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

NEBICARD LN

1. **Generic Name:**
   Nebivolol Hydrochloride & Cilnidipine Tablets
2. **Qualitative and quantitative composition:**

NEBICARD LN 2.5

Each film-coated bilayered tablet contains:

Nebivolol Hydrochloride I.P.

Equivalent to Nebivolol..……..…2.5 mg

Cilnidipine I.P. ……...10 mg

Colours: Sunset Yellow and Titanium Dioxide I.P.

The excipients used are Colour sunset yellow lake, Lactose, Maize starch, HPMC, Purified water, Tween-80, Colloidal Silicon Dioxide, Magnesium Stearate, Microcrystalline Cellulose, N. Methyl D. Glucemine, Isopropyl Alcohol, Polyvinyl pyrrolidone, Sodium lauryl sulphate, Croscarmellose sodium, Dichloromethane, Hypromellose, Diethyl phthalate and Ethyl cellulose.

NEBICARD LN 5

Each film-coated bilayered tablet contains:

Nebivolol Hydrochloride I.P.

Equivalent to Nebivolol..……..…5 mg

Cilnidipine I.P. ……...10 mg

Colours: Brilliant Blue and Titanium Dioxide I.P.

The excipients used are Lactose, Maize starch, HPMC, Tween-80, Colloidal Silicon Dioxide, Magnesium Stearate, Microcrystalline Cellulose, N. Methyl D. Glucemine, Isopropyl Alcohol, Polyvinyl pyrrolidone, Sodium lauryl sulphate, Croscarmellose sodium, Colour Brilliant Blue Lake, Dichloromethane, Hypromellose, Diethyl phthalate, Ethyl cellulose, Talc and Titanium dioxide.

3. **Dosage form and strength:**

Dosage form: Film coated bilayered tablet

Strength: Nebivolol 2.5/5 mg and Cilnidipine 10 mg

4. **Clinical particulars:**

4.1 Therapeutic indication:

Treatment of essential hypertension

4.2 Posology and method of administration:

<u>Posology</u>

<u>Hypertension</u> *Adults*

The recommended dose is one tablet per day, 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.

Patients with renal insufficiency

In patients with renal insufficiency, the recommended starting dose 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 tablets 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 population

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

Method of administration Oral use.

The tablet should be swallowed with a sufficient amount of fluid (e.g one glass of water). The tablet can be taken with or without food.

4.3 Contraindications:

- Contraindicated in patients with known hypersensitivity (e.g., anaphylaxis or angioedema) to the active substance or to any of the excipients.
- 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 < 60 bpm prior to start therapy).
    - hypotension (systolic blood pressure < 90 mmHg).
    - severe peripheral circulatory disturbances.

4.4 Special warnings and precautions for use:

<u>Nebivolol Hydrochloride</u>

The following warnings and precautions apply to beta-adrenergic antagonists, such as nebivolol, in general.

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 coronary 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:

- in patients with peripheral circulatory disorders (Raynaud's disease or syndrome, intermittent claudication), as aggravation of these disorders may occur;
- in patients with first degree heart block, because of the negative effect of beta-blockers on conduction time;
- in patients with Prinzmetal's angina due to unopposed alpha receptor mediated coronary artery vasoconstriction: beta-adrenergic antagonists may increase the number and duration of anginal attacks.

Combination of nebivolol with calcium channel antagonists of the verapamil and diltiazem type, with Class I antiarrhythmic drugs, and with centrally acting antihypertensive drugs is generally not recommended.

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

Patients with a history of psoriasis should take beta-adrenergic antagonists only after careful consideration.

Beta-adrenergic antagonists may increase the sensitivity to allergens and the severity of anaphylactic reactions.

The initiation of Chronic Heart Failure treatment with nebivolol necessitates regular monitoring. For the posology and method of administration. Treatment discontinuation should not be done abruptly unless clearly indicated.

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Cilnidipine

Cilnidipine should be used with caution in patients with Hypotension, poor cardiac reserve and heart failure. Sudden withdrawal of the drug to be avoided as may exacerbate angina.
Discontinue in patients who experience ischemic pain following administration.

4.5 Drug-Interaction:

Nebivolol Hydrochloride

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 ß-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 Tablets.

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 antihypertensive medication should be adjusted accordingly.

Mefloquine (antimalarian drug): Theoretically co-administration with β-adrenergic blocking agents might contribute to a prolongation of the QTc interval.

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. *Sympathicomimetic agents:* concomitant use may counteract the effect of betaadrenergic antagonists. Beta-adrenergic agents may lead to unopposed alpha-adrenergic activity of sympathicomimetic 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 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.

Cilnidipine
Cilnidipine can interact with aldesleukin, quinidine, phenytoin, rifampicin, erythromycin, other anti-hypertensive drugs and anti-psychotic drugs.

4.6 Use in special populations

Nebivolol Hydrochloride

Pregnancy

Nebivolol has pharmacological effects that may cause harmful effects on pregnancy and/or the fetus/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 fetus and newborn infant. If treatment with beta-adrenoceptor blockers is necessary, beta 1 -selective adrenoceptor blockers are preferable.

Nebivolol tablets should not be used during pregnancy unless clearly necessary. If treatment with nebivolol is considered necessary, the uteroplacental blood flow and the fetal growth should be monitored. In case of harmful effects on pregnancy or the fetus 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
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.

Fertility
There is limited human data on the effect of nebivolol on fertility. No preclinical data are available.

Cilnidipine

Pregnancy
There are no human clinical or animal data concerning the safety of cilnidipine during pregnancy. Until data are available, administration of cilnidipine during pregnancy should be avoided.

Lactation
Nursing mothers should consult a physician before taking Cilnidipine.

Renal impairment
Dose adjustment is not needed in patients with impaired renal function. Cilnidipine at a dose of 10 mg once a day for 7 days in patients with impaired renal function caused no differences in the pharmacokinetic profile compared with that in patients with normal renal function.

Hepatic impairment
Dosage recommendations have not been established in patients with mild to moderate hepatic impairment; therefore dose selection should be cautious and should start at the lower end of the dosing range. Transient and generally clinically insignificant elevations in SGOT, SGPT, alkaline phosphatase, and serum bilirubin have been reported during calcium antagonist therapy in less than 1% of patients.

4.7 Effects on ability to drive and use machines:

No studies on the effects on the ability to drive and use machine have been performed. Pharmacodynamic studies have shown that nebivolol hydrochloride and Cilnidipine tablets does not affect psychomotor function. Some patients may experience adverse effects which are mostly due to the reduction in blood pressure, such as dizziness or fainting. Should these occur, one should refrain from driving and other activities requiring alertness. These effects are more likely to occur after initiation of the treatment or after dose increases.

4.8 Undesirable effects:

Nebivolol Hydrochloride

The following terminologies have been used in order to classify the occurrence of undesirable effects:

<Very common (≥1/10)>

<Common (≥1/100 to <1/10)>

<Uncommon (≥1/1,000 to <1/100)>

<Rare (≥1/10,000 to <1/1,000)>

<Very rare (≤1/10,000)>

<Not known (cannot be estimated from the available data)>

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 cases of mild to moderate intensity, are tabulated below, classified by system organ class and ordered by frequency:

SYSTEM ORGAN CLASS	Common	Uncommon	Very rare	Not known
Immune system disorders				Angioneurotic oedema and hypersensitivity
Psychiatric disorders		nightmares, depression		
Nervous system disorders	headache, dizziness, paraesthesia		syncope	
Eye disorders		impaired vision		
Cardiac disorders		bradycardia, heart failure, slowed AV conduction/ AVblock		
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.

Beta-blockers may cause decreased lacrimation.

Chronic heart failure

Reported 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 reported 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 approximately 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 compared to 5.2% of placebo patients.
- Postural hypotension was reported in 2.1 % of nebivolol patients compared to 1.0% of placebo patients.
- Drug intolerance occurred in 1.6% of nebivolol patients compared to 0.8% of 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 was reported by 1.0% of nebivolol patients compared to 0.2% of placebo patients.

Cilnidipine

- Dizziness
- Flushing
- Headache
- Hypotension
- peripheral oedema
- Tachycardia
- Palpitations
- GI disturbances
- Increased micturition frequency
- Lethargy

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 any point of contact of Torrent Pharma available at:

http://www.torrentpharma.com/Index.php/site/info/adverse_event_reporting.

4.9 Overdose:

No data are available on overdose with Nebivolol Hydrochloride & Cilnidipine Tablets.

5. Pharmacological properties:

5.1 Mechanism of Action:

Nebivolol Hydrochloride

Pharmacotherapeutic group: Beta blocking agents, selective.
Nebivolol is a racemate of two enantiomers, SRRR-nebivolol (or d-nebivolol) and RSSSnebivolol (or l-nebivolol). It combines two pharmacological activities:

- It is a competitive and selective beta-receptor antagonist: this effect is attributed to the SRRRenatiomer (d-enantiomer).
- It has mild vasodilating properties due to an interaction with the L-arginine/nitric oxide pathway.

Cilnidipine

Cilnidipine acts on the L-type calcium channels of blood vessels by blocking the incoming calcium and suppressing the contraction of blood vessels, thereby reducing blood pressure. Cilnidipine also works on the N-type calcium channel located at the end of the sympathetic nerve, inhibiting the emission of norepinephrine and suppressing the increase in stress blood pressure.

5.2 Pharmacodynamic properties:

Nebivolol Hydrochloride

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 a 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 ± 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 reported 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 vitro and in vivo experiments in animals showed that Nebivolol has no intrinsic sympathicomimetic 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.

Cilnidipine

Cilnidipine is a third generation dihydropyridine calcium antagonist with a slow onset and long duration of action. Calcium antagonists inhibit influx of extracellular calcium ions into the cells, resulting in decreased vascular smooth muscle tone and vasodilation, leading to a reduction in blood pressure.

In vitro and animal studies suggest that cilnidipine blocks both the L and N type calcium channels. Cilnidipine inhibits the pressor to cold stress by suppressing sympathetic nerve activity in spontaneously hypertensive rats. It does not induce tachycardia caused by hypotensive baroreflexes. In vitro, cilnidipine inhibits norepinephrine release in electrically stimulated rabbit mesenteric arteries.

In human studies, cilnidipine had weak inotropic effects and suppressed cardiac sympathetic overactivity. Therefore it may decrease the risk and mortality from long term cardiovascular complications. Once-daily cilnidipine was associated with less reflex tachycardia and had fewer effect on the autonomic nervous system in hypertensive patients. In contrast to other long acting calcium channel blockers, cilnidipine and amlodipine did not increase plasma renin activity, thus they may decrease the risk of cardiovascular complications due to metabolic imbalances. Cilnidipine may inhibit norepinephrine and dopamine production, therby improving insulin resistance in patients with diabetes. It also had beneficial effects on lipid profiles in hypertensive patients by decreasing total cholesterol, triglyceride, and very low density lipoprotein cholesterol level, and increasing high density lipoprotein cholesterol and the ratio of high density lipoprotein cholesterol to total cholesterol.

5.3 Pharmacokinetic properties:

Nebivolol Hydrochloride

Absorption

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.

Distribution

In plasma, both nebivolol enantiomers are predominantly bound to albumin. Plasma protein binding is 98.1% for SRRR-nebivolol and 97.9% for RS S S-nebivolol.

Metabolism

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 2.5 mg, Nebivolol 5 mg or Nebivolol 10 mg tablets 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 RSSSenantiomer 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 is not affected by age.

Excretion
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.

Cilnidipine
Cilnidipine has a slow onset and long duration of action of 24 hours, partly explained by its high lipophilicity. Cilnidipine has a half-life of 2-8 hrs after administration of 5-20 mg.

6. Nonclinical properties:

Nebivolol Hydrochloride

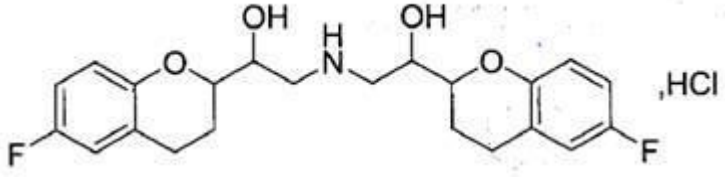
Preclinical data reveal no special hazard for humans based on conventional studies of genotoxicity and carcinogenic potential.

Cilnidipine

No data available.

7. Description:

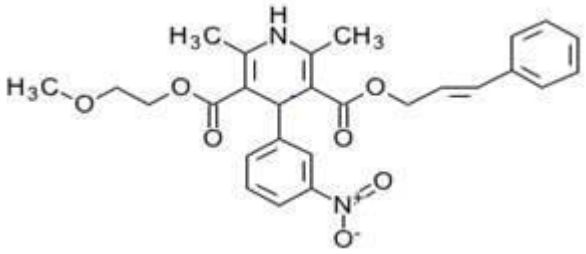
Nebivolol Hydrochloride
Nebivolol Hydrochloride is a beta 1 receptor blocker that works specifically on the heart to slow down the heart rate. Nebivolol Hydrochloride is chemically (1RS, 1 'RS)-1, 1 '-[(2RS,2'SR)-bis (6-flurochroman-2-yl)]-2,2'-iminodiethanol hydrochloride. Its empirical formula is $C_{22}H_{25}F_2NO_4$,HCl and its structural formula is:



Nebivolol Hydrochloride is a white to off-white powder with a molecular weight of 441.9. It is sparingly soluble in dimethyl form amide and slightly soluble in methanol.

Cilnidipine

Cilnidipine is a calcium channel blocker which works by relaxing blood vessels. Cilnidipine is chemically 1, 4-Dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylic acid 2methoxyethyl (2E)-3-phenyl-2-propenyl ester. Its empirical formula is $C_{27}H_{28}N_2O_7$.HCl and its structural formula is:



Cilnidipine is light yellow, crystalline powder with a molecular weight of 492.5. It is very soluble in N, N-Dimethyl acetamide, freely soluble in acetone, sparingly soluble in methanol and practically insoluble in water.

Product Description:

NEBICARD LN 2.5

Nebivolol Hydrochloride & Cilnidipine Tablets are light orange coloured, round, biconvex, film coated tablets, plain on both sides.

The excipients used are colour sunset yellow lake, Lactose, Maize starch, HPMC, Purified water, Tween-80, Colloidal Silicon Dioxide, Magnesium Stearate, Microcrystalline Cellulose, N. Methyl D. Glucemine, Isopropyl Alcohol, Polyvinyl pyrrolidone, Sodium lauryl sulphate, Croscarmellose sodium, Dichloromethane, Hypromellose, Diethyl phthalate and Ethyl cellulose.

NEBICARD LN 5

Nebivolol Hydrochloride & Cilnidipine Tablets are light blue coloured, round, biconvex, film coated tablets, plain on both sides.

The excipients used are Lactose, Maize starch, HPMC, Tween-80, Colloidal Silicon Dioxide, Magnesium Stearate, Microcrystalline Cellulose, N. Methyl D. Glucemine, Isopropyl Alcohol, Polyvinyl pyrrolidone, Sodium lauryl sulphate, Croscarmellose sodium, Colour Brilliant Blue Lake, Dichloromethane, Hypromellose, Diethyl phthalate, Ethyl cellulose, Talc and Titanium dioxide.

8. Pharmaceutical particulars:

8.1 Incompatibilities:

None stated.

8.2 Shelf-life:

Do not use later than the date of expiry.

8.3 Packaging information:

NEBICARD LN is available in blister strip of 10 tablets.

8.4 Storage and handing instructions:

Store protect from light & moisture at a temperature not exceeding 30ºC.

9. Patient Counselling Information Package leaflet: Information for the user

NEBICARD LN

Nebivolol Hydrochloride and Cilnidipine tablets

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you 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 LN is and what it is used for

NEBICARD LN contains Nebivolol Hydrochloride and Cilnidipine. Nebivolol Hydrochloride 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, controls heart pumping strength. It also exerts a dilating action on blood vessels, which contributes as well to lower blood pressure. Cilnidipine calcium channel blocker acting by blocking both L- and N-type calcium channels. NEBICARD LN is also used for treatment of essential hypertension.

9.2. What you need to know before you take NEBICARD LN

Do not take NEBICARD LN

If you are allergic to NEBICARD LN 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
- metabolic disorder (metabolic acidosis), for example, diabetic ketoacidosis.

Warnings and precautions

Talk to your doctor or pharmacist before taking NEBICARD LN. 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 NEBICARD LN before being anaesthetized.
- Hypotension
- Liver dysfunction, or elevated liver enzymes
- Peripheral edema (confounding physical findings in congestive failure)

If you have serious kidney problems, do not take NEBICARD LN 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, NEBICARD LN is not recommended for use in them.

Other medicines and NEBICARD LN

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Certain medicines cannot be used at the same time, while other drugs require specific changes (in the dose, for example).

Always tell your doctor if you are using or receiving any of the following medicines in addition to NEBICARD LN:

- 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 anesthesia 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 NEBICARD LN may influence the blood pressure and/or heart function.
- Medicines for treating excessive stomach acid or ulcers (antacid drug): you should take NEBICARD LN during a meal and the antacid drug between meals.
- Anti malarials (mefloquine).
- Cilnidipine can interact with aldesleukin, quinidine, phenytoin, rifampicin, erythromycin, other anti-hypertensive drugs and anti-psychotic drugs.

NEBICARD LN with food and drink

NEBICARD LN can be taken with food or on an empty stomach, but the tablet is best taken with some water.

Pregnancy, breast-feeding and fertility

NEBICARD LN 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.

Renal impairment

Dose adjustment is not needed in patients with impaired renal function. Cilnidipine at a dose of 10 mg once a day for 7 days in patients with impaired renal function caused no differences in the pharmacokinetic profile compared with that in patients with normal renal function.

Hepatic impairment

Dosage recommendations have not been established in patients with mild to moderate hepatic impairment; therefore dose selection should be cautious and should start at the lower end of the dosing range. Transient and generally clinically insignificant elevations in SGOT, SGPT, alkaline phosphatase, and serum bilirubin have been reported during calcium antagonist therapy in less than 1% of patients.

Driving and using machines

This medicine may cause dizziness or fatigue. If affected, do not drive or operate machinery.

Nebivolol contains lactose

If your doctor has told you that you have intolerance to some sugars, contact your doctor before taking this medicine.

Nebivolol contains sodium

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

9.3. How to take NEBICARD LN

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

NEBICARD LN 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.
- Elderly patients and patients with a kidney disorder will usually start with 2.5 mg daily.
- It may take up to 4 weeks for this medicine to have full effect.
- If you are aged over 75 years, your doctor may need to monitor you more closely.
- The therapeutic effect on blood pressure becomes evident after 1-2 weeks of treatment. Occasionally, the optimal effect is reached only after 4 weeks.
- Maintaining dose- physician will titrate the dose as per patient's symptoms.

Use in children and adolescents

NEBICARD LN is not recommended in children and adolescents.

If you take more NEBICARD LN than you should

If you take more NEBICARD LN than prescribed by your doctor, talk to your doctor or pharmacist straight away. The most frequent symptoms and signs of a NEBICARD LN 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 NEBICARD LN

If you forget to take your medicine, 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 dose the next, scheduled, normal dose at the usual time. Do not take a double dose to make up for a forgotten dose. Repeated skipping, however, should be avoided.

9.4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. When NEBICARD LN tablets are used for the treatment of raised blood pressure, the possible side effects are:

Common side effects (affects 1 to 10 users in 100):

- Headache
- Dizziness
- Tiredness
- An unusual itching or tingling feeling

- Diarrhoea
- Constipation
- Nausea
- Shortness of breath
- Swollen hands or feet
- Flushing
- Hypotension
- peripheral oedema
- Tachycardia
- Palpitations
- GI disturbances
- Increased micturition frequency
- Lethargy

The following side effects have been reported only in some isolated cases during NEBICARD LN treatment (contact a doctor immediately)
- Whole body allergic reaction, with generalised skin eruption (hypersensitivity reactions)

Uncommon side effects (affects 1 to 10 users in 1000):
- Slow heartbeat or other heart complaints
- Low blood pressure
- Cramp-like leg pains on walking
- Abnormal vision
- Impotence
- Feeling 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 (affects less than 1 user in 10,000):
- Fainting
- Worsening of psoriasis (a skin disease - scaly pink patches).

The following side effects have been reported only in some isolated cases during Nebivolol 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 reported clinical study for chronic heart failure, the following side effects were seen:

Very common side effects (affects more than 1 user in 10):
- Slow heart beat
- Dizziness

Common side effects (affects 1 to 10 users in 100)

- Worsening of heart failure
- Low blood pressure (such as feeling faint when getting up too quickly)
- Inability to tolerate this medicine
- 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. You can also report side effects directly via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/Index.php/site/info/adverse_event_reporting.

9.5. How to store NEBICARD LN

- Keep this medicine out of the sight and reach of children.
- Store protect from light & moisture at a temperature not exceeding 30ºC.
- Do not use this medicine after the expiry date, which is stated on the carton and bottle after expiry. The expiry date refers to the last day of that month.
- Store this medicine in the original package (blister) or keep the bottle tightly closed in order to protect from moisture.
- Do not throw away any medicines 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.

9.6. Contents of the pack and other information

What NEBICARD LN contains

The active substance is Nebivolol Hydrochloride and Cilnidipine, film-coated bilayered tablet, comes in two strengths containing Nebivolol Hydrochloride 2.5 mg or 5 mg and Cilnidipine 10 mg.

NEBICARD LN 2.5

The other ingredients are Lactose, Maize starch, HPMC, Purified water, Tween-80, Colloidal Silicon Dioxide, Magnesium Stearate, Microcrystalline Cellulose, N. Methyl D. Glucemine, Isopropyl Alcohol, Polyvinyl pyrrolidone, Sodium lauryl sulphate, Croscarmellose sodium, Dichloromethane, Hypromellose, Diethyl phthalate and Ethyl cellulose.

Colours: Sunset Yellow and Titanium Dioxide I.P.

NEBICARD LN 5

The other ingredients are Lactose, Maize starch, HPMC, Tween-80, Colloidal Silicon Dioxide, Magnesium Stearate, Microcrystalline Cellulose, N. Methyl D. Glucemine, Isopropyl Alcohol, Polyvinyl pyrrolidone, Sodium lauryl sulphate, Croscarmellose sodium, Colour Brilliant Blue Lake, Dichloromethane, Hypromellose, Diethyl phthalate, Ethyl cellulose, Talc and Titanium dioxide.

Colours: Brilliant Blue and Titanium Dioxide I.P.

NEBICARD LN is packed in blister strip of 10 tablets.

10. Details of manufacturer

Manufactured in India by:
Windlas Biotech Limited (Plant-2)

Khasra No.: 141 to 143 & 145,
Mohabewala Industrial Area,
Dehradun-248110, Uttarakhand.

11. Details of permission or licence number with date

Mfg. Lic. No. 34/UA/2013 issued on 05.10.2021.

12. Date of revision

FEB-2022

MARKETED BY

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TORRENT PHARMACEUTICALS LTD.

IN/NEBICARD LN 2.5, 5, 10 mg/Feb-22/02/PI