SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

1.1 Product Name:

Nebivolol Tablets

Nebilong

1.2 Strength:

2.5mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each uncoated tablet contains:

Nebivolol Hydrochloride equivalent to Nebivolol ……2.5mg

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Uncoated tablet

4. CLINICAL PARTICULARS

4.1 Therapeutic 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.

4.2 Posology and method of administration

Hypertension: The dose of Nebivolol must be individualized to the needs of the patient. For most patients, the recommended starting dose is 5 mg once daily, with or without food, as monotherapy or in combination with other agents. For patients requiring further reduction in blood pressure, the

dose can be increased at 2-week intervals up to 40 mg. A more frequent dosing regimen is unlikely to be beneficial.

Renal Impairment: In patients with severe renal impairment (ClCr less than 30 mL/min) the recommended initial dose is 2.5 mg once daily; titrate up slowly if needed. It has not been studied in patients receiving dialysis.

Hepatic Impairment: In patients with moderate hepatic impairment, the recommended initial dose is 2.5 mg once daily; titrate up slowly if needed. It has not been studied in patients with severe hepatic impairment and therefore it is not recommended in that population.

Children and adolescents: The safety and efficacy of Nebivolol in children aged less than 18 years have not been established. 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 Up titration 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 drug 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 Up titration 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.

Patients with hepatic insufficiency

Data in patients with hepatic insufficiency are limited. Therefore the use of Nebivolol in these patients is contra-indicated.

Elderly: No dose adjustment is required since Up titration to the maximum tolerated dose is individually adjusted.

Older people: No dose adjustment is required since up titration to the maximum tolerated dose is individually adjusted.

Paediatric population: The efficacy and safety of Nebivolol in children and adolescents aged below 18 years has not been established. Therefore, use in children and adolescents is not recommended. No data are available.

Method of administration

Oral use. Tablets may be taken with meals.

4.3 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 i.v. inotropic therapy.

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

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

4.4 Special warnings and precautions for use

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-receptor mediated coronary artery vasoconstriction: beta-adrenergic antagonists may increase the number and duration of Anginal attacks.

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

Metabolic/Endocrinological

Nebivolol does not affect glucose levels in diabetic patients. Care should be taken in diabetic patients however, as Nebivolol may mask certain symptoms of hypoglycaemia (tachycardia, palpitations).

Beta-adrenergic blocking agents may mask 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. Treatment discontinuation should not be done abruptly unless clearly indicated.

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

4.5 Interaction with other medicinal products and other forms of interaction

Combinations not recommended:

Class I antiarrhythmics (quinidine, hydroquinidine, cibenzoline, flecainide, disopyramide, lidocaine, mexiletine, propafenone)*:* effect on atrio-ventricular conduction time may be potentiated and negative inotropic effect increased.

Calcium channel antagonists of verapamil/diltiazem type: negative influence on contractility and atrio-ventricular conduction. Intravenous administration of verapamil in patients with ß-blocker treatment may lead to profound hypotension and atrio-ventricular block.

Centrally-acting antihypertensives (clonidine, guanfacin, moxonidine, methyldopa, rilmenidine): concomitant use of centrally acting antihypertensive drugs may worsen heart failure by a decrease in the central sympathetic tonus (reduction of heart rate and cardiac output, vasodilation).

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.

Insulin and oral antidiabetic drugs: although Nebivolol does not affect glucose level, concomitant use may mask certain symptoms of hypoglycaemia (palpitations, tachycardia).

Baclofen (antispastic agent), amifostine (antineoplastic adjunct): concomitant use with antihypertensives is likely to increase the fall in blood pressure; therefore the dosage of the antihypertensive medication 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 the dihydropyridine type (amlodipine, felodipine, lacidipine, nifedipine, nicardipine, nimodipine, nitrendipine): concomitant use may increase the risk of hypotension, and an increase in the risk of a further deterioration of the ventricular pump function in patients with heart failure cannot be excluded.

Antipsychotics, antidepressants (tricyclics, barbiturates and phenothiazines): concomitant use may enhance the hypotensive effect of the beta-blockers (additive effect).

Non steroidal anti-inflammatory drugs (NSAID): no effect on the blood pressure lowering effect of Nebivolol.

Sympathicomimetic agents: concomitant use may counteract the effect of 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 pharmacokinetics of Nebivolol. Provided Nebivolol is taken with the meal, and an antacid between meals, the two treatments can be co-prescribed.

Combining Nebivolol with nicardipine slightly increased the plasma levels of both drugs, without changing the clinical effect. Co-administration of alcohol, furosemide or hydrochlorothiazide did not affect the pharmacokinetics of Nebivolol. Nebivolol does not affect the pharmacokinetics and pharmacodynamics of warfarin.

4.6 Pregnancy and lactation

Pregnancy

Nebivolol has pharmacological effects that may cause harmful effects on pregnancy and/or the foetus/new-born. 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, $beta_1$-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 new-born infant must be closely monitored. Symptoms of hypoglycaemia 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 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.

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 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.

4.8 Undesirable 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 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,		syncope	

	paraesthesia			
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	dyspnoea	Bronchospasm		
Gastrointestinal disorders	constipation, nausea, diarrhoea	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, Reynaud 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.

4.9 Overdose

***Symptoms*:** Symptoms of over dosage with beta-blockers are: bradycardia, hypotension, Bronchospasm and acute cardiac insufficiency.

***Treatment*:** In case of over dosage 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 methyl atropine. Hypotension and shock should be treated with plasma/plasma substitutes and, if necessary, catecholamine. 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Nebivolol is a β-adrenergic receptor blocking agent. In extensive metabolizers (most of the population) and at doses less than or equal to 10 mg, Nebivolol is preferentially β1 selective. In poor metabolizers and at higher doses, Nebivolol inhibits both β1 - and β2 - adrenergic receptors. Nebivolol lacks intrinsic sympathomimetic and membrane stabilizing activity at therapeutically relevant concentrations.

Nebivolol is a third-generation, highly selective beta-1-blocker with vasodilating properties mediated by the endothelial release of nitric oxide (NO). Nebivolol administration decreases peripheral resistance, improves endothelial function, decreases arterial stiffness, reduces preload and after load due to systemic vasodilation, and increases stroke volume, resulting in the preservation of cardiac output despite reduced heart rate. In addition, Nebivolol exhibits anti-proliferative and antioxidant properties. Moreover, studies have shown that Nebivolol use is

associated with a more beneficial metabolic profile compared with atenolol in hypertensive patients with dyslipidaemia.

5.2 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 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 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 faeces. Urinary excretion of unchanged Nebivolol is less than 0.5% of the dose.

5.3 Preclinical safety data

In a two-year study of Nebivolol in mice, a statistically significant increase in the incidence of testicular Leydig cell hyperplasia and adenomas was observed at 40 mg/kg/day (5 times the maximally recommended human dose of 40 mg on an mg/m2 basis). Similar findings were not reported in mice administered doses equal to approximately 0.3 or 1.2 times the maximum recommended human dose. No evidence of a tumorigenic effect was observed in a 24-month study in Wistar rats receiving doses of Nebivolol 2.5, 10 and 40 mg/kg/day (equivalent to 0.6, 2.4, and 10 times the maximally recommended human dose). Co-administration of dihydrotestosterone reduced blood LH levels and prevented the Leydig cell hyperplasia, consistent with an indirect LH-mediated effect of Nebivolol in mice and not thought to be clinically relevant in man.

A randomized, double-blind, placebo- and active-controlled, parallel-group study in healthy male volunteers was conducted to determine the effects of Nebivolol on adrenal function, luteinizing hormone, and testosterone levels. This study demonstrated that 6 weeks of daily dosing with 10 mg of Nebivolol had no significant effect on ACTH-stimulated mean serum cortisol AUC0-120 min, serum LH, or serum total testosterone.

Effects on spermatogenesis were seen in male rats and mice at ≥ 40 mg/kg/day (10 and 5 times the MRHD, respectively). For rats the effects on spermatogenesis were not reversed and may have worsened during a four week recovery period. The effects of Nebivolol on sperm in mice, however, were partially reversible.

Mutagenesis: Nebivolol was not genotoxic when tested in a battery of assays (Ames, *in vitro* mouse lymphoma TK+/-, *in vitro* human peripheral lymphocyte chromosome aberration, *in vivo* Drosophila melanogaster sex-linked recessive lethal, and *in vivo* mouse bone marrow micronucleus tests).

6. PHARMACEUTICAL PARTICULARS

6. Pharmaceutical Particulars

6.1 List of excipients

Lactose Monohydrate, Microcrystalline Cellulose, Betadex (Betacyclodextrin), Croscarmellose Sodium, Dioctyl Sodium Sulpho Succinate, Povidone, Isopropyl Alcohol, Dichloromethane, Betadex, Colloidal Anhydrous Silica, Talc, Magnesium Stearate.

6.2 Incompatibilities

None known

6.3 Shelf life

36 Months from the date of manufacture.

6.4 Special precautions for storage

Store below 30°C. Keep away from reach of children

6.5 Nature and contents of container

Alu/Alu Blister pack of 3 x 10's

6.6 Special precautions for disposal and other handling

Not applicable

7. Marketing Authorization Holder:

MICRO LABS LIMITED
92, SIPCOT,
HOSUR-635 126
INDIA

8. Marketing Authorization Numbers

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9. Date of first authorization

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10. Date of revision of the text

Dec 2017