

## **SUMMARY OF PRODUCT CHARACTERISTICS**

### **1. NAME OF THE MEDICINAL PRODUCT**

Nebilong 5

### **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each uncoated tablet contains:

Nebivolol Hydrochloride equivalent to Nebivolol .....5mg

*Excipient with known effect:* each tablet contains 60.440 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

### **3. PHARMACEUTICAL FORM**

Tablet

White, flat, circular, beveled uncoated tablets with breakline on one surface.

Breakline is to facilitate breaking for ease of swallowing and not for dividing into equal doses.

### **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  $\geq 70$  years.

#### **4.2 Posology and method of administration**

## **Posology**

### *Hypertension – Adults*

The dose is one tablet (5 mg) 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 5 mg 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 contra-indicated.

### *Older people*

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.

### *Paediatric population*

The efficacy and safety of Nebivolol in children and adolescents aged below 18 years has not been established. No data are available. 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 drug therapy including diuretics and/or digoxin and/or ACE inhibitors and/or angiotensin II antagonists, dosing of these drugs should be stabilised 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.

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 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 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 oedema, 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.

#### *Patients with renal insufficiency (CHF)*

No dose adjustment is required in mild to moderate renal insufficiency since up-titration to the maximum tolerated dose is individually adjusted. There is no experience in patients with severe renal insufficiency (serum creatinine  $\geq 250$   $\mu\text{mol/L}$ ). Therefore, the use of nebivolol in these patients is not recommended.

#### *Patients with hepatic insufficiency (CHF)*

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

### *Older people (CHF)*

No dose adjustment is required since up-titration to the maximum tolerated dose is individually adjusted.

### *Paediatric population (CHF)*

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 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 < 90 mmHg).
  - Severe peripheral circulatory disturbances.

## **4.4 Special warnings and precautions for use**

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 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.

## Lactose

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

### 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  $\beta$ -blocker treatment may lead to profound hypotension and atrio-ventricular block.
- **Centrally-acting antihypertensives** (clonidine, guanfacin, moxonidine, methyl dopa, rilmenidine): concomitant use may worsen heart failure by a

decrease in the central sympathetic tonus (reduction of heart rate and cardiac output, vasodilation).

- **Class III antiarrhythmic drugs** (Amiodarone): effect on atrio-ventricular conduction time may be potentiated.
- **Anaesthetics – volatile halogenated:** concomitant use 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, amifostine:** 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 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.
  - **Sympathomimetic agents:** concomitant use may counteract the effect of beta-adrenergic antagonists.

### **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, 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.

### **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**



The following terminologies have been used in order to classify the occurrence of undesirable effects:

Very common ( $\geq 1/10$ ); Common ( $\geq 1/100$  to  $< 1/10$ ); Uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); Rare ( $\geq 1/10,000$  to  $< 1/1,000$ ); Very rare ( $\leq 1/10,000$ ); Not known (cannot be estimated from the available data)

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 cases of mild to moderate intensity, are tabulated below:

| SYSTEM ORGAN CLASS       | Common                            | Uncommon                                                  | Very rare | Not known                              |
|--------------------------|-----------------------------------|-----------------------------------------------------------|-----------|----------------------------------------|
| Immune system disorders  |                                   |                                                           |           | Angioneurotic oedema, 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)                                |           |                                        |

| SYSTEM ORGAN CLASS                                   | Common                          | Uncommon                        | Very rare            | Not known |
|------------------------------------------------------|---------------------------------|---------------------------------|----------------------|-----------|
|                                                      |                                 | 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 | urticaria |
| 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, Raynaud phenomenon, dry eyes, and oculo-mucocutaneous toxicity of the practolol-type. Beta-blockers may cause decreased lacrimation.

### **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.

#### **Reporting of suspected adverse reactions:**

Healthcare professionals are asked to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS): <https://pv.pharmacyboardkenya.org/>

#### **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**

Pharmacotherapeutic group: Beta blocking agent, selective. ATC code: C07AB12

Nebivolol is a  $\beta$ -adrenergic receptor blocking agent. In extensive metabolizers (most of the population) and at doses less than or equal to 10 mg, Nebivolol is preferentially  $\beta_1$  selective. In poor metabolizers and at higher doses, Nebivolol inhibits both  $\beta_1$ - and  $\beta_2$ -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 afterload 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/m<sup>2</sup> 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 AUC<sub>0-120</sub> min, serum LH, or serum total testosterone.

Effects on spermatogenesis were seen in male rats and mice at  $\geq 40$  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<sup>+</sup>/-, 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**

### **6.1 List of excipients**

Lactose, Microcrystalline cellulose, Betadex, Cross carmellose sodium, Dioctyl sodium sulpho succinate, Povidone, Colloidal silicon dioxide, Talc, Magnesium stearate

### **6.2 Incompatibilities**

None known

### **6.3 Shelf life**

24 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 Pack of 10 Tablets

**6.6 Special precautions for disposal and other handling**

No special requirements

**7. MARKETING AUTHORIZATION HOLDER**

MICRO LABS LIMITED  
31, Race Course Road  
Bangalore-560001  
INDIA

**8. MARKETING AUTHORIZATION NUMBERS**

H2009/20324/349

**9. DATE OF FIRST AUTHORIZATION**

06/08/2009

**10. DATE OF REVISION OF THE TEXT**

28/05/2026