UNILAB

Nebivolol Nitroxel™

5 mg Tablet

Beta Blocking Agent

℞

FORMULATION
Each uncoated tablet contains:
Nebivolol Hydrochloride
Equivalent to Nebivolol ..... 5 mg

PRODUCT DESCRIPTION
Orange coloured, round, flat, bevel edged uncoated tablet with plain surface on both sides.

PHARMACODYNAMIC PROPERTIES
Pharmacotherapeutic group: Beta-blocking agents.
Nebivolol is a racemate of two enantiomers, SRRR-nebivolol (or d-nebivolol). It combines two pharmacological activities:
• It is a competitive and selective beta-receptor antagonist; this effect is attributed to the SRRR-enantiomer (d-enantiomer).
• It has mild vasodilating properties due to an interaction with the L-arginine/nitric oxide pathway.
Single and repeated doses of nebivolol reduces 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 hemodynamic 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 > 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 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 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 pharmacologic 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 hydroxymetabolites. Nebivolol is metabolized 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 CYP2D6 dependent genetic oxidative polymorphism. The oral bioavailability of nebivolol averages 12% in fast metabolizers and is virtually complete in slow metabolizers than in extensive metabolizers.
When unchanged active substance plus active metabolites are considered, the difference in peak plasma concentrations is 1.3 to 1.4 fold. Because of the variations in the rates of metabolism, the dose of nebivolol tablet should always be adjusted to the individual requirements of the patient: poor metabolizers therefore may require lower doses.
In fast metabolizers, elimination half-lives of the nebivolol enantiomers average 10 hours. In slow metabolizers, they are 3-5 times longer. In fast metabolizers, plasma levels of the RSSS-enantiomer are slightly higher than for the SRRR-enantiomer. In slow metabolizers, this difference is larger. In fast metabolizers, elimination half-lives of the hydroxymetabolites of both the enantiomers average 24 hours, and are about twice as long in 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 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 feces. Urinary excretion of the unchanged nebivolol is less than 0.5% of the dose.

INDICATIONS
Hypertension
Treatment of essential hypertension.
Chronic heart failure (CHF)
Treatment of stable mild and moderate chronic heart failure in addition to standard therapies in elderly patients ≥ 70 years.

DOSAGE AND ADMINISTRATION
Route of administration: Oral

Posology
Hypertension
Adults
The dose is 5 mg (one 5 mg tablet or two 2.5 mg tablets) daily, preferably at the same time of the day.
The blood pressure lowering effect becomes evident after 1-2 weeks of treatment.
Occasionally, the optimal effect is reached only after 4 weeks.
Combination with other antihypertensive agents
Beta-blockers can be used alone or concomitantly with other antihypertensive agents. To date, an additional antihypertensive effect has been observed only when nebivolol is combined with hydrochlorothiazide 12.5-25 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
Data in patients with hepatic insufficiency or impaired liver function are limited. Therefore, the use of nebivolol in these patients is contraindicated.
Elderly
In patients over 65 years, the recommended starting dose is 2.5 mg daily. If needed, the daily dose may be increased to 5 mg. However, in view of the limited experience in patients above 75 years, caution must be exercised and these patients monitored closely.
Pediatric population
No data are available. Nebivolol should therefore not be used in children and adolescents.
Chronic heart failure (CHF)
The treatment of 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 experience in the management of chronic heart failure.
For those patients receiving cardiovascular medicinal therapy including diuretics and/or digoxin and/or ACE inhibitors and/or angiotensin II antagonists, dosing of these medicines should be stabilized during the past two weeks prior to initiation of nebivolol tablets 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 to 10 mg once daily.
The maximum recommended dose is 10 mg nebivolol once daily.
Initiation of therapy and every dose increase should be 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 to 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 dose. If necessary, the dose reached can also be decreased step by step and reintroduced as appropriate.
During the titration phase, in case of the worsening of 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 transitory worsening of heart failure. If discontinuation is necessary, the dose should be gradually decreased divided into halves weekly.
Patients with renal insufficiency
No dose adjustment is required in 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 μmol/L). Therefore, the use of nebivolol in these patients is not recommended.
Patients with hepatic insufficiency
Data in patients with hepatic insufficiency are limited. Therefore, the use of nebivolol tablet in these patients is contraindicated.
Elderly
No 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, use in children and adolescents is not recommended.
Method of administration
The tablet should be taken with some water. They may be taken with meals or as prescribed by the physician.

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 decompensation requiring intravenous inotropic therapy.
In addition, as with other beta-blocking agents, nebivolol are contraindicated in:
• sick sinus syndrome, including sino-atrial block,
• second and third degree heart block (without a pacemaker),
• history of bronchospasm and bronchial asthma,
• untreated phaeochromocytoma,
• metabolic acidosis,
• bradycardia (heart rate < 60 bpm prior to start therapy),
• hypotension (systolic blood pressure < 90mmHg),
• severe peripheral circulatory disturbances.

WARNINGS AND PRECAUTIONS
The following warnings and precautions apply to beta-adrenergic antagonists in general.
Anesthesia
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 anesthetics 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 ischemic heart disease, treatment with 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 or intermittent claudication), as aggravation of these disorders may occur;
• in patients with first degree heart block, because of the negative effect of the beta-blockers on conduction time;
• In patients with Prinzmetals' 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 active substance, and with centrally acting antihypertensive active substance is generally 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 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.
Treatment discontinuation should not be done abruptly unless clearly indicated.

PREGNANCY AND LACTATION
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., hypoglycemia and bradycardia) may occur in the fetus and newborn infant. If treatment with beta-adrenoceptor blockers is necessary, beta1-selective adrenoceptor blockers are preferable.
Nebivolol should not be used in 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 hypoglycemia and bradycardia are generally to be expected within the first 3 days.
Lactation
Animal studies have shown that nebivolol is excreted in breast milk. It is not known whether this medicine 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.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
Nebivolol has minor influence on the ability to drive and use machines.
Pharmacodynamic studies have shown that nebivolol does not affect psychomotor function. When driving vehicles or operating machines it should be taken into account that dizziness and fatigue may occasionally occur.

DRUG INTERACTIONS
The following interactions apply to beta-adrenergic antagonists in general.
Combinations not recommended
Class I antiarrhythmics (quinidine, hydroquinidine, cibenzoline, flecainide, disopyramide, lidocaine, mexiletine, propafenone) effect on atrio-ventricular conduction time may be potentiated and negative inotropic effect increased.
Calcium channel antagonists of verapamil/diltiazem type: negative influence on contractility and atrio-ventricular conduction. Intravenous administration of verapamil in patients with β-blocker treatment may lead to profound hypotension and atrio-ventricular block.
Centrally-acting antihypertensives (clonidine, guanfacin, moxonidine, methyldopa, rilmenidine). Concomitant use of centrally-acting antihypertensive medicinal products 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 substances (Amiodarone): effect on atrio-ventricular conduction time may be potentiated.
Anesthetics - volatile halogenated: concomitant use of beta-adrenergic antagonists and anesthetics 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 tablet.
Insulin and oral antidiabetic substances: although nebivolol does not affect glucose level, concomitant use may mask certain symptoms of hypoglycemia (palpitations, tachycardia).
Baclofen (antispastic agent), amifostine (antineoplastic adjunct): Concomitant use with antihypertensives is likely to increase the fall in high blood pressure, therefore, the dosage of the antihypertensive medicinal products should be adjusted accordingly.

Combinations to be considered
Digitalis glycosides: concomitant use may increase atrio-ventricular conduction time. Clinical trials with nebivolol have not shown any clinical evidence of an interaction. Nebivolol does not influence the kinetics of digoxin.
Calcium antagonists of 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 beta-adrenergic 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, 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 pharmacokinetic of nebivolol. Provided nebivolol tablets are taken with the meal, the two treatments can be co-prescribed. Combining nebivolol with nicardipine slightly increased the plasma levels of both active substances, without changing the clinical effect. Co-administration of alcohol, furosemide and hydrochlorothiazide did not affect the pharmacokinetics of nebivolol.
Nebivolol does not affect the pharmacokinetics and pharmacodynamics of warfarin.

ADVERSE DRUG REACTIONS
Adverse reactions 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 (≥1/1,100 to ≤1/100)	Very rare (≥1/10,000)	Not known
Immune system disorders				angioneurotic edema, hypersensitivity
Psychiatric disorder		nightmares, depression		
Nervous system disorders	Headache, dizziness, paresthesia		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 aggravate	
Reproductive system and and breast disorders		impotence		
General disorders and administration site conditions	tiredness, edema			

The following adverse reactions have also been reported with some beta-adrenergic antagonists: hallucinations, psychoses, confusion, cold/ cyanotic extremities, Raynaud phenomenon, dry eyes, and oculo-mucocutaneous toxicity of the practolol-type.
Chronic heart failure
Data on adverse reactions in CHF patients are available from one placebo-controlled clinical trial involving 1067 patients taking nebivolol and 1061 patients taking placebo. In this study, a total of 449 nebivolol patients (42.1%) reported at least possibly causally related adverse reactions compared to 334 placebo patients (31.5%). The most commonly reported adverse reactions in nebivolol 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 substance-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.
- Intolerance to the substance 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.
- Edema of the lower limb were reported by 1.0% of nebivolol patients compared to 0.2% of placebo patients

OVERDOSE AND TREATMENT
No data are available on overdosage with nebivolol.
Symptoms
Symptoms of overdosage with beta-blockers are: bradycardia, hypotension, bronchospasm and acute cardiac insufficiency.
Treatment
In case of overdosage or hypersensitivity, the patient should be kept under close supervision and be treated in an intensive care ward. Blood glucose levels should be checked. Absorption of any active substance residues still present in the gastrointestinal 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 intravenous may be considered. If required, the injection should be repeated within one hour, to be followed - if required - by an intravenous infusion of glucagon 70 μg/kg/hr. In extreme cases of treatment-resistant bradycardia, a pacemaker may be inserted.

STORAGE CONDITION
Store at temperatures not exceeding 30°C.

Keep all medicines out of reach of children.

ADVERSE DRUG REACTION REPORTING STATEMENT
For suspected adverse drug reaction, seek medical attention immediately and report to the FDA at www.fda.gov.ph **AND** Unilab at +632-8-**UNILAB**-1 (+632-8-**864522**-1) for Metro Manila or toll-free +1-800-10-UNILAB-1 for provinces, or e-mail productsafety@unilab.com.ph. By reporting undesirable effects, you can help provide more information on the safety of this medicine.

CAUTION
Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

AVAILABILITY
Nebivolol (Nitroxel™) 5 mg Tablet, In Alu-Alu Blister Pack x 10's (Box of 30's)

Manufactured by STALLION LABORATORIES PVT. LTD.
C-1B, 305/2, 3, 4 & 5 G.I.D.C. Kerala, Bavla-382 220
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