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

# NEBICARD-H

## 1. Generic Name

Nebivolol Hydrochloride and Hydrochlorothiazide Tablets

## 2. Qualitative and quantitative composition

Each uncoated tablet contains:

Nebivolol hydrochloride I.P.

Equivalent to Nebivolol ..……5 mg

Hydrochlorothiazide I.P. ……..12.5 mg

Colour: Yellow Oxide of Iron

The excipients used are Lactose, starch, croscarmellose sodium, Yellow oxide of Iron, Hydroxy propyl methyl Cellulose, Polysorbate 80, Croscarmellose Sodium, Microcrystalline Cellulose, Magnesium Stearate, Colloidal Silicon Dioxide.

## 3. Dosage form and strength

**Dosage form**: Uncoated tablet
**Strength:** Nebivolol 5 mg, Hydrochlorothiazide 12.5 mg

## 4. Clinical particulars

### 4.1 Therapeutic indication

It is indicated for the treatment of Essential Hypertension.

### 4.2 Posology and method of administration

**Dose**: As directed by the Physician.

### 4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients or to sulfonamide derived drugs
- Liver insufficiency or liver function impairment.
- Acute heart failure, cardiogenic shock or episodes of heart failure decompensation requiring i.v. inotropic therapy.
- 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.
- Anuria

## 4.4 Special warnings and precautions for use

### Nebivolol Hydrochloride

The following warnings and precautions apply to beta-adrenergic antagonists 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 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:

- 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-receptors mediated coronary artery vasoconstriction: beta-adrenergic antagonists may increase the number and duration of angina 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 Hydrochloride 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 tachycardia 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 glucosegalactose malabsorption should not take this medicinal product.

**Hydrochlorothiazide**

*Acute Myopia and Secondary Angle-Closure Glaucoma*

Hydrochlorothiazide, a sulfonamide, can cause an idiosyncratic reaction, resulting in acute transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue hydrochlorothiazide as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy.

*Diabetes and Hypoglycemia*

Latent diabetes mellitus may become manifest and diabetic patients given thiazides may require adjustment of their insulin dose.

*Renal Disease*

Cumulative effects of the thiazides may develop in patients with impaired renal function. In such patients, thiazides may precipitate azotemia.

*Electrolyte and Fluid Balance Status*

In published studies, clinically significant hypokalemia has been consistently less common in patients who received 12.5 mg of hydrochlorothiazide than in patients who received higher doses. Nevertheless, periodic determination of serum electrolytes should be performed in patients who may be at risk for the development of hypokalemia. Patients should be observed for signs of fluid or electrolyte disturbances, i.e., hyponatremia, hypochloremic alkalosis, and hypokalemia and hypomagnesemia.

Warning signs or symptoms of fluid and electrolyte imbalance include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Hypokalemia may develop, especially with brisk diuresis when severe cirrhosis is present, during concomitant use of corticosteroid or adrenocorticotropic hormone (ACTH) or after prolonged therapy. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia and hypomagnesemia can provoke ventricular arrhythmias or sensitize or exaggerate the response of the heart to the toxic effects of digitalis. Hypokalemia may be avoided or treated by potassium supplementation or increased intake of potassium rich foods.

Dilutional hyponatremia is life-threatening and may occur in edematous patients in hot weather; appropriate therapy is water restriction rather than salt administration, except in rare

instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

*Hyperuricemia*

Hyperuricemia or acute gout may be precipitated in certain patients receiving thiazide diuretics.

*Impaired Hepatic Function*

Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate hepatic coma in patients with severe liver disease.

*Parathyroid Disease*

Calcium excretion is decreased by thiazides, and pathologic changes in the parathyroid glands, with hypercalcemia and hypophosphatemia, have been observed in a few patients on prolonged thiazide therapy.

*Non-melanoma skin cancer:*

An increased risk of non-melanoma skin cancer (NMSC) [basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)] with increasing cumulative dose of hydrochlorothiazide (HCTZ) exposure has been observed in two epidemiological studies based on the Danish National Cancer Registry. Photosensitizing actions of HCTZ could act as a possible mechanism for NMSC.

Patients taking HCTZ should be informed of the risk of NMSC and advised to regularly check their skin for any new lesions and promptly report any suspicious skin lesions. Possible preventive measures such as limited exposure to sunlight and UV rays and, in case of exposure, adequate protection should be advised to the patients in order to minimize the risk of skin cancer. Suspicious skin lesions should be promptly examined potentially including histological examinations of biopsies. The use of HCTZ may also need to be reconsidered in patients who have experienced previous NMSC.

*Choroidal effusion:*

Choroidal effusion, acute myopia and secondary angle-closure glaucoma: Sulfonamide or sulfonamide derivative drugs can cause idiosyncratic reaction resulting in choroidal effusion with visual field defect, transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue drug intake as rapidly as possible. Prompt medical or surgical tratments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy.

## 4.5 Drugs interactions

**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 antihypertensive (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 Hydrochloride. 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 antihypertensive 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: concomitant use may increase atrio-ventricular conduction time. Reported 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).

<u>Pharmacokinetic interactions</u>

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 Hydrochloride 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.

**Hydrochlorothiazide**

When given concurrently the following drugs may interact with thiazide diuretics:

Alcohol, barbiturates, or narcotics: potentiation of orthostatic hypotension may occur.

Antidiabetic drugs (oral agents and insulin): dosage adjustment of the antidiabetic drug may be required.

Other antihypertensive drugs: additive effect or potentiation.

Cholestyramine and colestipol resins: Cholestyramine and colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85 and 43 percent, respectively.

Corticosteroid, ACTH: intensified electrolyte depletion, particularly hypokalemia.

Pressor amines (e.g., norepinephrine): possible decreased response to pressor amines but not sufficient to preclude their use.

Skeletal muscle relaxants, nondepolarizing (e.g., tubocurarine): possible increased responsiveness to the muscle relaxant.

Lithium: generally should not be given with diuretics. Diuretic agents reduce the renal clearance of lithium and greatly increase the risk of lithium toxicity. Refer to the package insert for lithium preparations before use of such preparations with MICROZIDE.

Non-steroidal anti-inflammatory drugs: In some patients, the administration of a non-steroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics. When MICROZIDE and non-steroidal antiinflammatory agents are used concomitantly, the patients should be observed closely to determine if the desired effect of the diuretic is obtained.

Drug/Laboratory Test Interactions: Thiazides should be discontinued before carrying out tests for parathyroid function.

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

**Nebivolol Hydrochloride**

*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 newborn 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*

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.

**Hydrochlorothiazide**

*Pregnancy*

Teratogenic Effects - Pregnancy Category B: Studies in which hydrochlorothiazide was orally administered to pregnant mice and rats during their respective periods of major organogenesis at doses up to 3000 and 1000 mg hydrochlorothiazide/kg, respectively, provided no evidence of harm to the fetus.

Thiazides cross the placental barrier and appear in cord blood. There is a risk of fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions that have occurred in adults.

*Breast-feeding*

Thiazides are excreted in breast milk. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue hydrochlorothiazide, taking into account the importance of the drug to the mother.

*Elderly Use*: A greater blood pressure reduction and an increase in side effects may be observed in the elderly (i.e., > 65 years) with hydrochlorothiazide. Starting treatment with the lowest available dose of hydrochlorothiazide (12.5 mg) is therefore recommended. If further titration is required, 12.5 mg increments should be utilized.

## 4.7 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 Nebicard H 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 | | Acute myopia, acute angleclosure glaucoma, choroidal effusion |
| Cardiac disorders | | bradycardia, failure, slowed AV conduction AV-block | | Hypotension including orthostatic hypotension (may be aggravated by alcohol, barbiturates, narcotics or Antihypertensive drugs). |
| Vascular disorde | | hypotension, (increase of) intermittent claudication | | |
| Respiratory, thoracic and mediastinal disorders | dyspnoea | bronchospasm | | |

| | | | | |
|---|---|---|---|---|
| Gastrointestinal disorders | constipation, diarrhoea | dyspepsia, flatulence, vomiting | | Pancreatitis, jaundice (intrahepatic) |
| Skin and subcutaneous disorders | | pruritus, rash erythematous | psoriasis aggravated | urticaria |
| Reproductive system and breast disorders | | impotence | | |
| General disorders and administration conditions | tiredness, oedema | | | |
| Hematologic | | | | Aplastic anemia,agranulocytosis, leukopenia, hemolytic anemia, thrombocytopenia. |

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 a reported 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 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 were reported by 1.0% of nebivolol patients compared to 0.2% of placebo patients.

**Hydrochlorothiazide**

The following adverse reactions have been reported for hydrochlorothiazide:

*Body as a whole*: Weakness.

*Cardiovascular*: Hypotension including orthostatic hypotension (may be aggravated by alcohol, barbiturates, narcotics or antihypertensive drugs).

*Digestive*: Pancreatitis, jaundice (intrahepatic cholestatic jaundice), diarrhea, vomiting, sialadenitis, cramping, constipation, gastric irritation, nausea, anorexia.

*Hematologic*: Aplastic anemia, agranulocytosis, leukopenia, hemolytic anemia, thrombocytopenia.

*Hypersensitivity*: Anaphylactic reactions, necrotizing angiitis (vasculitis and cutaneous vasculitis), respiratory distress including pneumonitis and pulmonary edema, photosensitivity, fever, urticaria, rash, purpura.

*Metabolic*: Electrolyte imbalance, hyperglycemia, glycosuria, hyperuricemia.

*Musculoskeletal*: Muscle spasm.

*Nervous System/Psychiatric*: Vertigo, paresthesia, dizziness, headache, restlessness.

*Renal*: Renal failure, renal dysfunction, interstitial nephritis.

*Skin*: Erythema multiforme including Stevens-Johnson syndrome, exfoliative dermatitis including toxic epidermal necrolysis, alopecia.

*Special Senses*: Transient blurred vision, xanthopsia.

*Urogenital*: Impotence.

*Neoplasms benign, malignant and unspecified (incl cysts and polyps):* Non-melanoma skin cancer (Basal cell carcinoma and Squamous cell carcinoma).

Whenever adverse reactions are moderate or severe, thiazide dosage should be reduced or therapy withdrawn.

**Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorisation of the medicinal product important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via any point of contact of Torrent Pharma available at:

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

## 4.9 Overdose

**Nebivolol Hydrochloride Tablets**

*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.

**Hydrochlorothiazide**

*Symptoms*

The most common signs and symptoms observed are those caused by electrolyte depletion (hypokalemia, hypochloremia, hyponatremia) and dehydration resulting from excessive diuresis. If digitalis has also been administered, hypokalemia may accentuate cardiac arrhythmias.

*Treatment*

In the event of overdosage, symptomatic and supportive measures should be employed. Emesis should be induced or gastric lavage performed. Correct dehydration, electrolyte imbalance, hepatic coma and hypotension by established procedures. If required, give oxygen or artificial respiration for respiratory impairment. The degree to which hydrochlorothiazide is removed by hemodialysis has not been established.

The oral LD50 of hydrochlorothiazide is greater than 10 g/kg in the mouse and rat.

## 5. Pharmacological properties

### 5.1 Mechanism of Action

**Nebivolol**

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.

**Hydrochlorothiazide**

Hydrochlorothiazide blocks the reabsorption of sodium and chloride ions, and it thereby increases the quantity of sodium traversing the distal tubule and the volume of water excreted. A portion of the additional sodium presented to the distal tubule is exchanged there for potassium and hydrogen ions. With continued use of hydrochlorothiazide and depletion of sodium, compensatory mechanisms tend to increase this exchange and may produce excessive loss of potassium, hydrogen and chloride ions. Hydrochlorothiazide also decreases the excretion of calcium and uric acid, may increase the excretion of iodide and may reduce glomerular filtration rate. Metabolic toxicities associated with excessive electrolyte changes caused by hydrochlorothiazide have been shown to be dose-related.

### 5.2 Pharmacodynamics properties

**Nebivolol**

Pharmacotherapeutic group: Beta blocking agent, selective.

ATC code: C07AB12

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.
- 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 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 ± 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 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.

Available preclinical and clinical evidence in hypertensive patients has not shown that nebivolol has a detrimental effect on erectile function.

**Hydrochlorothiazide**

Pharmacotherapeutic group: Diuretics.

ATC code: C03AA03

Acute antihypertensive effects of thiazides are thought to result from a reduction in blood volume and cardiac output, secondary to a natriuretic effect, although a direct vasodilatory mechanism has also been proposed. With chronic administration, plasma volume returns toward normal, but peripheral vascular resistance is decreased. The exact mechanism of the antihypertensive effect of hydrochlorothiazide is not known.

Thiazides do not affect normal blood pressure. Onset of action occurs within 2 hours of dosing, peak effect is observed at about 4 hours, and activity persists for up to 24 hours.

*Non-melanoma skin cancer:*

Based on reported available data from epidemiological studies, cumulative dose-dependent association between HCTZ and NMSC has been observed. One study included a population comprised of 71,533 cases of BCC and of 8,629 cases of SCC matched to 1,430,833 and 172,462 population controls, respectively. High HCTZ use (≥50,000 mg cumulative) was associated with an adjusted OR of 1.29 (95% CI: 1.23-1.35) for BCC and 3.98 (95% CI: 3.68-4.31) for SCC. A clear cumulative dose response relationship was observed for both BCC and SCC. Another study showed a possible association between lip cancer (SCC) and exposure to HCTZ: 633 cases of lip-cancer were matched with 63,067 population controls, using a risk-set sampling strategy. A cumulative dose-response relationship was demonstrated with an adjusted OR 2.1 (95% CI: 1.7-2.6) increasing to OR 3.9 (3.0-4.9) for high use (~25,000 mg) and OR 7.7 (5.7-10.5) for the highest cumulative dose (~100,000 mg).

## 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 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.

**Hydrochlorothiazide**

Hydrochlorothiazide is well absorbed (65% to 75%) following oral administration. Absorption of hydrochlorothiazide is reduced in patients with congestive heart failure.

Peak plasma concentrations are observed within 1 to 5 hours of dosing, and range from 70 to 490 ng/mL following oral doses of 12.5 to 100 mg. Plasma concentrations are linearly related to the administered dose. Concentrations of hydrochlorothiazide are 1.6 to 1.8 times higher in whole blood than in plasma. Binding to serum proteins has been reported to be approximately 40% to 68%. The plasma elimination half-life has been reported to be 6 to 15 hours. Hydrochlorothiazide is eliminated primarily by renal pathways. Following oral doses of 12.5 to 100 mg, 55% to 77% of the administered dose appears in urine and greater than 95% of the absorbed dose is excreted in urine as unchanged drug. In patients with renal disease, plasma concentrations of hydrochlorothiazide are increased and the elimination half-life is prolonged. When MICROZIDE is administered with food, its bioavailability is reduced by 10%, the maximum plasma concentration is reduced by 20%, and the time to maximum concentration increases from 1.6 to 2.9 hours.

## 6. Nonclinical properties

### 6.1 Animal Toxicology or Pharmacology

**Nebivolol**

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

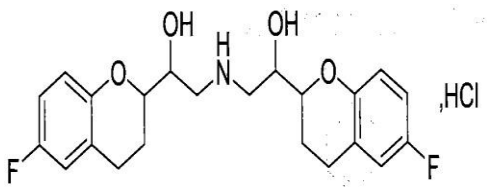
**Hydrochlorothiazide**

Two-year feeding studies in mice and rats conducted under the auspices of the National Toxicology Program (NTP) uncovered no evidence of a carcinogenic potential of hydrochlorothiazide in female mice (at doses of up to approximately 600 mg/kg/day) or in male and female rats (at doses of approximately 100 mg/kg/day). The NTP, however, found equivocal evidence for hepatocarcinogenicity in male mice. Hydrochlorothiazide was not genotoxic in vitro in the Ames mutagenicity assay of Salmonella typhimurium strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 and in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations, or in vivo in assays using mouse germinal cell chromosomes, Chinese hamster bone marrow chromosomes, and the Drosophila sex-linked recessive lethal trait gene. Positive test results were obtained only in the in vitro CHO Sister Chromatid Exchange (clastogenicity) and in the Mouse Lymphoma Cell (mutagenicity) assays, using concentrations of hydrochlorothiazide from 43 to 1300 mcg/mL, and in the Aspergillus nidulans non-disjunction assay at an unspecified concentration.

Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed, via their diet, to doses of up to 100 and 4 mg/kg, respectively, prior to conception and throughout gestation.

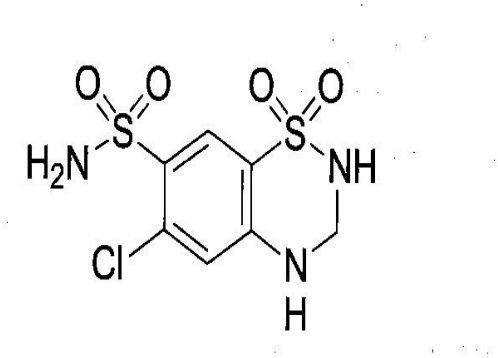
## 7. Description

Nebivolol Hydrochloride is (1RS, 1'RS)-1, 1'-[(2RS, 2'SR)-bis(6-flurochroman-2-yl)]-2,2'iminodiethanol hydrochloride having molecular formula of $C_{22}H_{25}F_2NO_4$, HCL and molecular weight is 441.9 the chemical structure is:




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

Hydrochlorothiazide is 6- chloro-3, 4-dihydro-2H-1, 2,4- benzothiadiazine-7-sulphonamide 1,1-dioxide. Having molecular formula of $C_7H_8CLN_3O_4S_2$ and molecular weight is 297.7 the chemical structure is:




Hydrochlorothiazide is white or almost white crystalline powder odourless.

NEBICARD-H tablets are yellow coloured, round, flat uncoated tablets with 'H' debossed on one side and plain on other side. The excipients used are Lactose, starch, croscarmellose sodium, Ferric oxide Yellow, Hydroxy propyl methyl Cellulose, Polysorbate 80, Croscarmellose Sodium, Microcrystalline Cellulose, Magnesium Stearate, Colloidal Silicon 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-H is packed in blister strips of 15 tablets.

### 8.4 Storage and handing instructions

- Store protected from light and moisture at a temperature not exceeding $25^0$C.
- Keep all tablets out of the reach of children.

## 9. Patient Counselling Information

- **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 H** are and what they are used for
9.2 What you need to know before you use **Nebicard H**
9.3 How to use **Nebicard H**
9.4 Possible side effects
9.5 How to store **Nebicard H**
9.6 Contents of the pack and other information


### 9.1 What Nebicard H is and what they are used for

Nebicard H is combination of Nebivolol 5 mg (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) and Hydrochlorothiazide 12.5 mg( Hydrochlorothiazide blocks the reabsorption of sodium and chloride ions, and it thereby increases the quantity of sodium traversing the distal tubule and the volume of water excreted.)

Nebicard H is indicated for the treatment of Essential Hypertension.

### 9.2 What you need to know before you use Nebicard H

Do not use Nebicard H

if you are allergic to nebivolol, Hydrochlorothiazide or any of the other ingredients of this medicine or to sulphonamide derived drugs, 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.
- Anuria

**Warnings and precautions**

Talk to your doctor or pharmacist before taking Nebicard H.

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: If you are diabetic your blood glucose level may rise.
- Overactive thyroid gland: This medicine may mask the signs of an abnormally fast heart rate due to this condition
- Disease of the parathyroid gland
- 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 H before being anaesthetised.
- If you have serious kidney problems.
- Eye pain and visual disturbance
- Hyperuricemia
- Electrolyte imbalance

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 H is not recommended for use in them.

*Other medicines and Nebicard H*

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 Nebicard H:

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, Alcohol, narcotics
- 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 Nebicard H during a meal and the antacid drug between meals.

Antidiabetic drugs- (oral agents and insulin)

Cholestyramine and colestipol resins - Cholestyramine and colestipol resins

Corticosteroid, increases electrolyte depletion, particularly low level of potassium.

Norepinephrine, tubocurarine, Lithium, Pain killer

**Pregnancy and breast-feeding**

Nebicard H 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.

Nebicard H contains lactose

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

## 9.3 How to take Nebicard H

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

Dose: As directed by the Physician.

**If you take more Nebicard H than you should consult your doctor immediately**.

The most frequent symptoms and signs of a Nebicard H 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 H**

If you forget a dose of Nebicard H, 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 Nebicard H**

You should always consult with your doctor before stopping Nebicard H treatment, whether you are taking it for high blood pressure or chronic heart failure.

You should not stop Nebicard H treatment abruptly as this can temporarily make your heart failure worse. If it is necessary to stop Nebicard H 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

## 9.4 Possible side effects

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

**Not Known**

- Weakness
- Low blood pressure (such as feeling faint when getting up quickly)
- Diarrhoea
- Constipation
- Nausea
- Reduced appetite
- Jaundice
- Inflammation of pancreas
- Anemia
- Electrolyte imbalance
- Muscle spasm
- Vertigo, feeling of tingling, dizziness, headache, restlessness.
- Kidney function impairment  blurred vision inflammation of skin
- Neoplasms benign, malignant and unspecified (incl cysts and polyps): Non-melanoma skin cancer (Basal cell carcinoma and Squamous cell carcinoma).

**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:
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 H

Store protected from light and moisture at a temperature not exceeding $25^0$C.

## 9.6 Contents of the pack and other information

Nebicard H contains Nebivolol 5 mg and Hydrochlorothiazide 12.5 mg as active ingredients

The excipients used are Lactose, starch, croscarmellose sodium, Yellow oxide of Iron, Hydroxy propyl methyl Cellulose, Polysorbate 80, Croscarmellose Sodium, Microcrystalline Cellulose, Magnesium Stearate, Colloidal Silicon Dioxide.

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

**10 Details of manufacturer**

TORRENT PHARMACEUTICALS LTD.

32 No.Middle Camp, NH-10

East District, Gangtok, Sikkim-737 135.

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**

**TORRENT PHARMACEUTICALS LTD.**

Mfg Lic No.: M/563/2010 issued on 16.09.2017

OR

**Innova Captab Limited.**

Mfg Lic No.: MNB/16/970 issued on 01.10.2020

**12 Date of revision**

JAN 2022

**MARKETED BY**

torrent PHARMA

TORRENT PHARMACEUTICALS LTD.

**IN/ NEBICARD-H 5, 12.5 /JAN-22/04/PI**