# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. NAME OF THE MEDICINAL PRODUCT

Nebivolol and Amlodipine

NEBILONG AM

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each uncoated bilayered tablet contains:

Nebivolol Hydrochloride equivalent to Nebivolol 5mg

Amlodipine Besilate BP equivalent to Amlodipine 5mg

Excipient(s) with known effect: 60.190 mg of lactose monohydrate/tablet

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTIAL FORM

Tablets

White and Yellow coloured, circular, flat, bevel edged uncoated, bilayered tablets with breakline on one surface

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

## 4. CLINICAL PARTICULAR

### 4.1 Indication:

It is indicated for the treatment of mild to moderate essential hypertension

### 4.2 Posology and method of Administration:

The recommended dosage is one tablet of Nebilong –AM once daily. In elderly patients and in patients with renal insufficiency, the recommended starting dose is half tablet of Nebilong – AM once daily, which may be increased to one tablet once daily.

*Adolescents and children*

Since there are no studies on Nebivolol in adolescents and children, this combination is not recommended in these populations.

***Method of administration***

Oral use

Tablets may be taken with meals

**4.3 Contraindication:**

***Nebivolol***

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

***Amlodipine***

Amlodipine is contraindicated in patients with known sensitivity to amlodipine.

**4.4 Warning and Precaution:**

***Nebivolol***

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. For the posology and method of administration please refer to section 4.2. Treatment discontinuation should not be done abruptly unless clearly indicated.

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

***Amlodipine***

***Hypotension***

Symptomatic hypotension is possible, particularly in patients with severe aortic stenosis. Because of the gradual onset of action, acute hypotension is unlikely.

***Use in patients with Heart Failure:*** In a long-term, placebo controlled study (PRAISE-2) of Amlodipine in patients with NYHA III and IV heart failure of nonischaemic aetiology, Amlodipine was associated with increased reports of pulmonary oedema despite no significant difference in the incidence of worsening heart failure as compared to placebo.

***Use in patients with impaired hepatic function:*** As with all calcium antagonists, Amlodipine half-life is prolonged in patients with impaired liver function and dosage recommendations have not been established. The drug should therefore be administered with caution in these patients.

**4.5 Interaction with other medicinal product and other forms of interactions:**

***Nebivolol***

*Pharmacodynamic interactions:*

The following interactions apply to beta-adrenergic antagonists in general.

***Combinations not recommended:***

*Class I antiarrhythmics (quinidine, hydroquindine, 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 antihypertensive (clonidine, guanfacine, 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, vasodilatation).

*Combinations to be used with caution*

*Class III antiarrhythmics drugs (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.

*Insulin and oral Antidiabetic drugs:* 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 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 Dihydropyridines 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 (tricyclic, 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. Beta-adrenergic agents may lead to unopposed alpha-adrenergic activity of sympathomimetic 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.

***Amlodipine***

**Impact of Other Drugs on Amlodipine**

*CYP3A Inhibitors*

Co-administration with CYP3A inhibitors (moderate and strong) results in increased systemic exposure to amlodipine and may require dose reduction. Monitor for symptoms of hypotension and edema when amlodipine is co-administered with CYP3A inhibitors to determine the need for dose adjustment.

*CYP3A Inducers*

No information is available on the quantitative effects of CYP3A inducers on amlodipine. Blood pressure should be closely monitored when amlodipine is co-administered with CYP3A inducers.

*Sildenafil*

Monitor for hypotension when sildenafil is co-administered with amlodipine

***Impact of Amlodipine on Other Drugs***

*Simvastatin*

Co-administration of simvastatin with amlodipine increases the systemic exposure of simvastatin. Limit the dose of simvastatin in patients on amlodipine to 20 mg daily.

*Immunosuppressants*

Amlodipine may increase the systemic exposure of cyclosporine or tacrolimus when co-administered. Frequent monitoring of trough blood levels of cyclosporine and tacrolimus is recommended and adjust the dose when appropriate

**4.6 Pregnancy and Lactation:**

***Nebivolol***

***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 new-born 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.

***Amlodipine***

***Pregnancy***

The limited available data based on post-marketing reports with Amlodipine use in pregnant women are not sufficient to inform a drug-associated risk for major birth defects and miscarriage. There are risks to the mother and fetus associated with poorly controlled hypertension in pregnancy

***Lactation***

Limited available data from a published clinical lactation study reports that amlodipine is present in human milk at an estimated median relative infant dose of 4.2%. No adverse effects of amlodipine on the breastfed infant have been observed. There is no available information on the effects of amlodipine on milk production.

**4.7 Effect on the ability to drive and use machines:**

When driving vehicles or operating machines it should be taken into account that dizziness and fatigue may occasionally occur.

Amlodipine can have minor or moderate influence on the ability to drive and use machines. If patients taking Amlodipine suffer from dizziness, headache, fatigue or nausea the ability to react may be impaired.

**4.8 Undesirable effects:**

***Undesirable effects***

***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:

| 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, paraesthesia | | syncope | |
| Eye disorders | | impaired vision | | |
| Cardiac disorders | | bradycardia, heart failure, slowed AV conduction/AV-block | | |
| Vascular disorders | | hypotension, (increase of) intermittent claudication | | |

| | | | | |
|---|---|---|---|---|
| Respiratory, thoracic and mediastinal disorders | 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.

***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.

***Amlodipine***

The following events occurred in <1% but >0.1% of patients in controlled clinical trials or under conditions of open trials or marketing experience where a causal relationship is uncertain; they are listed to alert the physician to a possible relationship:

**Cardiovascular:** arrhythmia (including ventricular tachycardia and atrial fibrillation), bradycardia, chest pain, peripheral ischemia, syncope, tachycardia, vasculitic.

**Central and Peripheral Nervous System:** hypoesthesia, neuropathy peripheral, paresthesia, tremor, vertigo.

**Gastrointestinal:** anorexia, constipation, dysphagia, diarrhea, flatulence, pancreatitis, vomiting, gingival hyperplasia.

**General:** allergic reaction, asthenia, back pain, hot flushes, malaise, pain, rigors, weight gain, weight decrease.

**Musculoskeletal System:** arthralgia, arthrosis, muscle cramps, myalgia.

**Psychiatric:** sexual dysfunction (male and female), insomnia, nervousness, depression, abnormal dreams, anxiety, depersonalization.

**Respiratory System:** dyspnea, epistaxis.

**Skin and Appendages:** angioedema, erythema multiforme, pruritus, rash, rash erythematous, rash maculopapular.

**Special Senses:** abnormal vision, conjunctivitis, diplopia, eye pain, tinnitus.

**Urinary System:** micturition frequency, micturition disorder, nocturia.

**Autonomic Nervous System:** dry mouth, sweating increased.

**Metabolic and Nutritional:** hyperglycemia, thirst.

**Haemapoietic:** leukopenia, purpura, thrombocytopenia.

**4.9 Overdosage:**

***Nebivolol***

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's. 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.

***Amlodipine***

Over dosage might be expected to cause excessive peripheral vasodilation with marked hypotension and possibly a reflex tachycardia. In humans, experience with intentional over dosage of Amlodipine is limited.

Single oral doses of amlodipine maleate equivalent to 40 mg amlodipine/kg and 100 mg amlodipine/kg in mice and rats, respectively, caused deaths. Single oral amlodipine maleate doses equivalent to 4 or more mg amlodipine/kg or higher in dogs (11 or more times the maximum recommended human dose on a mg/m2 basis) caused a marked peripheral vasodilation and hypotension.

If massive overdose should occur, initiate active cardiac and respiratory monitoring. Frequent blood pressure measurements are essential. Should hypotension occur, provide cardiovascular support including elevation of the extremities and the judicious administration of fluids. If hypotension remains unresponsive to these conservative measures, consider administration of vasopressors (such as phenylephrine) with attention to circulating volume and urine output. As Amlodipine is highly protein bound, hemodialysis is not likely to be of benefit.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamics:

***Nebivolol***

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 vasodilatation, 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.

***Amlodipine***

Amlodipine is a calcium ion influx inhibitor of the dihydropyridines group (slow channel blocker or calcium ion antagonist) and inhibits the transmembrane influx of calcium ions into cardiac and vascular smooth muscle.

The mechanism of the antihypertensive action of Amlodipine is due to a direct relaxant effect on vascular smooth muscle.

Amlodipine dilates peripheral arterioles and thus, reduces the total peripheral resistance (after load) against which the heart works. Since the heart rate remains stable, this unloading of the heart reduces myocardial energy consumption and oxygen requirements.

The mechanism of action of Amlodipine also probably involves dilatation of the main coronary arteries and coronary arterioles, both in normal and ischemic regions. This dilatation increases myocardial oxygen delivery in patients with coronary artery spasm (Prinzmetal's or variant angina).

**5.2 Pharmacokinetic Properties:**

***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, glucuronide 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 metabolizers and is virtually complete in slow metabolizers. At steady state and at the same dose level, the peak plasma concentration of unchanged Nebivolol is about 23 times higher in poor metabolizers than in extensive metabolizers. When unchanged drug plus active metabolites are considered, the difference in peak plasma concentrations is 1.3 to 1.4 fold. Because of the variation in rates of metabolism, the dose of Nebivolol 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-enantiomers are slightly higher than for the SRRR-enantiomers. In slow metabolizers, this difference is larger. In fast metabolizers, elimination half-lives of the hydroxymetabolites of both 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 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.

***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 are 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.

**5.3 Preclinical safety data**
Preclinical data reveal no special hazard for humans of a combination of Nebivolol.
*Reproductive toxicology*
Reproductive studies in rats and mice have shown delayed date of delivery, prolonged duration of labour and decreased pup survival at dosages approximately 50 times greater than the maximum recommended dosage for humans based on mg/kg.

*Impairment of fertility*
There was no effect on the fertility of rats treated with amlodipine (males for 64 days and females 14 days prior to mating) at doses up to 10 mg/kg/day (8 times* the maximum recommended human dose of 10 mg on a mg/m2 basis). In another rat study in which male rats were treated with amlodipine Besilate for 30 days at a dose comparable with the human dose based on mg/kg, decreased plasma follicle-stimulating hormone and testosterone were found as well as decreases in sperm density and in the number of mature spermatids and Sertoli cells.

*Carcinogenesis, mutagenesis*

Rats and mice treated with amlodipine in the diet for two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 mg/kg/day showed no evidence of carcinogenicity. The highest dose (for mice, similar to, and for rats twice* the maximum recommended clinical dose of 10 mg on a mg/m2 basis) was close to the maximum tolerated dose for mice but not for rats.

Mutagenicity studies revealed no drug related effects at either the gene or chromosome levels.

## 6. PHARMACEUTICAL PARTICULARS:

### 6.1 List of Excipients:

Lactose

Microcrystalline cellulose

Betadex (Betacyclodextrin)

Cross carmellose (Primellose)

Lake of Quinoline Yellow

Dioctyl Sodium sulphate succinate

Povidone (PVP)

Crosscarmellose sodium

Colloidal silicon dioxide

Talc

Magnesium Stearate

### 6.2 Incompatibilities:

No major incompatibilities are known.

### 6.3 Shelf Life:

24 months from the date of manufacturing

### 6.4 Special Storage Conditions:

Keep in a cool and dry place. Keep out of reach of children.

### 6.5 Nature and Contents of container:

Alu/Alu blister pack of 10 tablets

### 6.6 Special Precautions for disposal and other handlings:

Not applicable.

**7. Marketing Authorization Holder:**

MICRO LABS LIMITED
31, race course road
Bangalore-560001
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 2020