Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:

NEBIDAY 5 (Nebivolol Tablets 5 mg)

2. Qualitative and quantitative composition

Each uncoated tablet contains nebivolol hydrochloride equivalent to 5 mg of nebivolol.
Excipient with known effect: this medicinal product contains lactose.
For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Uncoated tablet.
A white coloured, round shaped, biconvex uncoated tablet, plain on both sides. No score line is present; the tablet cannot be divided into equal doses.

4. Clinical particulars

4.1 Therapeutic indications

Hypertension

Treatment of essential hypertension.

Chronic heart failure (CHF)

Treatment of stable mild and moderate chronic heart failure, in addition to standard therapies, in elderly patients aged ≥ 70 years.

4.2 Posology and method of administration

Posology – hypertension

Adults: The dose is 5 mg (one tablet) daily, preferably at the same time each 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 may be used alone or concomitantly with other antihypertensive agents. To date, an additional antihypertensive effect has been observed only when nebivolol is combined with hydrochlorothiazide 12.5–25 mg.
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. The use of nebivolol 2.5 mg or 5 mg tablets in these patients is therefore contraindicated.
Elderly: 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. In view of the limited experience in patients above 75 years, caution must be exercised and these patients monitored closely.
Paediatric population: nebivolol is not recommended for use in children and adolescents below 18 years of age due to a lack of data on safety and efficacy.

Posology – chronic heart failure

Treatment of stable chronic heart failure must be initiated with gradual up-titration of the dose until the optimal individual maintenance dose is reached. Patients should have stable chronic heart failure without acute failure during the preceding six weeks. It is recommended that the treating physician be experienced in the management of chronic heart failure.

For patients receiving cardiovascular therapy including diuretics and/or digoxin and/or ACE inhibitors and/or angiotensin II antagonists, dosing of these medicinal products should have been stabilised during the two weeks prior to initiation of treatment.

Initial up-titration should be carried out at 1–2 weekly intervals based on patient tolerability: 1.25 mg nebivolol, increased to 2.5 mg once daily, then to 5 mg once daily and then to 10 mg once daily. The maximum recommended dose is 10 mg nebivolol once daily.

Initiation of therapy and every dose increase should be carried out under the supervision of an experienced physician over a period of at least 2 hours, to ensure that the clinical status (particularly blood pressure, heart rate, conduction disturbances and signs of worsening heart failure) remains stable.

Occurrence of adverse events may prevent all patients from being treated with the maximum recommended dose. If necessary, the dose reached may be decreased step by step and reintroduced as appropriate.

During the titration phase, in case of worsening heart failure or intolerance, it is recommended first to reduce the dose of nebivolol, or to stop it immediately if necessary (in cases of severe hypotension, worsening of heart failure with acute pulmonary oedema, cardiogenic shock, symptomatic bradycardia or AV block).

Treatment of stable chronic heart failure with nebivolol is generally long-term. Treatment should not be stopped abruptly, as this might lead to 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 ≥ 250 µmol/L); use in these patients is not recommended.

Patients with hepatic insufficiency: data are limited. The use of nebivolol 2.5 mg or 5 mg tablets in these patients is contraindicated.

Elderly: no dose adjustment is required, since up-titration to the maximum tolerated dose is individually adjusted.

Paediatric population: nebivolol is not recommended for use in children and adolescents below 18 years of age.

Method of administration

For oral use. The tablet should be swallowed with a sufficient amount of fluid (e.g. one glass of water). The tablet may be taken with or without food.

4.3 Contraindications

Nebivolol is contraindicated in the following:

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

4.4 Special warnings and precautions for use

The following warnings and precautions apply to beta-adrenergic antagonists, 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 unless their condition has been stabilised. In patients with coronary heart disease, treatment 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 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; and in patients with Prinzmetal's angina, due to unopposed alpha-receptor mediated coronary artery vasoconstriction, as 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 medicinal products, and with centrally acting antihypertensive medicinal products is generally not recommended; for details refer to section 4.5.

Metabolic / endocrinological

Nebivolol does not affect glucose levels in diabetic patients. Care should nevertheless be taken in diabetic patients, 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 sensitivity to allergens and the severity of anaphylactic reactions. Beta-blockers may rarely cause decreased lacrimation.

The initiation of chronic heart failure treatment with nebivolol necessitates regular monitoring. For posology and method of administration refer to section 4.2. Treatment discontinuation should not be done abruptly unless clearly indicated.

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

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions

Combinations not recommended:

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

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

Centrally acting antihypertensives (clonidine, guanfacine, moxonidine, methyldopa, rilmenidine): concomitant use may worsen heart failure by decreasing central sympathetic tone (reduction of heart rate and cardiac output, vasodilation). Abrupt withdrawal, particularly prior to beta-blocker discontinuation, may increase the risk of rebound hypertension.

Combinations to be used with caution:

Class III antiarrhythmics (amiodarone): the effect on atrio-ventricular conduction time may be potentiated.

Volatile halogenated anaesthetics: concomitant use may attenuate reflex tachycardia and increase the risk of hypotension. As a general rule, sudden withdrawal of beta-blocker treatment should be avoided. The anaesthetist should be informed when the patient is receiving nebivolol tablets.

Insulin and oral antidiabetic medicinal products: although nebivolol does not affect glucose levels, concomitant use may mask certain symptoms of hypoglycaemia (palpitations, tachycardia).
Baclofen (antispastic agent) and amifostine (antineoplastic adjunct): concomitant use with antihypertensives is likely to increase the fall in blood pressure; the dosage of antihypertensive medication should be adjusted accordingly.
Mefloquine: theoretically, co-administration with beta-adrenergic blocking agents might contribute to 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, and 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 further deterioration of ventricular pump function in patients with heart failure cannot be excluded.
Antipsychotics, antidepressants and sedatives (phenothiazines, tricyclics and barbiturates), organic nitrates and other antihypertensive agents: concomitant use may enhance the hypotensive effect of the beta-blocker (additive effect).
Non-steroidal anti-inflammatory medicinal products (NSAIDs): 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 a meal and an antacid between meals, the two treatments can be co-prescribed.
Combining nebivolol with nicardipine slightly increased the plasma levels of both medicinal products, 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 or pharmacodynamics of warfarin.

4.6 Pregnancy and Lactation

Pregnancy

Nebivolol 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.
Nebivolol tablets should not be used during pregnancy unless clearly necessary. If treatment is considered necessary, uteroplacental blood flow and 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 nebivolol is excreted in breast milk. It is not known whether nebivolol is excreted in human milk. Most beta-blockers, particularly lipophilic compounds such as nebivolol and its active metabolites, pass into breast milk, although to a variable extent. Breast-feeding is therefore not recommended during administration of nebivolol.

Fertility

[Not addressed in the submitted document. To be completed by the applicant.]

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Pharmacodynamic studies have shown that nebivolol does not affect psychomotor function. Some patients may experience adverse effects (see section 4.8) which are mostly due to the reduction in blood pressure, such as dizziness or fainting. Should these occur, patients should refrain from driving and other activities requiring alertness. These effects are more likely to occur after initiation of treatment or after dose increases.

4.8 Undesirable effects

The following terminology has been used 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 chronic heart failure because of differences in the background diseases.

Hypertension

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

System Organ Class	Common	Uncommon	Very rare	Not known
Immune system disorders				Angioneurotic oedema, hypersensitivity

System Organ Class	Common	Uncommon	Very rare	Not known
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. Beta-blockers may cause decreased lacrimation.

Chronic heart failure

Data on adverse reactions in patients with chronic heart failure are available from one placebo-controlled clinical trial involving 1,067 patients taking nebivolol and 1,061 patients taking placebo. In this study, a total of 449 nebivolol patients (42.1%) reported at least possibly causally related adverse reactions, compared with 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 medicinal-product related) considered specifically relevant in the treatment of chronic heart failure:

Aggravation of cardiac failure: 5.8% of nebivolol patients versus 5.2% of placebo patients.

Postural hypotension: 2.1% versus 1.0%.

Drug intolerance: 1.6% versus 0.8%.

First degree atrio-ventricular block: 1.4% versus 0.9%.

Oedema of the lower limb: 1.0% versus 0.2%.

Reporting of suspected adverse reactions

Healthcare professionals are asked to report any suspected adverse reactions via the Pharmacy and Poisons Board, Pharmacovigilance Electronic Reporting System (PvERS): https://pv.pharmacyboardkenya.org

4.9 Overdose

No data are available on overdose with nebivolol.

Symptoms

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

Treatment

In case of overdose or hypersensitivity, the patient should be kept under close supervision and treated in an intensive care ward. Blood glucose levels should be checked. Absorption of any medicinal product residues still present in the gastrointestinal 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 or plasma substitutes and, if necessary, catecholamines. The beta-blocking effect can be counteracted by slow intravenous administration of isoprenaline hydrochloride, starting at approximately 5 µg/minute, or dobutamine, starting at 2.5 µg/minute, until the required effect is obtained. In refractory cases isoprenaline may be combined with dopamine. If this does not produce the desired effect, intravenous glucagon 50–100 µg/kg may be considered; if required the injection should be repeated within one hour, followed if necessary by an intravenous 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 agents, selective. ATC code: C07AB12.

Nebivolol is a racemate of two enantiomers, SRRR-nebivolol (d-nebivolol) and RSSS-nebivolol (l-nebivolol). It combines two pharmacological activities: it is a competitive and selective beta-receptor antagonist, an effect attributed to the SRRR-enantiomer; and it has mild vasodilating properties due to an interaction with the L-arginine/nitric oxide pathway.

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 compared with other beta1-receptor antagonists has not been fully established.

In hypertensive patients, nebivolol increases the nitric oxide-mediated vascular response to acetylcholine, which is reduced in patients with endothelial dysfunction.
In a mortality-morbidity, placebo-controlled trial performed in 2,128 patients aged ≥ 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%), followed for a mean of 20 months, nebivolol on top of standard therapy significantly prolonged the time to occurrence of death or hospitalisation for cardiovascular reasons (primary efficacy endpoint), with a relative risk reduction of 14% (absolute reduction 4.2%). This risk reduction developed after 6 months of treatment and was maintained throughout the treatment period (median duration 18 months). The effect was independent of age, gender or left ventricular ejection fraction. The benefit on all-cause mortality did not reach statistical significance compared with placebo (absolute reduction 2.3%). A decrease in sudden death was observed in nebivolol-treated patients (4.1% versus 6.6%; relative reduction 38%).
In vitro and in vivo experiments in animals showed that nebivolol has no intrinsic sympathomimetic activity and, at pharmacological doses, no membrane stabilising action. In healthy volunteers, nebivolol has no significant effect on maximal exercise capacity or endurance.

5.2 Pharmacokinetic properties

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.

Biotransformation

Nebivolol is extensively metabolised, partly to active hydroxy-metabolites, via alicyclic and aromatic hydroxylation, N-dealkylation and glucuronidation; in addition, glucuronides of the hydroxy-metabolites are formed. Metabolism by aromatic hydroxylation is subject to 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 medicinal product plus active metabolites are considered, the difference in peak plasma concentrations is 1.3 to 1.4-fold. Because of this variation in rates of metabolism, the dose should always be adjusted to the individual requirements of the patient: poor metabolisers may therefore require lower doses.
In fast metabolisers, elimination half-lives of the nebivolol enantiomers average 10 hours; in slow metabolisers they are 3–5 times longer. In fast metabolisers, plasma levels of the RSSS-enantiomer are slightly higher

than those of the SRRR-enantiomer, and this difference is larger in slow metabolisers. In fast metabolisers, elimination half-lives of the hydroxy-metabolites 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 are not affected by age.

Elimination

One week after administration, 38% of the dose is excreted in the urine and 48% in the faeces. Urinary excretion of unchanged nebivolol is less than 0.5% of the dose.

5.3 Preclinical safety data

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

6. Pharmaceutical Particulars

6.1 List of Excipients

As per dossier

6.2 Incompatibilities

Not applicable.

6.3 Shelf-Life

3 years.

6.4 Special Precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and Content of container

10 × 1 × 30 tablets in Alu-Alu blister.

6.6 Special precautions for disposal and other handling

No special requirements.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Marketing Authorization Holder

Krishna Chemists Ltd

8. Marketing Authorization Number

[H2025/CTD11407/24026

9. Date of first authorization/renewal of the authorization

2025 May 26

10. Date of revision of the text

2025 May 26