xxxxxxxxx-5343

# NEBIVOLOL Hydrochloride

## TORICARD-5

### 5 mg Tablet

### Beta Adrenoceptor Blocker

**FORMULATION:**
Each tablet contains:
Nebivolol (as Hydrochloride) ..... 5 mg
**PRODUCT DESCRIPTION:**
Nebivolol Hydrochloride (Toricard-5) 5 mg Tablet is a white to off-white, round, biconvex, uncoated tablet with cross break line on one side and plain on other side.
**PHARMACOLOGICAL PROPERTIES:**
**Pharmacodynamic Properties:** Nebivolol is a racemeate of two enantiomers, SRRR-nebivolol (or d-nebivolol) and RSSS-nebivolol (or l-nebivolol). It combines two pharmacological activities:
• It is a competitive and selective beta-receptor antagonist; this effect is atttibuted to the SRRR-enantiomer (d-enantiomer)
• It has mild vasodilating properties due to an interaction with 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 beta 1 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 > 70years (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 that 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 hospitalizations 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 38%).
In vitro and in vivo experiments in animals showed that nebivolol has no intrinsic sympathicomometic activity.
In vitro and in vivo experiments in animals showed that at pharmacological doses nebivolol has no membrane stabilizing action.
In healthy volunteers, nebivolol has no significant effect on maximal exercise capacity or endurance.
**Pharmacokinetic Properties:** 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 metabolized, partly to active hydroxyl-metabolites. Nebivolol is metabolized via alicylic and aromatic hydroxylation, N-dealkylation and glucuronidation; in addition, glucuronides of the hydroxyl-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 metabolizers and is virtually complete in slow metabolizers. At steady state and the same dose level, the peak plasma concentration of unchanged nebivolol is about 23 times higher in poor metabolizers than in extensive metabolizers. 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 rate of metabolism, the dose of nebivolol should always be adjusted to the individual requirements of the patient: poor metabolizers therefore may require lower dose.
In fast metabolizers. Elimination half-lives of nebivolol enantiomers average 10 hours. In slow metabolizers, there are 3-5 times longer. In fast metabolizers, plasma levels of the RSSS-enantiomer are slightly higher than SRRR-enantiomer. In slow metabolizers, this difference is larger. In fast metabolizers, eliminations half-lives of the hydroxyl metabolites of both enantiomers average 24 hours, and are about twice as long as slow metabolizers.
Steady-state plasma levels in most subjects (fast metabolizers) are reached within 24 hours for nebivolol and within a few days for the hydroxyl-metabolites. Plasma concentrations are dose-proportional between 1 mg and 30 mg. The pharmacokinetics is 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 feces. Urinary excretion of unchanged nebivolol is less than 0.5% of the dose.
**INDICATIONS:**
It is indicated in the treatment of essential hypertension. Treatment of stable mild and moderate chronic heart failure in addition to standard therapies in elderly patients.
**DOSAGE AND ADMINISTRATION:**
**Hypertension**
**Adults:** The dose is one tablet daily, preferably at the same time of the day. Tablets may be taken with meals. The blood pressure lowering effect becomes evident after 1-2 weeks of treatment. Occasionally the optimal effect is reached only after 4 weeks.
**Combination with other antihypertensive agents:** Beta-blockers can be used alone or concomitantly with other antihypertensive agents. To date, an additional antihypertensive effect has been observed only when nebivolol 5 mg is combined with hydrochlorothiazide 12.5 mg - 25 mg.
**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:** In patients with hepatic insufficiency or impaired liver function are limited. Therefore the use of nebivolol in these patients is contraindicated.
**Elderly:** In patients over 65 years the recommended starting dose is 2.5 mg daily. If needed, the daily dose may be increased to 5 mg. However, in view of the limited experience in patients above 75 years, caution must be exercised and these patients monitored closely.
**Children and adolescents:** No studies have been conducted in children and adolescents. Therefore, use in children and adolescents is not recommended.
**Chronic Heart Failure (CHF)**
The treatment of stable chronic heart failure has to be initiated with a gradual uptitration of dosage until the optimal individual maintenance dose is reached. Patients should have stable chronic heart failure without acute failure during the past six weeks. It is recommended that the treating physician should be experienced in the management of chronic heart failure.
For those patients receiving cardiovascular therapy including diuretics and/or digoxin and/or ACE inhibitors and/or angiotensin II antagonists, dosing of these drugs should be stabilized during the past two weeks prior to initiation of Nebivolol treatment.
The initial uptitration should be done according to the following steps at 1-2 weekly intervals based on patient tolerability: 1.25 mg nebivolol, to be increased to 2.5 mg nebivolol once daily, then to 5 mg once daily and then 10 mg once daily. The maximum recommended dose is 10 mg once daily.
Initiation of therapy and every dose increase should done under the supervision of an experienced physician over a period of at least 2 hours to ensure that the clinical status (especially as regards blood pressure, heart rate, conduction disturbances, signs of worsening of heart failure) remains stable.
Occurrence of adverse events may prevent all patients being treated with the maximum recommended doe. If necessary the dose reached can also be decreased step by step and reintroduced as appropriate.
During titration phase, in case of worsening of the heart failure or intolerance, it is recommended first to reduce the dose of nebivolol, or to stop it immediately if necessary ( in case of severe hypotension worsening of heart failure with acute pulmonary edema, cardiogenic shock, symptomatic bradycardia or AV block).
Treatment of stable chronic heart failure with nebivolol is generally a long-term treatment. The treatment with nebivolol is not recommended to be stopped abruptly since this might lead to a transitory worsening of heart failure. If discontinuation is necessary, the dose should be gradually decreased divided into halves weekly. Tablets maybe taken with meals.
**Patients with renal insufficiency:** No dose adjustment is required to mild to moderate renal insufficiency since uptitration to the maximum tolerated dose is individually adjusted. There is no experience in patients with severe renal insufficiency (serum creatinine > 250$\mu$mol/L). Therefore the use of nebivolol in these patients is not recommended.
Patients with hepatic insufficiency: Data in patients with hepatic are limited. Therefore the use of Nebivolol in those patients is contraindicated.
**Elderly:** No dose adjustment is required since uptitration to the maximum tolerated dose is individually adjusted.
**Children and adolescents:** No studies have been conducted in children and adolescents. Therefore, the use in children and adolescents is not recommended.
The tablet may be broken down in half at break line if required.
**CONTRAINDICATIONS:**
Hypersensitivity 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 decomposition requiring i.v. inotropic therapy.
In addition, as with other beta-blocking agents, nebivolol is contraindicated in:
Sick sinus syndrome, including sino-atrial block.
Second and third degree heart block (without pacemaker).
History of bronchospasm and bronchial asthma.
Untreated pheochromocytoma
Metabolic acidosis
Bradycardia (heart rate < 60 bpm prior to start therapy)
Hypotension (systolic blood pressure <90 mmHg).
Severe peripheral circulatory disturbances.
**SPECIAL WARNINGS AND PRECAUTIONS:**
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 stabilized.
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 negative effect of beta-blockers on conduction time;
In patients with Prinzmetal's angina due to unopposed alpharecepter 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 does not affect glucose levels in diabetic patients. Care should be taken in diabetic patients however, as nebivolol may mask certain symptoms of hypoglycemia (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 maybe aggravated.

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| **PRODUCT NAME** | : Toricard-5 | **COUNTRY :** Philippines | | **LOCATION :** Chhatral | | **REMARK :** | |
| **ITEM / PACK** | : Insert | **NO. OF COLORS:** 1 | | **SUBSTRATE :** | | | |
| **DESIGN STYLE** | : Front-Back | **PANTONE SHADE NOS.:** | | | | | |
| **CODE** | : xxxxxxxxx-5343 | ■ Black | | **Activities** | **Department** | **Name** | **Signature** | **Date** |
| **DIMENSIONS (MM)** | : 150 x 420 | | | Prepared By | **Pkg.Dev** | | | |
| **ART WORK SIZE** | : S/S | | | Reviewed By | **Pkg.Dev** | | | |
| **DATE** | : 20-07-2016 | | | Approved By | **Quality** | | | |

**Other:** Patients with 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 recations.
The initiation of Chronic Heart Failure with nebivolol necessitates regular monitoring. 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-lactose deficiency or glucose-galactose malabsoprtion should not take this medicinal product.
**ADVERSE EFFECTS:**
Adverse events are listed separately for hypertension and CHF because of differences in the background diseases.
**Hypertension**
The adverse reactions reported, which are in the most 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 oedma, hypersensitivity |
| Psychiatric Disorders | | Nightmares, depression | | |
| Nervous System Disorders | Headache, dizziness, paraesthesia | | syncope | |
| Eye Disorders | | Impaired vision | | |
| Cardiac Disorders | | Bradycardia, heart failure, slowed AV conduction/AV-block | | |
| Vascular Disorders | | Hypotension (increase of) intermittent claudication | | |
| Respiratory, thoracic and mediastinal disorders | Dyspnea | Bronchospasm | | |
| Gastrointestinal Disorders | Constipation, nausea diarrhea | Dyspepsia, flatulence, vomiting | | |
| Skin and Subcutaneous Tissue Disorders | | Pruritus, rash, erythematous | Psoriasis aggravated | |
| 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, Raynauds phenomenon dry eyes, and oculo-mucocutaneous toxicity of the practolol-type.
**Chronic Heart Failure**
Data on adverse reactions in CHF patients are available from one placebo-controlled clinical trial involving 1067 patients taking nebivolol and 1061 patients taking placebo. In this study, a total of 449 nebivolol patients (42.1%) reported at least possibly causally related adverse reactions compared to 334 placebo patients (31.5%). The most commonly reported adverse reactions in nebivolol patients were bradycardia and dizziness, both occurring in approximately 11% of patients. The corresponding frequencies among placebo patients were 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.

"For suspected adverse drug reaction, report to FDA: www.fda.gov.ph or to TORRENT: www.torrentpharma.com".
Patient to seek medical attention immediately at the first sign of any adverse drug reaction shall appear.
**OVERDOSAGE:**
No data are available on overdosage with Nebivolol.
**Symptoms:** Symptoms of overdosage with betablockers are: bradycardia, hypotension, bronchospasm and acute cardiac insufficiency.
**Treatment:** In case of overdosage or hypersensitivity, the patients 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 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$\mu$g/minute, or dobutamine, starting with a dose of 2.55$\mu$g/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 500-100 $\mu$g/kg i.v. may be considered. If required, the injection should be repeated within in one hour, to be followed if required by an i.v. infusion of glucagon 70 $\mu$g/kg/h. In extreme cases of treatment-resistant bradycardia, a pacemaker maybe inserted.
**DRUG INTERACTIONS:**
**Pharmacodynamic Interactions:**
The following interactions apply to beta-adrenergic antagonists in general.
**Combinations not recommended:**
**Class I anti-arrhytmics (quinidine, hydroquinidine, cibenzoline, flecainide, disopyramide, lidocaine, mexiletine, propafenone):** effect on atrio-ventricular conduction time may be potentiated and negative inotropic effect increased.
**Calcium channel antagonists of verapamil / diltiazem type:** negative influence on contractility and atrio-ventricular conduction. Intravenous administration of verapamil in patients with β-bocker treatment may lead to profound hypotension and atrio-ventricular block.
**Centrally-acting hypertensives (clonidine, guanfacin, monoxidine, 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 antiarrythmic drugs (Amiodarone):** effect on atrio-ventricular conduction may be potentiated.
**Anaesthetics: volatile halogenated:** concomitant use of beta-adrenergic antagosnists and anaesthetics may attenuate reflex tachycardia and increase the risk of hypotension. As a general rule, avoid sudden withdrawal of beta-blocker treatment. The anesthesiologist should be informed when the patient is receiving Nebivolol.
**Insulin and oral antidiabetic drugs:** although nebivolol does not affect glucose level, concomitant use may mark certain symptoms of hypoglycemia (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 antihypertensive medication should be adjusted accordingly.
**Combinations to be considered**
**Digitalis glycosides:** concomitant use may increase artrio-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 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 fraction 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 (NSAIDS):** no effect on the blood pressure lowering effect of nebivolol.
**Sympathicomimetic Agents:** concomitant use may counteract the effect of beta-adrenergic antagonists. Beta-adrenergic agents may lead to unopposed alpha-adrenergic activity of the sympathicomimetic agents with both alpha- and beta-adrenergic effects (risk of hypertension, severe bradyardia and heart block).
**Pharmacokinetic interactions:**
As Nebivolol metabolism involves the CYP2D6 isoenzyme, co-administration with substances inhibiting this enzyme, especially paroxetine, fluoxetine, thioridazine and quinidine may lead to increased plasma levels of nebivolol associated with an increased risk of excessive bradycardia and adverse events.
Co-administration of cimetidine increased the plasma levels of nebivolol, without changing the clinical effect. Co-administration of ranitidine did not affect the pharmacokinetics of nebivolol. Provided Nebivolol is taken with the meal, and an antacid between meals, the two treatments can be co-prescribed. Combining nebivolol with nicardipine slightly increased the plasma levels of both drugs, without changing the clinical effect. Co-administration of alcohol, furosemide or hydrochlorthiazide did not affect pharmacokinetics of nebivolol. Nebivolol does not affect the pharmacodynamics of warfarin.
**PREGNANCY AND LACTATION**
**Use in Pregnancy:** Nebivolol has pharmacological effects that may cause harmful effects on pregnancy and/or the fetus / newborn. In general, beta-receptor blockers reduce placental perfusion, which has been associated with growth retardation, intrauterine death, abortion or early labour. Adverse effects (e.g. hypoglycemia and bradycardia) may occur in the fetus and newborn infant. If treatment with beta-adrenoceptor blockers is necessary, beta-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 fetal growth should be monitored. In case harmful effects on pregnancy of the fetus alternative treatment should be considered. The newborn infant must be closely monitored. Symptoms of hypoglycemia and bradycardia are generally to be expected within first 3 days.
**Use in lactation**
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 content. Therefore, breast feeding is not recommended during administration of nebivolol.
**EFFECTS ON ABILITY TO DRIVE AND USE MACHINES**
No studies on the effects on the ability to drive and use machines have been performed. Pharmacodynamic studies have shown that Nebivolol 5 mg does not affect psychomotor function. When driving vehicles or operating machines it should be taken into account that dizziness and fatigue may occasionally occur.
**CAUTION:**
Foods, Drugs, Devices and Cosmetic Act prohibits dispensing without presciption.
**STORAGE:**
Store at temperatures not exceeding 30°C. Protect from light.
**AVAILABILITY**
Nebivolol Hydrochloride (Toricard-5) 5 mg Tablet - Alu-Alu Blister pack of 10's (Box of 100's) - DR-XY37962
**DATE OF FIRST AUTHORIZATION**
May 20, 2010
**DATE OF REVISION**
June 2016

torrent PHARMA

Manufactured by :
TORRENT PHARMACEUTICALS LTD.
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Imported and Distributed by :
**TORRENT PHARMA PHILIPPINES INC.**
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