

For the use of a Registered Medical Practitioner or Hospital or a Laboratory only

NEBICARD

1. Generic Name

Nebivolol Hydrochloride Tablets I.P.

2. Qualitative and quantitative Composition

NEBICARD-2.5

Each uncoated tablet contains:

Nebivolol Hydrochloride I.P. equivalent to

Nebivolol.....2.5 mg

The excipients used are Lactose, starch, croscarmellose sodium, Hydroxy propyl methyl Cellulose, Polysorbate 80, Microcrystalline Cellulose, Magnesium Stearate, Colloidal Silicon Dioxide.

NEBICARD-5

Each uncoated tablet contains:

Nebivolol Hydrochloride I.P. equivalent to

Nebivolol.....5 mg

The excipients used are Lactose, starch, croscarmellose sodium, Hydroxy propyl methyl Cellulose, Polysorbate 80, Microcrystalline Cellulose, Magnesium Stearate, Colloidal Silicon Dioxide.

NEBICARD-10

Each uncoated tablet contains:

Nebivolol Hydrochloride I.P. equivalent to

Nebivolol.....10 mg

Colour: Lake of sunset yellow

The excipients used are Lactose, starch, croscarmellose sodium, Hydroxy propyl methyl Cellulose, Polysorbate 80, Microcrystalline Cellulose, Magnesium Stearate, Colloidal Silicon Dioxide, Lake of sunset yellow, Polyvinyl pyrrolidone, Iso propyl alcohol.

3. Dosage form and strength

Dosage form: Tablet

Strength: Nebivolol 2.5, 5, 10 mg

4. Clinical particulars

4.1 Therapeutic indication

Nebivolol is indicated in the treatment of Hypertension.

4.2 Posology and method of administration

Hypertension

Adults

The Nebivolol dose is one tablet (5 mg) daily, preferably at the same time of the day.

The blood pressure lowering effect becomes evident after 1-2 weeks of treatment. Occasionally, the optimal effect is reached only after 4 weeks.

Combination with other antihypertensive agents

Beta-blockers can be used alone or concomitantly with other antihypertensive agents. An additional antihypertensive effect has been observed only when Nebivolol 5 mg tablets are combined with hydrochlorothiazide 12.5-25 mg.

Patients with renal insufficiency

The recommended starting dose of Nebivolol 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 contra-indicated.

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 hypertension 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.

Method of administration

One tablet of Nebicard daily, preferably at the same time of the day.

Tablets may be taken with meals.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed.
- 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 contraindicated 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 < 60 bpm prior to start therapy).
- Hypotension (systolic blood pressure < 90 mmHg).
- Severe peripheral circulatory disturbances.

4.4 Special warnings and precautions for use

NEBIVOLOL:

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 that are suggestive of bradycardia, the dosage should be reduced.

Beta-adrenergic antagonists should be used with caution:

- 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 intensify symptoms.

Respiratory

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

Other

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.

4.5 Drugs interactions

Nebivolol:

Pharmacodynamic interactions:

Combinations not recommended:

Class I antiarrhythmics (quinidine, hydroquinidine, cibenzoline, flecainide, disopyramide, lidocaine, mexiletine, propafenone): effect on atrio-ventricular conduction time may be potentiated and negative inotropic effect increased.

Calcium channel antagonists of verapamil/diltiazem type: 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 “rebound hypertension”.

Combinations to be used with caution:

Class III antiarrhythmic drugs (Amiodarone): effect on atrio-ventricular conduction time may be potentiated.

Anaesthetics - volatile halogenated: concomitant use of beta-adrenergic antagonists and anaesthetics may attenuate reflex tachycardia and increase the risk of hypotension. As a general rule, avoid sudden withdrawal of beta-blocker treatment. The anaesthesiologist should be informed when the patient is receiving Nebivolol.

Insulin and oral antidiabetic drugs: although nebivolol does not affect glucose level, concomitant use may mask certain 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 considered:

Digitalis glycosides: concomitant use may increase atrio-ventricular conduction time. 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): concomitant use may increase the risk of hypotension, and an increase in the risk of a further deterioration of the ventricular pump function in patients with heart failure cannot be excluded.

Antipsychotics, antidepressants (tricyclics, barbiturates and phenothiazines): concomitant use may enhance the hypotensive effect of the beta-blockers (additive effect).

Non steroidal anti-inflammatory drugs (NSAID): 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 (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 and quinidine 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.

4.6 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Nebicard:

Pregnancy

Nebivolol has pharmacological effects that may cause harmful effects on pregnancy and/or the foetus/newborn. In general, beta-adrenoceptor blockers reduce placental perfusion, 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-adrenoceptor blockers is necessary, beta1-selective adrenoceptor 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 the foetal growth should be monitored. In case of harmful effects on pregnancy or the foetus alternative treatment should be considered. The newborn infant must be closely monitored. Symptoms of hypoglycaemia and bradycardia are generally to be expected within the first 3 days.

Breast-feeding

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

4.7 Effects on ability to drive and use machines

No reported 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.

4.8 Undesirable effects

Nebivolol:

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:

SYSTEM 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.

Reporting of suspected adverse reactions

Torrent Pharma available at:
https://torrentpharma.com/index.php/site/info/adverse_event_reporting

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

4.9 Overdose

No data are available on overdosage with Nebivolol.

Symptoms

Symptoms of overdosage with beta-blockers are bradycardia, hypotension, bronchospasm and acute cardiac insufficiency.

Treatment

In case of overdosage 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.

5 Pharmacological properties

5.1 Mechanism of Action

The mechanism of action of the antihypertensive response of nebivolol has not been definitively established. Possible factors that may be involved include: (1) decreased heart rate, (2) decreased myocardial contractility, (3) diminution of tonic sympathetic outflow to the periphery from cerebral vasomotor centers, (4) suppression of renin activity and (5) vasodilation and decreased peripheral vascular resistance.

5.2 Pharmacodynamic properties

Pharmacotherapeutic group: Beta blocking agent, selective.

Nebivolol is a racemate of two enantiomers, SRRR-nebivolol (or d-nebivolol) and RSSS-nebivolol (or l-nebivolol). It combines two pharmacological activities:

It is a competitive and selective beta-receptor antagonist: this effect is attributed to the SRRR-enantiomer (d-enantiomer).

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, 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 beta1 receptor antagonists has not been fully established.

In hypertensive patients, nebivolol increases the NO-mediated vascular response to acetylcholine (ACh) which is reduced in patients with endothelial dysfunction.

In reported mortality–morbidity, placebo-controlled trial performed in 2128 patients ≥ 70 years (median age 75.2 years) with stable chronic heart failure with or without impaired left ventricular ejection fraction (mean LVEF: $36 \pm 12.3\%$, with the following distribution: LVEF less than 35% in 56% of patients, LVEF between 35% and 45% in 25% of patients and LVEF greater than 45% in 19% of patients) followed for a mean time of 20 months, nebivolol, on top of standard therapy, significantly prolonged the time to occurrence of deaths or hospitalisations for cardiovascular reasons (primary end-point for efficacy) with a relative risk reduction of 14% (absolute reduction: 4.2%). This risk reduction developed after 6 months of treatment and was maintained for all treatment duration (median duration: 18 months). The effect of nebivolol was independent from age, gender, or left ventricular ejection fraction of the population on study. The benefit on all cause mortality did not reach statistical significance in comparison to placebo (absolute reduction: 2.3%).

A decrease in sudden death was observed in nebivolol treated patients (4.1% vs 6.6%, relative reduction of 38%).

In reported vitro and in vivo experiments in animals showed that Nebivolol has no intrinsic sympathicomimetic activity.

In reported 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.

5.3 Pharmacokinetic properties

Nebivolol:

Both nebivolol enantiomers are rapidly absorbed after oral administration. The absorption of nebivolol is not affected by food; nebivolol 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 metabolisers 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 R_{SSS}-enantiomer are slightly higher than for the S_{RRR}-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 S_{RRR}-nebivolol and 97.9% for R_{SSS}-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.

6. Nonclinical properties

6.1 Animal toxicology or Pharmacology

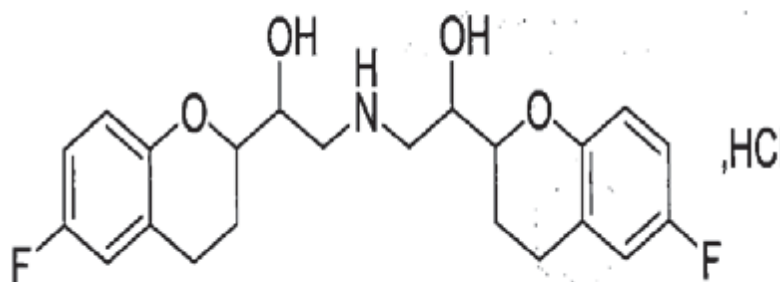
Nebivolol:

Preclinical reported data reveal no special hazard for humans based on conventional studies of genotoxicity and carcinogenic potential.

7. Description

Nebivolol:

Nebivolol Hydrochloride is (1R_S, 1'R_S)-1, 1'-[(2R_S, 2'S_R)-bis(6-fluorochroman-2-yl)]-2,2'-iminodiethanol hydrochloride having molecular formula of C₂₂H₂₅F₂NO₄.HCl and molecular weight is 441.9 the chemical structure is:



Nebivolol Hydrochloride is a white to off white Powder, Sparingly soluble in dimethyl-formamide; slightly soluble in methanol.

NEBICARD-2.5 tablets are white to off white, round, flat beveled edge uncoated tablets with torrent logo debossed on one side and plain on other side.

NEBICARD-5 tablets are white to off white, round, flat beveled edge uncoated tablets with torrent logo debossed on one side and break line on other side.

The excipients used are Lactose, starch, croscarmellose sodium, Hydroxy propyl methyl Cellulose, Polysorbate 80, Microcrystalline Cellulose, Magnesium Stearate, Colloidal Silicon Dioxide.

NEBICARD-10 tablets are light orange colored round shaped flat bevelled edge uncoated tablets with “torrent logo” on one side and break-line on other side.

The excipients used are Lactose, starch, croscarmellose sodium, Hydroxy propyl methyl Cellulose, Polysorbate 80, Microcrystalline Cellulose, Magnesium Stearate, Colloidal Silicon Dioxide, Lake of sunset yellow, Polyvinyl pyrrolidone, Iso propyl alcohol.

8. Pharmaceutical particulars

8.1 Incompatibilities

Not applicable

8.2 Shelf-life

Do not use later than date of expiry.

8.3 Packaging information

NEBICARD-2.5 is packed in blister strips of 15 tablets.

NEBICARD-5 and 10 are packed in blister strips of 10 tablets.

8.4 Storage and handing instructions

Store below 30°C. Protected from light and moisture.

9. Patient Counselling Information

NEBICARD

Nebivolol Hydrochloride Tablets I.P.

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. This includes any possible side effects not listed in this leaflet.

What is in this leaflet

9.1. What NEBICARD and what they are used for

9.2. What you need to know before you take NEBICARD

9.3 How to take NEBICARD

9.4. Possible side effects

9.5. How to store NEBICARD Tablets

9.6. Contents of the pack and other information

9.1 What is NEBICARD and what it is used for

NEBICARD contains combination of Nebivolol Hydrochloride.

The mechanism of action of the antihypertensive response of nebivolol has not been definitively established. Possible factors that may be involved include: (1) decreased heart rate, (2) decreased myocardial contractility, (3) diminution of tonic sympathetic outflow to the periphery from cerebral vasomotor centers, (4) suppression of renin activity and (5) vasodilation and decreased peripheral vascular resistance.

Nebivolol is used in the treatment of essential hypertension.

9.2 What you need to know before you take NEBICARD

Do not take NEBICARD

- if you are allergic to Nebicard 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 pheochromocytoma, 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 NEBICARD.

Nebicard:

- Abnormally slow heartbeat
- A type of chest pain due to spontaneously occurring heart cramp called Prinzmetal angina
- Untreated chronic heart failure
- If you have severe kidney disease or if you are undergoing dialysis.
- If you are suffering from a narrowing of the kidney artery.
- If you have recently undergone kidney transplantation (received a new kidney).
- If you are treated after a heart attack or for heart failure, your doctor may check your kidney function.
- If you have severe heart disease other than heart failure or heart attack.
- 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 Nebivolol before being anaesthetised.

Children and adolescents:

Because of the lack of reported data on the use of the product in children and adolescents, Nebivolol is not recommended for use in them.

Other medicines and NEBICARD

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

Nebivolol:

Pharmacodynamic interactions:

The following interactions apply to beta-adrenergic antagonists in general.

Combinations not recommended:

Class I antiarrhythmics (quinidine, hydroquinidine, cibenzoline, flecainide, disopyramide, lidocaine, mexiletine, propafenone): effect on atrio-ventricular conduction time may be potentiated and negative inotropic effect increased.

Calcium channel antagonists of verapamil/diltiazem type: 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 tone (reduction of heart rate and cardiac output, vasodilation). Abrupt withdrawal, particularly if prior to beta-blocker discontinuation, may increase risk of "rebound hypertension".

Combinations to be used with caution

Class III antiarrhythmic drugs (Amiodarone): effect on atrio-ventricular conduction time may be potentiated.

Anaesthetics - volatile halogenated: concomitant use of beta-adrenergic antagonists and anaesthetics may attenuate reflex tachycardia and increase the risk of hypotension. As a general rule, avoid sudden withdrawal of beta-blocker treatment. The anaesthesiologist should be informed when the patient is receiving Nebivolol.

Insulin and oral antidiabetic drugs: although nebivolol does not affect glucose level, concomitant use may mask certain 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 considered

Digitalis glycosides: concomitant use may increase atrio-ventricular conduction time. 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): concomitant use may increase the risk of hypotension, and an increase in the risk of a further deterioration of the ventricular pump function in patients with heart failure cannot be excluded.

Antipsychotics, antidepressants (tricyclics, barbiturates and phenothiazines): concomitant use may enhance the hypotensive effect of the beta-blockers (additive effect).

Non-steroidal anti-inflammatory drugs (NSAID): 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 (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 and quinidine 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.

Driving and using machines

No reported 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.

9.3 How to take NEBICARD

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

Nebivolol can be taken with or without food unless you take antacids. The tablet should be swallowed with a glass of water or other liquid.

If you take more NEBICARD than you should:

If you had taken too many NEBICARD tablets contact your doctor or nearest hospital for advice.

If you forget to take NEBICARD

If you forget to take a dose of NEBICARD, take the next dose at the usual time. Do not take a double dose to make up for the forgotten dose.

If you stop taking NEBICARD

Do not stop the treatment unless your doctor tells you so. Contact your doctor or pharmacist before stopping.

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

9.4 Possible side effects**Nebivolol:**

Like all medicines, this medicine can cause side effects, although not everybody gets them. When Nebivolol 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 Nebicard 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).

Side effects in children and adolescents are similar to those seen in adults.

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 any point of

contact of Torrent Pharma available at:

https://torrentpharma.com/index.php/site/info/adverse_event_reporting

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

9.5 How to store NEBICARD

Store below 30°C. Protected from light and moisture.

9.6 Contents of the pack and other information

The active substance in NEBICARD are Nebivolol Hydrochloride

NEBICARD-2.5 is packed in blister strips of 15 tablets.

NEBICARD-5 and 10 are packed in blister strips of 10 tablets.

10 Details of manufacturer

Manufactured in India by:

NEBICARD-2.5 & 5

TORRENT PHARMACEUTICALS LTD.

32 No.Middle Camp, NH-10

East District, Gangtok, Sikkim-737135.

NEBICARD-10

TORRENT PHARMACEUTICALS LTD.

32 No.Middle Camp, NH-10

East District, Gangtok, Sikkim-737135.

OR

INNOVA CAPTAB LIMITED

Kh. No. 1281/1, Hilltop, Industrial Estate,

Nr. EPIP, Phase-1, Jharmajri,

Baddi, Distt. Solan (H.P.)- 173205

11 Details of permission or licence number with date

NEBICARD-2.5 & 5

M/563/2010 issued on 05.03.2011, 31.03.2015 for NEBICARD-2.5, NEBICARD-5 respectively.

NEBICARD-10

M/563/2010 issued on 05.04.2017

OR

MNB/16/970 issued on 01.10.2020

12. Date of revision

DEC 2021

MARKETED BY



TORRENT PHARMACEUTICALS LTD.

Torrent House, Off Ashram Road,

Ahmedabad-380 009, INDIA

IN/ NEBICARD 2.5, 5, 10 mg /JAN 2022/02/PI