinzmetal angina
- untreated chronic heart failure
- 1st degree heart block (a kind of light heart conduction disorder that affects heart rhythm)
- poor circulation in the arms or legs, e.g. Raynaud's disease or syndrome, cramp-like pains when walking
- prolonged breathing problems
- diabetes: This medicine has no effect on blood sugar, but it could conceal the warning signs of a low sugar level (e.g. palpitations, fast heartbeat).
- overactive thyroid gland: This medicine may mask the signs of an abnormally fast heart rate due to this condition
- allergy: This medicine may intensify your reaction to pollen or other substances you are allergic to
- psoriasis (a skin disease - scaly pink patches) or if you have ever had psoriasis
- if you have to have surgery, always inform your anaesthetist that you are on Nebunta before being anaesthetised.

If you have serious kidney problems, do not take Nebunta for heart failure and tell your doctor.
You will be regularly monitored at the beginning of your treatment for chronic heart failure by an experienced physician.
This treatment should not be stopped abruptly unless clearly indicated and evaluated by your doctor.

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

Other medicines and Nebunta
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 Nebunta:
Medicines for controlling the blood pressure or medicines for heart problems (such as Amiodarone, Amlodipine, Cibenzoline, Clonidine, Digoxin, Diltiazem, Disopyramide, Felodipine, Flecainide, Guanfacin, Hydroquinidine, Lacidipine, Lidocaine, Methyldopa,
- Mexiletine, Moxonidine, Nicardipine, Nifedipine, Nimodipine, Nitrendipine, Propafenone, Quinidine, Rilmenidine, Verapamil).
- Sedatives and therapies for psychosis (a mental illness) e.g. barbiturates (also used for epilepsy), Phenothiazine (also used for vomiting and nausea) and Thioridazine.
- Medicines for depression e.g. Amitriptyline, Paroxetine, Fluoxetine.
- 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)

All these drugs as well as Nebivolol may influence the blood pressure and/or heart function.
- Medicines for treating excessive stomach acid or ulcers (antacid drug): you should take Nebunta during a meal and the antacid drug between meals.

Pregnancy and breast-feeding
Nebunta should not be used during pregnancy, unless clearly necessary.
It is not recommended for use while 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.

3. How to take Nebunta tablets
Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.
Nebunta may be taken before, during or after the meal, but, alternatively, you can take it independently of meals. The tablet is best taken with some water.

Treatment of raised blood pressure (hypertension)
- The usual dose is 1 tablet per day. The dose should be taken preferably at the same time of the day.
- Elderly patients and patients with a kidney disorder will usually start with ½ (half) tablet daily.
- The therapeutic effect on blood pressure becomes evident after 1-2 weeks of treatment. Occasionally, the optimal effect is reached only after 4 weeks.

Treatment of chronic heart failure
- Your treatment will be started and closely supervised by an experienced physician.
- Your doctor will start your treatment with ¼ (quarter) tablet per day. This may be increased after 1-2 weeks to ½ (half) tablet per day, then to 1 tablet per day and then to 2 tablets per day until the correct dose is reached for you. Your doctor will
- prescribe the dose that is right for you at each step and you should closely follow his/her instructions.
- The maximum recommended dose is 2 tablets (10mg) a day.
- You will need to be under the close supervision for 2 hours by an experienced physician when you start treatment and every time your dose is increased
- Your doctor may reduce your dose if necessary
- You should **not stop treatment abruptly** as this can make your heart failure worse.
- Patients with serious kidney problems should not take this medicine.
- Take your medicine once daily, preferably at about the same time of day.
- Your doctor may decide to combine Nebunta tablets with other medicines to treat your condition.
- Do not use in children or adolescents.

If you take more Nebunta than you should
If you accidentally take an overdose of this medicine, tell your doctor of pharmacist **immediately**. The most frequent symptoms and signs of a Nebunta overdose are very slow heart beat (bradycardia), low blood pressure with possible fainting (hypotension), breathlessness such as in asthma (bronchospasm), and acute heart failure.
You can take activated charcoal (which is available at your pharmacy) while you wait for the arrival of the doctor.

If you forget to take Nebunta
If you forget a dose of Nebunta, 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 Nebunta
You should always consult with your doctor before stopping Nebunta treatment, whether you are taking it for high blood pressure or chronic heart failure.
You should not stop Nebunta treatment abruptly as this can temporarily make your heart failure worse. If it is necessary to stop Nebunta treatment for chronic heart failure, the daily dose should be decreased gradually, by halving the dose, at weekly intervals.
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.
When Nebunta is **used for the treatment of raised blood pressure**, the possible side effects are:
Common side effects (may affect up to 1 in 10 people):
- Headache
- dizziness
- tiredness
- an unusual itching or tingling feeling
- 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 (dyspepsia), 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 - scaly pink patches).

The following side effects have been reported only in some isolated cases during Nebunta treatment:
- 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).

In a clinical study for **chronic heart failure,** the following side effects were seen:
Very common side effects (may affect more than 1 in 10 people):
- slow heart beat
- dizziness
- Common side effects (may affect up to 1 in 10 people):
- worsening of heart failure
- low blood pressure (such as feeling faint when getting up quickly)
- inability to tolerate this medicine
- a kind of light heart conduction disorder that affects heart rhythm (1st degree AV-block)
- swelling of the lower limbs (such as swollen ankles).

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. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Nebunta tablets
Keep this medicine out of the sight and reach of children.
This medicinal product does not require any special storage conditions. Do not use this medicine after the expiry date which is stated on the carton label and blister foil after EXP. The expiry date refers to the last day of that month.
Do not throw 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 nebunta tablet contains:
The active ingredient is

Each uncoated tablet contains:

Nebivolol Hydrochloride equivalent to Nebivolol	5 mg
Excipients (Contains Lactose)	q.s.

List of Excipients:
Nebunta 5 (Nebivolol Tablets 5 mg), Pregelatinized Starch (1500 LM), Lactose monohydrate (Pharmatose 200 M), croscarmellose sodium (Ac di sol type SD 711), Hypromellose (Methocel E15 Premium LV), Polysarbate 80 (Tween 80-LQ), Sodium Lauryl Sulfate (Kolliphore SLS Fine), Purified water, Microcrystalline cellulose (Avicel PH-102), Lake Pigment HT 6027 D&C Red #27 (Phloxine Aluminum Lake), Lake Pigment HT 5284 FD&C yellow #6 (Sunset yellow FCF Aluminum Lake), Lake Pigment HT 5624 FD&C Blue #2 (Indigo Carmine Aluminum Lake), Magnesium Stearate.

What Nebunta tablet looks like and contents of the pack
Nebunta 5 (Nebivolol Tablets 5 mg)
Beige coloured, mottled, triangular shaped biconvex uncoated tablets debossed with 'NE1' on one side and plain on other side.

10 tablets in Alu-Alu blister pack, 3 such blister in a printed carton along with Pack Insert.

MANUFACTURING AUTHORISATON HOLDER AND MANUFACTURER

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For any information about this medicinal product, please contact Manufacturing Authorization Holder.

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