

Size: 260 (L) x 360 (H) mm
Folding size: 30 x 150 mm
Drg. No. : 9917306-005
Carton size: 53 x 25 x 130 mm

Paper 35 to 50 gsm

Front side

260 mm

110 mm

150 mm



NEBIVOLOL + AMLODIPINE

NEBILONG-AM
5 mg/5 mg Tablet

Beta-Blocker-Calcium Channel Blocker Combination

PRODUCT NAME:
Nebilong-AM

NAME AND STRENGTH:
5 mg / 5 mg Tablets

PHARMACOLOGIC CATEGORY:
Beta-Blocker-Calcium Channel Blocker Combination

PRODUCT DESCRIPTION:
White and Yellow colored, circular, flat, bevel edged uncoated, bilayered tablets with break line on one surface.

FORMULATION/COMPOSITION:
Each uncocated bilayered tablet contains:
Nebivolol Hydrochloride equivalent to Nebivolol..... 5 mg
Amlodipine Besilate BP equivalent to Amlodipine..... 5 mg

PHARMACODYNAMICS/PHARMACOKINETICS:

Amlodipine:
Amlodipine is a dihydropyridine calcium ion antagonist (calcium ion antagonist or slow-channel blocker) that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. Experimental data suggest that amlodipine binds to both dihydropyridine and nondihydropyridine binding sites. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. Amlodipine inhibits calcium ion influx across cell membranes selectively, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells. Negative inotropic effects can be detected in vitro but such effects have not been seen in intact animals at therapeutic doses. Serum calcium concentration is not affected by amlodipine. Within the physiologic pH range, amlodipine is an ionized compound ($pK_a=8.6$), and its kinetic interaction with the calcium channel receptor is characterized by a gradual rate of association and dissociation with the receptor binding site, resulting in a gradual onset of effect.

Amlodipine is a peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and reduction in blood pressure.

Haemodynamics: Following administration of therapeutics to patients with hypertension, amlodipine produces vasodilation resulting in a reduction of supine and standing blood pressures. These decreases in blood pressure are not accompanied by a significant change in heart rate or plasma catecholamine levels with chronic dosing. Although the acute intravenous administration of amlodipine decreases arterial blood pressure and increases heart rate in hemodynamic studies of patients with chronic stable angina, chronic oral administration of amlodipine in clinical trials did not lead to clinically significant changes in heart rate or blood pressures in normotensive patients with angina.

With chronic once daily oral administration, antihypertensive effectiveness is maintained for at least 24 hours. Plasma concentrations correlate with effect in both young and elderly patients. The magnitude of reduction in blood pressure with amlodipine is also correlated with the height of pretreatment elevation; thus, individuals with moderate hypertension (diastolic pressure 105-114 mmHg) had about a 50% greater response than patients with mild hypertension (diastolic pressure 90-104 mmHg). Normotensive subjects experienced no clinically significant change in blood pressures (+1/-2 mmHg).

In hypertensive patients with normal renal function, therapeutic doses of amlodipine resulted in a decrease in renal vascular resistance and an increase in glomerular filtration rate and effective renal plasma flow without change in filtration fraction or proteinuria.

As with other calcium channel blockers, hemodynamic measurements of cardiac function at rest and during exercise (or pacing) in patients with normal ventricular function treated with amlodipine have generally demonstrated a small increase in cardiac index without significant influence on dP/dt or on left ventricular end diastolic pressure or volume. In hemodynamic studies, amlodipine has not been associated with a negative inotropic effect when administered in the therapeutic dose range to intact animals and man, even when co-administered with beta-blockers to man. Similar findings, however, have been observed in normal or well-compensated patients with heart failure with agents possessing significant negative inotropic effects.

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

It combines two pharmacological activities:

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

It has mild vasodilating properties due to an interaction with the L-arginine/nitric oxide pathway.

Single and repeated doses of nebivolol reduce heart rate and blood pressure at rest and during exercise, both in normotensive subjects and in hypertensive patients. The antihypertensive effect is maintained during chronic treatment.

At therapeutic doses, nebivolol is devoid of alpha-adrenergic antagonism.

During acute and chronic treatment with nebivolol in hypertensive patients, systemic vascular resistance is decreased.

Despite heart rate reduction, reduction in cardiac output during rest and exercise may be limited due to an increase in stroke volume. The clinical relevance of these haemodynamics differences as compared to other β 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 vitro and in vivo experiments in animals showed that nebivolol has no intrinsic Sympathomimetics 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.

Pharmacokinetics

Amlodipine: After oral administration of therapeutic doses of amlodipine, absorption produces peak plasma concentrations between 6 and 12 hours. Absolute bioavailability has been estimated to be between 64 and 90%. The bioavailability of amlodipine is not altered by the presence of food.

Amlodipine is extensively (about 90%) converted to inactive metabolites via hepatic metabolism with 10% of the parent compound and 60% of the metabolites excreted in the urine. Ex vivo studies have shown that approximately 93% of the circulating drug is bound to plasma proteins in hypertensive patients. Elimination from the plasma is biphasic with a terminal elimination half-life of about 30-50 hours. Steady-state plasma levels of amlodipine are reached after 7 to 8 days of consecutive daily dosing.

The pharmacokinetics of amlodipine is not significantly influenced by renal impairment. Patients with renal failure may therefore receive the usual initial dose.

Elderly patients and patients with hepatic insufficiency have decreased clearance of amlodipine with a resulting increase in AUC of approximately 40-60%, and a lower initial dose may be required. A similar increase in AUC was observed in patients with moderate to severe heart failure.

Pediatric Patients: Sixty-two hypertensive patients aged 6 to 17 years received doses of amlodipine between 1.25 mg and 20 mg. Weight-adjusted clearance and volume of distribution were similar to values in adults.

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 hydroxy-metabolites 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.

INDICATION(s): Nebivolol plus Amlodipine is indicated for the treatment of essential hypertension and the treatment of chronic stable angina.

DOSAGE AND MODE/ROUTE OF ADMINISTRATION: Hypertension and Chronic Stable Angina: Adults: The usual dosage is one 5 mg/5 mg tablet, with or without food, once a day. The maximum daily dose should not exceed 5mg/10mg once daily.

Elderly: In patients over 65 years of age, the recommended starting dose is one 2.5 mg/5 mg tablet daily. The dose may be upward titrated to 5mg/10mg if needed.

Or as prescribed by the physician.

Patients with renal Impairment: No dosage adjustment is required in patients with mild to moderate renal impairment. In patients with severe renal impairment ($CCr < 30 \text{ mL/min}$) the recommended starting dose is 2.5 mg/5 mg once daily. If needed, upward titration should be performed cautiously.

Patients with hepatic disease: In patients with moderate hepatic impairment (Child-Pugh B), the recommended starting dose is 2.5 mg/5 mg once daily. If needed, the dosage should be upward titrated cautiously. Nebivolol and Amlodipine have not been studied in patients with severe hepatic impairment and therefore the fixed dose combination of Nebivolol plus Amlodipine is not recommended in patients with this condition.

Children and Adolescents: No studies have been conducted in children and adolescents. Therefore, use in children and adolescents is not recommended.

CYP2D6 Polymorphism: Dose adjustments are not necessary for patients who are CYP2D6 poor metabolizers. The clinical effect and safety profile observed in poor metabolizers were similar to those of extensive metabolizers.

CONTRAINDICATION(s), PRECAUTION(s), WARNING(s):

Nebivolol: In addition, with other beta-blocking agents, Nebivolol is contra-indicated in:

- Sick sinus syndrome, including sino-atrial block.
- Second and third degree heart block (without a pacemaker).
- History of Bronchospasm and bronchial asthma.
- Untreated phaeochromocytoma.
- Metabolic acidosis.
- Bradycardia (heart rate < 60 bpm prior to start therapy).
- Hypotension (systolic blood pressure < 90 mmHg).
- Severe peripheral circulatory disturbances

Amlodipine: Amlodipine is contraindicated in patients with:

- Hypersensitivity to dihydropyridine derivatives, amlodipine or any of the excipients
- Severe hypotension
- Shock (including cardiogenic shock)
- Obstruction of the outflow tract of the left ventricle (e.g. high grade aortic stenosis)
- Haemodynamically unstable heart failure after acute myocardial infarction

PRECAUTIONS & WARNINGS:

Drug interactions: Class III antiarrhythmics drugs (Amiodarone): The 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.

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, anticonvulsant/antispastic 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.

Effects of other medicinal products on amlodipine:

CYP3A4 inhibitors: Concomitant use of amlodipine with strong or moderate CYP3A4 inhibitors (protease inhibitors, azole antifungals, macrolides like erythromycin or clarithromycin, verapamil or diltiazem) may give rise to significant increase in amlodipine exposure. The clinical translation of these PK variations may be more pronounced in the elderly. Clinical monitoring and dose adjustment may thus be required.

CYP3A4 inducers: There is no data available regarding the effect of CYP3A4 inducers on amlodipine. The concomitant use of CYP3A4 inducers (e.g., rifampicin, hypericum perforatum) may give a lower plasma concentration of amlodipine. Amlodipine should be used with caution together with CYP3A4 inducers.

Administration of amlodipine with grapefruit or grapefruit juice is not recommended as bioavailability may be increased in some patients resulting in increased blood pressure lowering effects.

Dantrolene (infusion): In animals, lethal ventricular fibrillation and cardiovascular collapse are observed in association with hyperkalaemia after administration of verapamil and dantrolene IV. Due to risk of hyperkalaemia, it is recommended that the co-administration of calcium channel blockers such as amlodipine be avoided in patients susceptible to malignant hyperthermia and in the management of malignant hyperthermia.

Effects of amiodarone on other medicinal products:

The blood pressure lowering effects of amlodipine adds to the blood pressure-lowering effects of other medicinal products with antihypertensive properties.

In clinical interaction studies, amlodipine did not affect the pharmacokinetics of atorvastatin, digoxin, warfarin or cyclosporin.

Simvastatin: Co-administration of multiple doses of 10 mg of amlodipine with 80 mg simvastatin resulted in a 77% increase in exposure to simvastatin compared to simvastatin alone. Limit the dose of simvastatin in patients on amlodipine to 20 mg daily.

ADVERSE DRUG REACTION(s):

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:

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150 mm

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psychoses, confusion, cold/cyanotic extremities, Reynaud phenomenon, dry eyes, and oculo-mucocutaneous toxicity of the proutol-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 setting of chronic heart failure:

Amlodipine:
Adverse events that have been reported in amlodipine trials are categorized below, according to system organ class and frequency. Frequencies are defined as: very common (>10%); common (>1%, <10%); uncommon (>0.1%, <1%); rare (>0.01%, <0.1%) and very rare (<0.01%).

Blood and the Lymphatic System Disorders	thrombocytopenia	Very Rare
Immune System Disorders	allergic reaction	Very Rare
Metabolism and Nutrition Disorders	hyperglycemia	Very Rare
Psychiatric Disorders	insomnia, mood changes	Uncommon
Nervous System Disorders	somnolence, dizziness, headache	Common
	tremor, taste perversion, syncope, hypoesthesia, paraesthesia	Uncommon
	peripheral neuropathy	Very Rare
Eye Disorders	visual disturbances	Uncommon
Ear and Labyrinth Disorders	tinnitus	Uncommon
Cardiac Disorders	palpitations	Common
	myocardial infarction, arrhythmia, ventricular tachycardia and atrial fibrillation)	Very Rare
Vascular Disorders	flushing	Common
	hypotension	Uncommon
	Vasculitis	Very Rare
Respiratory, Thoracic and Mediastinal Disorders	dyspnoea, rhinitis	Uncommon
Gastrointestinal Disorders	coughing	Very Rare

MICRO LABS LIMITED, BANGALORE, INDIA					
1	Product Name	Nebilong-AM		Colours Used	
2	Strength	5 mg and 5 mg		<input checked="" type="checkbox"/> BLACK	
3	Component	Leaflet			
4	Category	Export - Philippines			
5	Dimension	260 (L) x 360 (H) mm			
6	Artwork Code	EXG-ML01I-1822			
7	Pharma Code	390			
8	Reason for Change	New Artwork			
		Prepared by (DTP)	Checked by (PD)	Approved by	
Sign		Kantharaju L.		Head CQA	Head Production/ Packing (Site)
Date		12-01-2023		Head QC (Site)	Head QA (Site)