Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:

Cilneb 10/2.5 (Cilnidipine 10mg & Nebivolol 2.5mg Tablets)

2. Qualitative and quantitative composition

Each film coated tablet contains:
Cilnidipine 10mg
Nebivolol Hydrochloride equivalent to Nebivolol 2.5mg

For full list of excipients, see section 6.1

3. Pharmaceutical form

Film coated tablet.
An orange color circular shape biconvexed film coated tablet, plain on both the sides.

4. Clinical particulars

4.1 Therapeutic indications

CILNEB is used in the treatment of essential hypertension that occurs when you have abnormally high blood pressure. Cilnidipine is a Calcium channel blocker and Nebivolol is a Beta blocker. It helps to reduce high blood pressure, where nebivolol works by reducing the force of contraction of the heart muscles by the blocking the effects of certain hormones called adrenaline and making the heart to beat more easily thus it lowers the blood pressure and Cilnidipine works by decreases the blood pressure by relaxing the blood vessels and enhances easy flow of blood to the heart muscles.

4.2 Posology and method of administration

Posology
Hypertension
Adults
The recommended dose is one tablet per day, 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.

- Cilnidipine: The recommended adult oral dosage of Cilnidipine is 5-20 mg once daily. The dosage can be increased up to 20 mg, depending on the individual patient's response. Dose titration should be gradual, and because it may take about 2 weeks before the maximal antihypertensive effect is apparent.
- Nebivolol: The dose is 2.5mg/5mg daily, preferably at the same time of the day. Nebivolol 2.5mg and 5mg tablets are also available on the market.

Elderly patients:
Although the pharmacokinetic data and clinical experience suggest that no adjustment of the daily dosage is required, special care should be exercised when initiating treatment in the elderly.
Paediatric population:
CILNEB is not suitable for children.
Patients with renal or hepatic impairment:

Special care should be exercised when treatment is commenced in patients with mild to moderate renal or hepatic dysfunction. Although the usually recommended dose schedule may be tolerated by these subgroups, an increase in dose to 20mg/5mg daily must be approached with caution. The antihypertensive effect may be enhanced in patients with hepatic impairment and consequently an adjustment of the dosage should be considered.
Cilnidipine -20mg is contraindicated in patients with severe hepatic impairment or in patients with severe renal impairment (GFR < 30 ml/min), including patients undergoing dialysis.
Method of administration
Oral use
The tablet should be swallowed with a sufficient amount of fluid (e.g one glass of water). The tablet can be taken with or without food.

4.3 Contraindications

- Contraindicated in patients with known hypersensitivity (e.g., anaphylaxis or angioedema) 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, Cilneb 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

Nebivolol Hydrochloride
The following warnings and precautions apply to beta-adrenergic antagonists, such as nebivolol, 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 coronary 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 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 nebivolol necessitates regular monitoring. For the posology and method of administration. Treatment discontinuation should not be done abruptly unless clearly indicated.
This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.
Cilnidipine
Cardiovascular Disorders: Cilnidipine should be used with caution in patients with hypotension, heart failure, and poor cardiac reserve. Cilnidipine should be discontinued immediately in patients who feel chest pain following the administration of the drug.
Abrupt Cessation of Therapy: In case of angina, cilnidipine should not be discontinued abruptly to avoid withdrawal symptoms.
Grapefruit Juice: Grapefruit juice may intensify the effect of cilnidipine. Thus, avoid drinking grapefruit juice as much as possible while on cilnidipine therapy.
Laboratory Test: Cilnidipine therapy may interfere with the results of vanillyl mandelic acid test which is used to detect tumors such as pheochromocytoma and neuroblastoma.
Therefore, cilnidipine should be avoided for 72 hours before sample collection, but the patient should be monitored intensively in a clinical setting.
Liver dysfunction or elevated liver enzymes
Peripheral edema (confounding physical findings in congestive failure)
Pregnancy – There are no human clinical or animal data concerning the safety of Cilnidipine during pregnancy & therefore use during pregnancy should be avoided.

4.5 Interaction with other medicinal products and other forms of interaction

Nebivolol Hydrochloride

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 atrioventricular conduction. Intravenous administration of verapamil in patients with ß-blocker treatment may lead to profound hypotension and atrio-ventricular block.

Centrally-acting antihypertensives (clonidine, guanfacin, moxonidine, methyldopa, rilmenidine): concomitant use of centrally acting antihypertensive drugs may worsen heart failure by a decrease in the central sympathetic tonus (reduction of heart rate and cardiac output, vasodilation). 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. As a general rule, avoid sudden withdrawal of beta-blocker treatment. The anaesthesiologist should be informed when the patient is receiving Nebivolol Tablets.

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

Baclofen (antispastic agent), amifostine (antineoplastic adjunct): concomitant use with antihypertensives is likely to increase the fall in blood pressure, therefore the dosage of antihypertensive medication should be adjusted accordingly.

Mefloquine (antimalarian drug): Theoretically co-administration with β-adrenergic blocking agents might contribute to a prolongation of the QTc interval.

Combinations to be considered:

Digitalis glycosides: concomitant use may increase atrio-ventricular conduction time. Clinical trials with nebivolol have not shown any clinical evidence of an interaction. Nebivolol does not influence the kinetics of digoxin.

Calcium antagonists of the dihydropyridine type (amlodipine, felodipine, lacidipine, nifedipine, nicardipine, nimodipine, nitrendipine): concomitant use may increase the risk of hypotension, and an increase in the risk of a further deterioration of the ventricular pump function in patients with heart failure cannot be excluded.

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

Non steroidal anti-inflammatory drugs (NSAID): No effect on the blood pressure lowering effect of nebivolol. Sympathicomimetic agents: concomitant use may counteract the effect of betaadrenergic antagonists. Beta-adrenergic agents may lead to unopposed alpha-adrenergic activity of sympathicomimetic agents with both alpha- and beta-adrenergic effects (risk of hypertension, severe bradycardia and heart block).

Pharmacokinetic interactions

As nebivolol metabolism involves the CYP2D6 isoenzyme, co-administration with substances inhibiting this enzyme, especially paroxetine, fluoxetine 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.
Cilnidipine
Antipsychotic Drugs:
Co-administration of antipsychotic drugs with cilnidipine may result in low blood pressure. Thus, caution should be exercised while concomitant use of these drugs with cilnidipine.
Antidiabetic Drugs:
Co-administration of cilnidipine with antidiabetic drugs may result in changes in glucose levels, thus, monitoring of blood glucose levels may be required.
Other Drugs:
Antiepileptic drugs (such as phenytoin and carbamazepine), rifampin, quinidine, erythromycin, other antihypertensive drugs, and aldesleukin should also be used with caution along with cilnidipine.

4.6 Pregnancy and Lactation

Pregnancy
Nebivolol has pharmacological effects that may cause harmful effects on pregnancy and/or the fetus/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 fetus and newborn infant. If treatment with betaadrenoceptor blockers is necessary, beta 1 -selective adrenoceptor blockers are preferable.
Nebivolol tablets should not be used during pregnancy unless clearly necessary. If treatment with nebivolol is considered necessary, the uteroplacental blood flow and the fetal growth should be monitored. In case of harmful effects on pregnancy or the fetus 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 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.
Fertility
There is limited human data on the effect of nebivolol on fertility. No preclinical data are available.
Cilnidipine
Pregnancy
There are no human clinical or animal data concerning the safety of cilnidipine during pregnancy. Until data are available, administration of cilnidipine during pregnancy should be avoided.
Lactation
Nursing mothers should consult a physician before taking Cilnidipine.

4.7 Effects on ability to drive and use machines

CILNEB oral tablet may cause tiredness. Avoid driving or using heavy machinery until you know how this drug affects you.

4.8 Undesirable effects

a. Summary of the safety profile Nebivolol Hydrochloride

The distinct pharmacologic profile of nebivolol is associated with a number of hemodynamically relevant effects: (1) β_1-blockade, which decreases resting and exercise heart rate, myocardial contractility, and both systolic and diastolic blood pressure; (2) NO-mediated vasodilation that results in a decrease in peripheral vascular resistance, an increase in stroke volume and ejection fraction, and maintenance of cardiac output; (3) vasodilation and reduced oxidative stress that are thought to contribute to the neutral and possibly beneficial effects of nebivolol on glucose and lipid metabolism; and (4) reduced platelet volume and aggregation. These attributes suggest a potentially broad usefulness for nebivolol in the treatment of hypertension and chronic heart failure.

Cilnidipine

Cilnidipine was found to be safe and effective in reducing microalbuminuria and blood pressure in Indian mild-to-moderate hypertensive patients with type 2 diabetes mellitus. In this study, Cilnidipine caused a significant reduction in the mean (SD) SBP from 150.07 (5.44) mm Hg at baseline to 123.03 (5.23) mm Hg after six months. Cilnidipine also produced a significant reduction in the microalbuminuria from 66.62 (8.39) mg/L to 38.8 (6.45) mg/L after six months. In another large-scale prospective post-marketing surveillance study of post-stroke hypertensive patients (n = 2667, male 60.4%, 69.0 ± 10.9 years) who were treated with Cilnidipine, the blood pressure control with Cilnidipine treatment was very good.

b. Tabulated summary of adverse reactions Nebivolol Hydrochloride

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

< Very common (≥ 1/10)>, < Common (≥ 1/100 to <1/10)>, < Uncommon (≥1/1,000 to <1/100)>, < Rare (≥1/10,000 to <1/1,000)>, <Very rare (≤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.

<u>Hypertension</u>

The adverse reactions reported, which are in most cases of mild to moderate intensity, are tabulated below, classified by system organ class and ordered by frequency:

SYSTEM ORGAN CLASS	COMMON	UNCOMMON	VERY RARE	NOT KNOWN
Immune system disorders				Angioneurotic oedema and hypersensitivity
Psychiatric disorders		nightmares, depression		
Nervous system	headache,		syncope	

disorders	dizziness, paraesthesia			
Eye disorders		impaired vision		
Cardiac disorders		bradycardia, heart failure, slowed AV conduction/ AV block		
Vascular disorders		hypotension, (increase of) Intermittent claudication		
Respiratory, thoracic and mediastinal disorders	dyspnoea	bronchospasm		
Gastrointestinal Disorders	constipation, nausea, diarrhoea	dyspepsia, flatulence, vomiting		
Skin and subcutaneous tissue disorders		pruritus, rash erythematous	Psoriasis aggravated	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
Reported 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 reported 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.

Cilnidipine:

In the table below, adverse reactions reported in clinical trials and in the worldwide post-marketing experience for which a reasonable causal relationship exists are listed by MedDRA system organ class and frequency: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, the observed adverse reactions are presented in order of decreasing seriousness.

MedDRA System Organ Class	Common	Uncommon	Rare	Not known
Immune system disorders			Hypersensitivity	
Nervous system disorders	Headache	Dizziness	Somnolence Syncope	
Cardiac disorders	Tachycardia Palpitations		Angina pectoris	
Vascular disorders	Flushing	Hypotension		
Gastrointestinal disorders		Dyspepsia Nausea Abdominal pain	Vomiting Diarrhoea	Gingival hypertrophy[1]

				Peritoneal cloudy
		upper		effluent [1]
Hepatobiliary disorders				Serum transaminase increased [1]
Skin and subcutaneous tissue disorders		Rash Pruritus	Urticaria	Angioedema [1]
Musculoskeletal and connective tissue disorders		Myalgia		
Renal and urinary disorders		Polyuria	Pollakiuria	
General disorders and administration site conditions	Oedema peripheral	Asthenia Fatigue	Chest pain	

[1]adverse reactions from spontaneous reporting in the worldwide post-marketing experience

C. Description of selected adverse reactions Nebivolol Hydrochloride

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 Nebivolol Hydrochloride, 1061 placebo) over 70 years of age with chronic heart failure receiving a maximum dose of 10 mg per day for a median of 20 months, no worsening of heart failure was reported with nebivolol compared to placebo. However, if heart failure worsens consider discontinuation of Nebivolol Hydrochloride.

Labor and Delivery

Nebivolol caused prolonged gestation and dystocia at doses ≥ 5 mg/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 Nebivolol Hydrochloride during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Cilnidipine

Renal impairment

Dose adjustment is not needed in patients with impaired renal function. Cilnidipine at a dose of 10 mg once a day for 7 days in patients with impaired renal function caused no differences in the

pharmacokinetic profile compared with that in patients with normal renal function.

Hepatic impairment

Dosage recommendations have not been established in patients with mild to moderate hepatic impairment; therefore dose selection should be cautious and should start at the lower end of the dosing range. Transient and generally clinically insignificant elevations in SGOT, SGPT, alkaline phosphatase, and serum bilirubin have been reported during calcium antagonist therapy in less than 1% of patients. d. Paediatric population

Nebivolol is not recommended for use in children and adolescents below 18 years of age due to lack of data on safety and efficacy.

e. Other special population(s) Cilnidipine:

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 coronary 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.

Respiratory

In patients with chronic obstructive pulmonary disorders, beta-adrenergic antagonists should be used with caution as airway constriction may be aggravated.

Cilnidipine

Cilnidipine may cause following adverse reactions:

General:

Edema (facec, limb, etc.), Facial flush, thickening of gums, heat sensation, lethargy, generalized fatigue, frequent urination, impotence, liver dysfunction, jaundice, thrombocytopenia (nose/gum bleeding), allergic reaction, etc.,

Gastrointestinal:

Nausea, Vomiting, anorexia, stomach ache, gastrointestinal reflux disease (GERD).

Eye:

Transient blindness, eye pain.

Musculoskeletal:
Muscle ache, tremors.
Cardiovascular System:
Hypotension, Palpitations, ischemic chest pain.
Central Nervous System:
Dizziness, headache, depression, cerebral ischemia.
Dermatological:
Rashes, itching, photosensitivity.

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

No data are available on overdosage with nebivolol.

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 betablocking 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 50100 µg/kg intravenous may be considered. If required, the injection should be repeated within one hour, to be followed -if required- by an intravenous infusion of glucagon 70 µg/kg/h. In extreme cases of treatment-resistant bradycardia, a pacemaker may be inserted.

Cilnidipine

In humans, experience with cilnidipine overdose is limited. Overdose symptoms include confusion, dizziness, headache, fatigue, and sedation. If overdose occurs, it might cause excessive peripheral vasodilation with marked hypotension. If 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 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.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Nebivolol Hydrochloride

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

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

During acute and chronic treatment with nebivolol in hypertensive patients systemic vascular resistance is decreased. Despite heart rate reduction, reduction in cardiac output during rest and exercise may be limited due to an increase in stroke volume. The clinical relevance of these haemodynamic differences as compared to other beta 1 receptor antagonists has not been fully established.

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

In 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, nebivolol, 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 reduct ion developed after 6 months of treatment and was maintained for all treatment duration (median duration: 18 months). The effect of nebivolol was independent from age, gender, or left ventricular ejection fraction of the population on reported 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 nebivolol treated patients (4.1 % vs 6.6%, relative reduction of 38%).

In vitro and in vivo experiments in animals showed that Nebivolol has no intrinsic sympathicomimetic activity.

In vitro and in vivo experiments in animals showed that at pharmacological doses nebivolol has no membrane stabilising action.

In healthy volunteers, nebivolol has no significant effect on maximal exercise capacity or endurance.

Cilnidipine

Cilnidipine is a third generation dihydropyridine calcium antagonist with a slow onset and long duration of action. Calcium antagonists inhibit influx of extracellular calcium ions into the cells, resulting in decreased vascular smooth muscle tone and vasodilation, leading to a reduction in blood pressure.

In vitro and animal studies suggest that cilnidipine blocks both the L and N type calcium channels. Cilnidipine inhibits the pressor to cold stress by suppressing sympathetic nerve activity in spontaneously hypertensive rats. It does not induce tachycardia caused by hypotensive baroreflexes. In vitro, cilnidipine inhibits norepinephrine release in electrically stimulated rabbit mesenteric arteries.

In human studies, cilnidipine had weak inotropic effects and suppressed cardiac sympathetic overactivity. Therefore it may decrease the risk and mortality from long term cardiovascular complications. Once-daily cilnidipine was associated with less reflex tachycardia and had fewer effect on the autonomic nervous system in hypertensive patients. In contrast to other long acting calcium channel blockers, cilnidipine and amlodipine did not increase plasma renin activity, thus they may decrease the risk of cardiovascular complications due to metabolic imbalances. Cilnidipine may inhibit norepinephrine and dopamine production, therby improving insulin resistance in patients with diabetes. It also had beneficial effects on lipid profiles in hypertensive patients by decreasing total cholesterol, triglyceride, and very low density lipoprotein cholesterol level, and increasing high density lipoprotein cholesterol and the ratio of high density lipoprotein cholesterol to total cholesterol.

Clinical Efficay and Safety:

Cilnidipine:

Antihypertensive effect:

The antihypertensive effects of Cilnidipine have been demonstrated in a number of hypertensive disease models including; spontaneously hypertensive rats, renal hypertensive rats and dogs, DOCA salt hypertensive rats, and spontaneously hypertensive rats with stroke. The antihypertensive effects of Cilnidipine were slow in onset, long lasting, and increased in a dose-dependent manner from 1mg/kg. The antihypertensive effect on normotensive rats was weak. Increased doing did not prolong blood pressure lowering effects of Cilnidipine. The blood pressure lowering effect of Cilnidipine is additive when combined with β-blockers, Angiotensin Converting Enzyme inhibitors, and Angiotensin II Receptor Blockers in renal hypertensive dogs.Rebound hypertension was not observed upon withdrawal of treatment with Cilnidipine. Cilnidipine did not increase heart rate whilst lowering blood pressure after single dose tests in rats without spontaneous/unconstrained hypertension spontaneous syndrome. In subjects with essential hypertension, Cilnidipine once daily by oral route, produced an antihypertensive effect lasting for 24 hours. Analysis of heartbeat frequency (RR interval) fluctuation over 24 hours showed no sympathetic nervous activity accompanying Cilnidipine associated blood pressure reduction and no increase in heart rate.

Inhibitory effect of pressurization by sympathetic nerve electrical stimulation:

Cilnidipine suppressed blood pressure increases due to sympathetic stimulation in spontaneously hypertensive rats. Suppression of noradrenaline during sympathetic stimulation was suppressed in mesenteric arterial vascular perfusion specimens isolated from spontaneously hypertensive rats.

Effect on cerebral circulation:

Cilnidipine did not reduce the cerebral blood flow even at doses showing a 30 to 40% reduction in blood pressure in spontaneously hypertensive rats.In hypertensive patients with complications or cerebrovascular disease, cerebral blood flow was maintained despite reduction of blood pressure with Cilnidipine.

Effect on cardiac function:

At doses, greater than usually employed for reducing blood pressure, Cilnidipine decreased heart rate and myocardial contraction force in dogs. Cilnidipine lowered myocardial oxygen consumption at antihypertensive doses in dogs but did not increase heart rate or suppress cardiac contractile force. In patients with essential hypertension, Cilnidipine did not affect pulse rate during blood pressure reduction and improves Cardiac Thoracic Ratio (CTR) in subjects with CTR abnormality.

Effect on kidney:

Cilnidipine increased urine volume, the rate of renal blood flow and glomerular filtration rate at doses which reduce blood pressure in anesthetized spontaneously hypertensive rats. Furthermore, urine volume, the rate of renal blood flow and glomerular filtration rate were increased even when renal function was reduced with administration of endothelin. In patients with essential hypertension, Cilnidipine did worsen kidney function.

Effects on cardiovascular disorders associated with hypertension:

Cilnidipine, administered orally once a day in rats with spontaneously stroke prone hypertension, delayed onset of cerebral hemorrhage and stroke, improved survival rate. Cilnidipine was also associated with a reduction in cardiac hypertrophy (increase in heart weight), thickening of the left ventricle wall, myocardium fibrosis, and improved pathology in the kidney. Furthermore, Cilnidipine inhibited thickening of coronary artery media and reduced the calcium content of the aorta. In patients with essential hypertension, Cilnidipine reduces arteriosclerosis index and serum lipid peroxidation.

Nebivolol:

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

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

5.2 Pharmacokinetic properties

Cilnidipine:

Absorption:

After oral administration of cilnidipine, absorption is very rapid with peak plasma concentration reached after 2 hours.

Distribution:

Distribution of cilnidipine tends to be higher in the liver as well as in kidneys, plasma, and other tissues. Cilnidipine has a large volume of

distribution. Plasma protein binding of cilnidipine is very high i.e., 98% of the administered dose.

Metabolism:

Cilnidipine is metabolized by both liver and kidney. It is rapidly metabolized by liver microsomes by a dehydrogenation process. The major enzymatic isoform involved in cilnidipine dehydrogenation of the dihydropyridine ring is CYP3A.

Excretion:

Approximately 20% of the administered dose of cilnidipine gets eliminated through the urine, with the remainder (about 80%) being eliminated in feces.

Linearity/Non-Linearity

Oral administration of Cilnidpine leads to plasma levels of Cilnidipine not directly proportional to dosage (non-linear kinetics). After 5, 10 or 20 mg, peak plasma concentrations observed were in the ratio 1:3:8 and areas under plasma concentration-time curves in the ratio 1:4:18, suggesting a progressive saturation of first pass metabolism. Accordingly, availability increases with dosage elevation.

Nebivolol Hydrochloride

Absorption

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.

Distribution

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.

Metabolism

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 2.5 mg, Nebivolol 5 mg or Nebivolol 10 mg tablets 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 SRRR-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.
Excretion
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.
Linearity/Non-Linearity
Cilnidipine was linear with the concentration range of 1-5µg/ml. The linearity for nebivolol hydrochloride was in the range of 0.2-10 µg/ml.

5.3 Preclinical safety data

Nebivolol Hydrochloride
Preclinical data reveal no special hazard for humans based on conventional studies of genotoxicity and carcinogenic potential.
Cilnidipine
No data available.

6. Pharmaceutical Particulars

6.1 List of Excipients

Microcrystalline Cellulose
Maize Starch
Povidone K30
Croscarmellose Sodium
Colloidal Anhydrous Silica
Magnesium Stearate
Hypromellose E15
Putified Talc
Titanium Dioxide
Sunset Yellow

6.2 Incompatibilities

Not Applicable

6.3 Shelf-Life

24 months

6.4 Special Precautions for storage

Store below 30°C. Protect from light & moisture.

6.5 Nature and Content of container

Commercial Presentation: 4's, 10's, 20's, 30's & 100's

3 x 10's (10 tablets are packed in one Alu-Alu blister and 3 Alu-Alu blisters are kept in one carton along with package insert).

6.6 Special precautions for disposal and other handling
No special requirements

7. Marketing Authorization Holder
INNOCIA LIFESCIENCES PVT. LTD
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Country: India
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8. Marketing Authorization Number
CTD9699

9. Date of first authorization/renewal of the authorization
08/11/2023

10. Date of revision of the text
5/16/2025