Summary of Product Characteristics for Pharmaceutical Products

1. Name of the Medicinal Product

Nebivas-5 mg Tablet

2. Qualitative And Quantitative Composition

Each uncoated tablet contains 5 mg of Nebivolol (as hydrochloride)

Excipients with potential clinical effect:

Each tablet contains 4.955 mg of lactose monohydrate

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

Uncoated Tablet.

A white color circular shape biconvexed uncoated tablet, scored in the middle on one side and plain on other side of the 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

Posology

Hypertension

Adults

The dose is 5 mg (one 5 mg tablet) 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 Nebivas 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 Nebivas 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 Nebivas tablets 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 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 stabilised during the past two weeks prior to initiation of Nebivas 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 Nebivas, to be increased to 2.5 mg Nebivas once daily, then to 5 mg once daily and then to 10 mg once daily.
The maximum recommended dose is 10 mg Nebivas 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 Nebivas, 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 Nebivas is generally a long-term treatment.
The treatment with Nebivas 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
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 ≥
250µmol/L). Therefore, the use of Nebivas in these patients is not recommended.

Patients with hepatic insufficiency
Data in patients with hepatic insufficiency are limited. Therefore, the use of Nebivas Tablets in these patients is contra-indicated.
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 Nebivas tablets 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 listed in section 6.1.
• 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, Nebivas 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

See also 4.8 Undesirable effects.
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 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 alphareceptor mediated coronary artery vasoconstriction: beta-adrenergic antagonists may increase the number and duration of anginal attacks.
Combination of Nebivas 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, for details please refer to section 4.5.
Metabolic/Endocrinological
Nebivas does not affect glucose levels in diabetic patients. Care should be taken in diabetic patients however, as Nebivas may mask certain symptoms of hypoglycaemia (tachycardia, palpitations). Beta-blockers could further increase the risk of severe hypoglycaemia when used concurrently with sulfonylureas. Diabetic patients should be advised to carefully monitor blood glucose levels. (see Section 4.5).
Beta-adrenergic blocking agents may mask tachycardic symptoms in hyperthyroidism. Abrupt withdrawal may intensify symptoms.
Respiratory
In patients with chronic obstructive pulmonary disorders, beta-adrenergic antagonists should be used with caution as airway constriction may be aggravated.
Other
Patients with a history of psoriasis should take beta-adrenergic antagonists only after careful consideration.
Beta-adrenergic antagonists may increase the sensitivity to allergens and the severity of anaphylactic reactions.
The initiation of Chronic Heart Failure treatment with Nebivas 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. For further information please refer to section 4.2.

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

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 (see section 4.4).

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 (see section 4.4).

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) (see section 4.4).

Abrupt withdrawal, particularly if prior to beta-blocker discontinuation, may increase risk of “rebound hypertension”.

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 (see section 4.4). As a general rule, avoid sudden withdrawal of beta-blocker treatment. The anaesthesiologist should be informed when the patient is receiving Nebivas Tablets.

Insulin and oral antidiabetic drugs: although Nebivas does not affect glucose level, concomitant use may mask certain symptoms of hypoglycaemia (palpitations, tachycardia). The concomitant use of beta-blockers with sulfonylureas could increase the risk of severe hypoglycaemia. (see Section 4.4).

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 Nebivas have not shown any clinical

evidence of an interaction. Nebivas 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 Nebivas.
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 Nebivas 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 Nebivas associated with an increased risk of excessive bradycardia and adverse events.
Co-administration of cimetidine increased the plasma levels of Nebivas, without changing the clinical effect. Co-administration of ranitidine did not affect the pharmacokinetics of Nebivas. Provided Nebivas is taken with the meal, and an antacid between meals, the two treatments can be co-prescribed.
Combining Nebivas 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 Nebivas. Nebivas does not affect the pharmacokinetics and pharmacodynamics of warfarin.

4.6 Fertility, pregnancy and lactation

Pregnancy
Nebivas has pharmacological effects that may cause harmful effects on pregnancy and/or the foetus/newborn. In general, beta-adrenoceptor blockers reduce placental perfusion, which has been associated with growth retardation, intrauterine death, abortion or early labour. Adverse effects (e.g. 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.
Nebivas should not be used during pregnancy unless clearly necessary. If treatment with Nebivas 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.

Breast-feeding

Animal studies have shown that Nebivas is excreted in breast milk. It is not known whether this drug is excreted in human milk. Most beta-blockers, particularly lipophilic compounds like Nebivas and its active metabolites, pass into breast milk although to a variable extent. A risk to the newborns/infants cannot be excluded. Therefore, breastfeeding is not recommended during administration of Nebivas.

Fertility

Nebivas had no effect on rat fertility except at doses several fold higher than the human maximum recommended dose when adverse effects on male and female reproductive organs in rats and mice were observed. The effect of Nebivas on human fertility is unknown

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 Nebivas 5 mg tablets do 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, 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 Nebivas and 1061 patients taking placebo. In this study, a total of 449 Nebivas 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 Nebivas 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 Nebivas patients compared to 5.2% of placebo patients.

• Postural hypotension was reported in 2.1% of Nebivas patients compared to 1.0% of placebo patients.

• Drug intolerance occurred in 1.6% of Nebivas patients compared to 0.8% of placebo patients.

• First degree atrio-ventricular block occurred in 1.4% of Nebivas patients compared to 0.9% of placebo patients.

• Oedema of the lower limb were reported by 1.0% of Nebivas patients compared to 0.2% of placebo patients.

<u>Description of selected adverse reactions</u>

Thyrotoxicosis
β-blockers may mask clinical signs of hyperthyroidism such as tachycardia. Abrupt withdrawal of β-blockers may be followed by exacerbation of the symptoms of hyperthyroidism or may precipitate a thyroid storm.
Peripheral Vascular Disease
β-blockers can precipitate or aggravate symptoms of arterial insufficiency in patients with peripheral vascular disease.
Non-dihydropyridine Calcium Channel Blockers
Because of significant negative inotropic and chronotropic effects in patients treated with β-blockers and calcium channel blockers of the verapamil and diltiazem type, monitor ECG and blood pressure in patients treated concomitantly with these agents.
Use of CYP2D6 Inhibitors
Nebivolol exposure increases with inhibition of CYP2D6. The dose of Nebivas 5 may need to be reduced.
Renal impairment
Renal clearance of nebivolol is decreased in patients with severe renal impairment. Nebivas 5 has not been studied in patients receiving dialysis.
Hepatic impairment
Metabolism of nebivolol is decreased in patients with moderate hepatic impairment. BYSTOLIC has not been studied in patients with severe hepatic impairment.
Risk of Anaphylactic Reactions
While taking β-blockers, patients with a history of severe anaphylactic reactions to a variety of allergens may be more reactive to repeated accidental, diagnostic or therapeutic challenge. Such patients may be unresponsive to the usual dose of epinephrine used to treat allergic reactions.
Pheochromocytoma
In patients with known or suspected pheochromocytoma, initiate an α-blocker prior to the use of any β-blocker.
Bronchospastic Diseases
In general, patients with bronchospastic diseases should not receive β-blockers.
Pediatric population
Safety and effectiveness in pediatric patients have not been established. Pediatric studies in ages newborn to 18 years old have not been conducted because of incomplete characterization of developmental toxicity and possible adverse effects on long-term fertility.

Other special population(s)
Labor and Delivery
Nebivolol caused prolonged gestation and dystocia at doses ≥5mg/kg in rats (1.2 times the MRHD). These effects were associated with increased

fetal deaths and stillborn pups, and decreased birth weight, live litter size and pup survival rate, events that occurred only when nebivolol was given during the perinatal period (late gestation, parturition and lactation). No studies of nebivolol were conducted in pregnant women. Use nevivas-5 during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing mothers

Studies in rats have shown that nebivolol or its metabolites cross the placental barrier and are excreted in breast milk. Is it not known whether this drug is excreted in human milk. Because of potential for β-blockers to produce serious adverse reactions in nursing infants, especially bradycardia, Nebivas-5 is not recommended during nursing.

Geriatric

Use of the 2800 patients in the U.S. sponsored placebo-controlled clinical hypertension studies, 478 patients were 65 years of age or older. No overall differences in efficacy or in the incidence of adverse events were observed between older and younger patients.

Heart Failure

In a placebo-controlled trial of 2128 patients (1067 Nebivas 5, 1061 placebo) over 70 years of age with chronic heart failure receiving a maximum dose of 10mg per day for a median of 20months, no worsening of heart failure was reported with nebivolol compared to placebo. However, if heart failure worsens consider discontinuation of Nebivas 5.

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. 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

No data are available on overdosage with Nebivas Tablets.

Symptoms

Symptoms of overdosage with beta-blockers are: bradycardia, hypotension, bronchospasm and acute cardiac insufficiency.

Treatment

In case of overdosage or hypersensitivity, the patient should be kept under close supervision and be treated in an intensive care ward. Blood glucose levels should be checked. Absorption of any 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 methylatropine. Hypotension and shock should be treated with plasma/plasma substitutes and, if necessary, catecholamines. The beta-blocking effect can be counteracted by slow intravenous administration of

isoprenaline hydrochloride, starting with a dose of approximately 5 µg/minute, or dobutamine, starting with a dose of 2.5 µg/minute, until the required effect has been obtained. In refractory cases isoprenaline can be combined with
dopamine. If this does not produce the desired effect either, intravenous administration of glucagon 50-100 µg/kg 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

Mechanism of action

The mechanism of action of the antihypertensive response of Nebivas 5 has not been definitively established. Possible factors that may be involved include:

• Decreased heart rate,
• Decreased myocardial contractility,
• Diminution of tonic sympathetic outflow to the periphery from cerebral vasomotor centers,
• Suppression of renin activity, and
• Vasodilation and decreased peripheral vascular resistance.

Pharmacodynamics effects

Nebivas is a racemate of two enantiomers, SRRR-Nebivas (or d-Nebivas) and RSSS-Nebivas (or l-Nebivas). It combines two pharmacological activities:

• It is a competitive and selective beta-receptor antagonist: this effect is attributed to the SRRR-enatiomer (d-enantiomer).
• It has mild vasodilating properties due to an interaction with the L-arginine/nitric oxide pathway.

Single and repeated doses of Nebivas 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, Nebivas is devoid of alpha-adrenergic antagonism.

During acute and chronic treatment with Nebivas 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 haemodynamic differences as compared to other beta1 receptor antagonists has not been fully established.

In hypertensive patients, Nebivas increases the NO-mediated vascular response to acetylcholine (ACh) which is reduced in patients with endothelial dysfunction.

In a mortality–morbidity, placebo-controlled trial performed in 2128 patients ≥ 70 years (median age 75.2 years) with stable chronic heart failure with or without impaired left ventricular ejection fraction (mean LVEF: 36 ± 12.3%,
with the following distribution: LVEF less than 35% in 56% of patients, LVEF between 35% and 45% in 25% of patients and LVEF greater than 45% in 19% of patients) followed for a mean time of 20 months, Nebivas, on top of standard therapy, significantly prolonged the time to occurrence of deaths or hospitalisations for cardiovascular reasons (primary end-point for efficacy) with a relative risk reduction of 14% (absolute reduction: 4.2%). This risk reduction developed after 6 months of treatment and was maintained for all treatment duration (median duration: 18 months). The effect of Nebivas was independent from age, gender, or left ventricular ejection fraction of the population on study. The benefit on all-cause mortality did not reach statistical significance in comparison to placebo (absolute reduction: 2.3%).
A decrease in sudden death was observed in Nebivas treated patients (4.1% vs 6.6%, relative reduction of 38%).
In vitro and in vivo experiments in animals showed that Nebivas has no intrinsic sympathicomimetic activity.
In vitro and in vivo experiments in animals showed that at pharmacological doses Nebivas has no membrane stabilising action.
In healthy volunteers, Nebivas has no significant effect on maximal exercise capacity or endurance.
Available preclinical and clinical evidence in hypertensive patients has not shown that Nebivas has a detrimental effect on erectile function.

<u>Clinical efficacy and Safety</u>
The antihypertensive effectiveness of Nebivas-5 as monotherapy has been demonstrated in three randomized, double blind, multi-Centre, placebo-controlled trials at doses ranging from 1.25mg to 40mg for 12 weeks (Studies 1, 2, and 3). A fourth placebo-controlled trial demonstrated additional antihypertensive effects of Nebivas-10 at doses ranging from 5 to 20mg when administered concomitantly with up to two other antihypertensive agents (ACE Inhibitors, angiotensin II receptor anatagonists and thiazide diuretics) in patients with inadequate blood pressure control.
The three, monotherapy trials included a total of 1016 patients (1811 Nebivas 5, 205 placebo) with mild to moderate hypertension who had baseline diastolic blood pressure (DBP) of 95 to 109mmHg. Patients received either Nebivas or placebo once daily for 12weeks. Two of these monotherapy trials (Studies 1 and 2) studied 1716 patients in the general hypertensive population with a mean age of 54 years, 55% males, 26% non-Caucasians, 7% diabetics and 6% genotyped as PMs. The third monotherapy trial (study 3) studied 300 black patients with a mean age of 51 years, 45% males, 14% diabetics and 3% as PMs.

Placebo-subtracted blood pressure reductions by dose for each study are presented in the table below. Most studies showed increasing response to doses above 5mg
Placebo-Subtracted Least-Square Mean Reductions in Trough Sitting Systolic/ Diastolic Blood Pressure (SiSBP/ SiDBP mmHg) by dose in studies with once daily Nebivas.

	Nebivolol dose (mg)					
	1.25	2.5	5.0	10	20	30-40
Study 1	-6.6*/-5.1*	-8.5*/-5.6*	-8.1*/-5.5*	-9.2*/-6.3*	-8.7*/-6.9*	-11.7*/-8.3*
Study 2			-3.8/-3.2*	-3.1/-3.9*	-6.3*/-4.5*	
Study 3		-1.5/-2.9	-2.6/-4.9*	-6.0*/-6.1*	-7.2*/-6.1*	-6.8*/-5.5*
Study 4			-5.7*/-3.3*	-3.7*/-3.5*	-6.2*/-4.6*	

*p<0.05 based on pair-wise comparison vs placebo
Study enrolled only African-Americans.
^Study on top of one or two other antihypertensive medications.

Study 4 enrolled 669 patients with a mean age of 54 years, 55% males, 54% Caucasians, 29% Blacks, 15% Hispanics, 1% Asians, 14% diabetics and 5% PMs. Nebivas 5mg to 20mg administered once daily concomitantly with stable doses of up to two other antihypertensive agents (ACE inhibitors, angiotensin II receptor antagonists and thiazide diuretics) resulted in significant additional antihypertensive effects over placebo compared to baseline blood pressure.
Effectiveness was similar in subgroups analyzed by age and sex. Effectiveness was established in blacks, but as monotherapy the magnitude of effect was somewhat less than in Caucasians.
The blood pressure lowering effect of Nebivas-5 was seen within 2 weeks of treatment and was maintained over the 24-hour dosing interval.
There are no trials of Nebivas-5 demonstrating reductions in cardiovascular risk in patients with hypertension, but at least one pharmacologically similar drug demonstrated such benefits.
Nebivas-10 has been evaluated for safety in patients with hypertension and in patients with heart failure. The observed adverse reaction profile was consistent with the pharmacology of the drug and the health status of the patients in the clinical trials. Adverse reactions reported for each of these patient populations are provided below. Excluded are adverse reactions considered too general to be informative and those not reasonably associated with the use of the drug because they were

associated with the condition being treated or are very common in the treated population.

The data described below reflects worldwide clinical trial exposure to Nebivas-5 in 6545 patients including 5038 patients treated for hypertension and the remaining 1507 subjects treated for other cardiovascular diseases. Doses ranged from 0.5mg to 40mg. patients received Nebivas-5 for up to 24months, with over 1900 patients treated for at least 6months and approximately1300 patients for more than one year.

HYPERTENSION: In placebo-controlled clinical trials comparing Nebivas-10 with placebo, discontinuation of therapy due to adverse reactions was reported in 2.8% of patients treated with Nebivolol and 2.2.% of patients given placebo. The most common adverse reactions that led to discontinuation of Nebivas-5 were headache (0.4%), nausea (0.2%) and bradycardia (0.2%).

Treatment-emergent adverse reactions that were reported in three 12-week, placebo-controlled monotherapy trials involving 1597 hypertensive patients treated with either 5mg, 10mg or 20-40mg of Nebivas-5 and 205 patients given placebo and for which the rate of occurrence was at least 1% of patients related with nebivolol and greater than the rate for those treated with placebo in at least one dose group.

Treatment-Emergent Adverse Reactions with an incidence (over 6 weeks) ≥1% in Nebivas-5 treated patients and at a higher frequency than placebo-treated patients.

System Organ Class – Preferred term	Placebo (n=205) (%)	NEBIVAS 5mg (n=459) (%)	Nebivolol 10mg (n=461) (%)	Nebivolol 20 - 40mg (n=677) (%)
Cardiac Disorders				
Bradycardia	0	0	0	1
Gastrointestinal Disorders				
Diarrhoea	2	2	2	3
Nausea	0	1	3	2

General Disorders				
Fatigue	1	2	2	5
Chest pain	0	0	1	1
Peripheral edema	0	1	1	1
Nervous System Disorders				
Headache	6	9	6	7
Dizziness	2	2	3	4
Psychiatric Disorders				
Insomnia	0	1	1	1
Respiratory Disorders				

5.2 Pharmacokinetic properties

Nebivolol is a beta blocker. It is a prodrug and it works by affecting the response to nerve impulses in certain parts of the body, like the heart. As a result, the heart beats slower and decreases the blood pressure. When the blood pressure is lowered, the amount of blood and oxygen is increased to the heart. Solubility analysis as performed in distilled water, pure nebivolol hydrochloride showed 0.792 mg/mL concentration at 72h (RT 25°C) with continuous stirring.

Absorption

Absorption of Nebivas is similar to an oral solution. The absolute bioavailability has not been determined. Mean peak plasma nebivolol concentrations occur approximately 1.5- 4 hours post-dosing in Ems and PMs. Food does not alter the pharmacokinetics of nebivolol. Under fed

conditions, nebivolol glucuronides are slightly reduced. Nebivas maybe administered without regard to meals.

Distribution

The in-vitro human plasma protein binding of nebivolol is approximately 98%, mostly to albumin and is independent of nebivolol concentrations.

Biotransformation

Nebivolol is predominantly metabolized via direct glucuronidation of parent and to a lesser extent via N-dealkylation and oxidation via cytochrome P450 2D6. Its stereospecific metabolites contribute to the pharmacologic activity.

Elimination

After a single oral administration of 14C-Nebivolol, 38 % of the dose was recovered in urine and 44% in feces for Ems and 67% in urine and 13% in feces for PMs. Essentially, all nebivolol was excreted as multiple oxidative metabolites or their corresponding glucuronide conjugates.

Linearity/ non-linearity

The linearity for nebivolol hydrochloride was in the range of 0.2-10µg/mL. the recovery was found to be in the range of 98.68- 100.86%. the detection limit and quantification limit were found to be 0.06 µg/mL and 0.2µg/mL, respectively. The degraded product peaks were well-resolved from the pure drug peak with significant difference in their retention time values.

Characteristics in specific groups of subjects or patients

Gender

Nebivolol is a cardio selective lipophilic beta-blocker devoid of intrinsic sympathomimetic and membrane-stabilizing actions. The pharmacological profile differs from that of conventional cardio-selective beta-blockers in that it displays nitric oxide mediated vasodilator activity.

Elderly

In patients over 65 years, the recommended starting dose is 2.5mg daily. If needed, the daily dose may be increased to 5mg. However, in view of the limited experience in patients above 75years, caution must be exercised and these patients monitored closely in hypertension.

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

Hepatic impairment

d-Nebivolol peak plasma concentration increased 3-fold, exposure (AUC) increased 10-fold and the apparent clearance decreased by 86% in patients with moderate hepatic impairment (Child-pugh Class B). no formal studies have been performed in patients with severe hepatic impairment and nebivolol should be contraindicated for these patients.

Renal impairment

The apparent clearance of nebivolol was unchanged following a single 5mg dose of Nebivas-10 in patients with mild renal impairment (CrCL 50-

80 mL/min, n=7), and it was reduced negligibly in patients with moderate (CrCL 30-50 mL/min, n=9), but clearance was reduced by 53% in patients with severe renal impairment (CrCL 30 mL/min, n=5). No studies have been conducted in patients on dialysis.

Ethnic Group

Limited data suggest that race does not have any major influence on Nebivolol pharmacokinetics.

Pharmacokinetic/ Pharmacodynamic Relationship

The pharmacokinetic features of nebivolol vary according to the phenotype of the metabolizer. After a 15 mg dose, peak plasma concentrations were reached at 0.5- 2 hours in extensive metabolizers and in 3-6 hours in poor metabolizers. Absorption of nebivolol is very similar to that of an oral solution. The vasodilation, reduced oxidative stress and reduced platelet volume and aggregation of nebivolol may lead to benefits in heart failure patients. The absorption of nebivolol is not affected by food. Nebivolol has a T_{max} of 1.5-4 hours. Bioavailability can range from 12-96% for extensive to poor CYP2D6 metabolizers.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of genotoxicity, reproductive and developmental toxicity and carcinogenic potential.

Adverse effects on the reproductive function were only recorded at high doses, exceeding by several fold the maximum recommended human dose (see Section 4.6).

6. Pharmaceutical Particulars

6.1 List of excipients

Microcrystalline cellulose
Povidone K30
Purified Talc
Silica, colloidal anhydrous
Lactose monohydrate
Magnesium stearate
Maize starch

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

Commercial Presentation: 30's.

3x10's Alu-Alu Blister:

Each Alu-Alu blister is packed with 10 tablets in an opaque Alu-Alu blister pack.

3 such Alu-Alu blisters are packed in printed carton; 200 such cartons are packed in corrugated box.

6.6 Special precautions for disposal

No special requirements.

7. Marketing authorization holder

M/s. Innocia Lifesciences Pvt. Ltd.
Block A, No.12, Balaji nagar, Ambattur, Chennai – 53,
Tamilnadu, India.

8. Marketing authorization number(s)

H2021/CTD6570/2061ER

9. Date of first authorization/renewal of the authorization

2021 September 10

10. Date of revision of the text

2021 September 10