SUMMARY OF PRODUCT CHARACTERISTICS
NEBIGOOD 5 (Nebivolol Hydrochloride Tablets 5 mg)

1. NAME OF THE MEDICINAL PRODUCT

NEBIGOOD 5 (Nebivolol Hydrochloride Tablets 5 mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5 mg nebivolol hydrochloride equivalent to nebivolol.

Excipients with known effect:

Each tablet contains 59.50 mg of lactose monohydrate. For warnings, see section 4.4.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.

White, round, flat, bevelled uncoated tablet with a break-line on one side and plain on the other side.

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

Hypertension — Adults

The dose is 5 mg (one 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. To date, an additional antihypertensive effect has been observed only when nebivolol is combined with hydrochlorothiazide 12.5–25 mg.

Hypertension — Patients with renal insufficiency

The recommended starting dose is 2.5 mg daily. If needed, the daily dose may be increased to 5 mg.

Hypertension — Patients with hepatic insufficiency

Data in patients with hepatic insufficiency or impaired liver function are limited. Therefore, the use of nebivolol in these patients is contraindicated.

Hypertension — 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. However, in view of the limited experience in patients above 75 years, caution must be exercised and these patients monitored closely.

Chronic heart failure (CHF)

The treatment of stable chronic heart failure must be initiated with a gradual uptitration of dosage until the optimal individual maintenance dose is reached. Patients should have stable chronic heart failure without acute failure during the past six weeks. For those patients receiving cardiovascular drug therapy including diuretics and/or digoxin and/or ACE inhibitors and/or angiotensin II antagonists, dosing of these drugs should be stabilised during the past two weeks prior to initiation of nebivolol treatment.

The initial uptitration should be done according to the following steps at 1–2 weekly intervals based on patient tolerability: 1.25 mg nebivolol once daily, increased to 2.5 mg once daily, then to 5 mg once daily, then to 10 mg once daily. The maximum recommended dose is 10 mg nebivolol once daily.

Initiation of therapy and every dose increase should be done under the supervision of an experienced physician over a period of at least 2 hours to ensure clinical stability. Occurrence of adverse events may prevent all patients from being treated at the maximum recommended dose.

Treatment of stable chronic heart failure with nebivolol is generally a long-term treatment. The treatment should not be stopped abruptly as this might lead to a transitory worsening of heart failure. If discontinuation is necessary, the dose should be gradually decreased by halves weekly.

CHF — Patients with renal insufficiency

No dose adjustment is required in mild to moderate renal insufficiency since uptitration to the maximum tolerated dose is individually adjusted. There is no experience in patients with severe renal insufficiency (serum creatinine ≥250 µmol/L). Therefore, the use of nebivolol in these patients is not recommended.

Paediatric population

The efficacy and safety of nebivolol in children and adolescents aged below 18 years has not been established. Therefore, use in children and adolescents is not recommended.

Method of administration

Oral. 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

- 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 starting therapy).
- Hypotension (systolic blood pressure <90 mmHg).
- Severe peripheral circulatory disturbances.

4.4 Special warnings and precautions for use

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 over 1–2 weeks. 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, first-degree heart block, and in patients with Prinzmetal's angina.

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 (see section 4.5).

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. Beta-blockers may rarely cause decreased lacrimation. The initiation of CHF treatment with nebivolol necessitates regular monitoring. Treatment discontinuation should not be done abruptly unless clearly indicated.

Lactose content

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

Combinations not recommended

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

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

Centrally acting antihypertensives (clonidine, guanfacin, moxonidine, methyldopa, rilmenidine): concomitant use may worsen heart failure. Abrupt withdrawal of centrally acting antihypertensives, 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: may attenuate reflex tachycardia and increase risk of hypotension. The anaesthesiologist should be informed when the patient is receiving nebivolol.

Insulin and oral antidiabetic drugs: nebivolol may mask certain symptoms of hypoglycaemia (palpitations, tachycardia).

Baclofen, amifostine: may increase the fall in blood pressure.

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. Nebivolol does not influence the kinetics of digoxin.

Dihydropyridine calcium antagonists (amlodipine, felodipine, nifedipine, etc.): concomitant use may increase risk of hypotension.

Antipsychotics, antidepressants, sedatives, organic nitrates and other antihypertensive agents: concomitant use may enhance the hypotensive effect.

NSAIDs: no effect on the blood pressure lowering effect of nebivolol.

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 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. Nebivolol does not affect the pharmacokinetics and pharmacodynamics of warfarin.

4.6 Fertility, 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. Nebivolol should not be used during pregnancy unless clearly necessary. If treatment with nebivolol is considered necessary, the uteroplacental blood flow and the foetal growth should be monitored. 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 like nebivolol and its active metabolites, pass into breast milk although to a variable extent. A risk to the newborns/infants cannot be excluded. Therefore, mothers receiving nebivolol should not breast-feed.

Fertility

Nebivolol had no effect on rat fertility except at doses several fold higher than the human maximum recommended dose. The effect of nebivolol 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 nebivolol does not affect psychomotor function. Some patients may experience adverse effects which are mostly due to the reduction in blood pressure, such as dizziness or fainting. Should these occur, one 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

Summary of the safety profile

Adverse events are listed separately for hypertension and CHF because of differences in the background diseases.

Hypertension

System Organ Class	Common	Uncommon	Very Rare	Not Known
Immune system disorders				Angioneurotic oedema, hypersensitivity
Psychiatric disorders		Nightmares, depression		
Nervous system disorders	Headache, dizziness, paraesthesia		Syncope	
Eye disorders		Impaired vision		
Cardiac disorders		Bradycardia, heart failure, slowed AV conduction/AV block		
Vascular disorders		Hypotension, increase of intermittent claudication		
Respiratory disorders	Dyspnoea	Bronchospasm		
Gastrointestinal disorders	Constipation, nausea, diarrhoea	Dyspepsia, flatulence, vomiting		
Skin disorders		Pruritus, rash erythematous	Psoriasis aggravated	Urticaria
Reproductive disorders		Impotence		
General disorders	Tiredness, oedema			

Chronic heart failure

Data on adverse reactions in CHF patients are available from one placebo-controlled clinical trial involving 1,067 nebivolol patients and 1,061 placebo patients. The most commonly reported adverse reactions were bradycardia and dizziness, both occurring in approximately 11% of nebivolol patients (vs approximately 2% and 7% in placebo patients, respectively). Aggravation of cardiac failure occurred in 5.8% vs 5.2% (placebo); postural hypotension in 2.1% vs 1.0%; drug intolerance in 1.6% vs 0.8%; first-degree AV block in 1.4% vs 0.9%; and oedema of the lower limb in 1.0% vs 0.2%.

The following adverse reactions have also been reported with some beta-adrenergic antagonists: hallucinations, psychoses, confusion, cold/cyanotic extremities, Raynaud phenomenon, dry eyes, oculo-mucocutaneous toxicity of the practolol-type, and decreased lacrimation.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 the National Regulatory Authority.

4.9 Overdose

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

Treatment: The patient should be kept under close supervision in an intensive care ward. Blood glucose levels should be checked. Absorption of any drug 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/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 at 2.5 µg/minute. In refractory cases isoprenaline can be combined with dopamine. If this does not produce the desired effect, intravenous administration of glucagon 50–100 µg/kg 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Beta-blocking agent, 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 beta1-receptor antagonist (SRRR-enantiomer) and 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, in both normotensive subjects and hypertensive patients.

In a mortality-morbidity, placebo-controlled trial in 2,128 patients ≥70 years (median age 75.2 years) with stable chronic heart failure followed for a mean of 20 months, nebivolol on top of standard therapy significantly prolonged the time to occurrence of deaths or hospitalisations for cardiovascular reasons (primary endpoint) with a relative risk reduction of 14% (absolute reduction: 4.2%). A decrease in sudden death was observed in nebivolol-treated patients (4.1% vs 6.6%, relative reduction of 38%).

5.2 Pharmacokinetic properties

Absorption

Both nebivolol enantiomers are rapidly absorbed after oral administration. The absorption of nebivolol is not affected by food. The oral bioavailability of nebivolol averages 12% in fast metabolisers and is virtually complete in slow metabolisers. Nebivolol is extensively metabolised, partly to active hydroxy-metabolites, via CYP2D6-dependent aromatic hydroxylation.

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.

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. In fast metabolisers, elimination half-lives of the nebivolol enantiomers average 10 hours; in slow metabolisers they are 3–5 times longer. 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.

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The following excipients are present in the tablet:

No.	Ingredient
1	Maize starch
2	Lactose monohydrate (excipient with known effect)
3	Microcrystalline cellulose
4	Povidone (K 30)
5	Purified water
6	Purified talc
7	Magnesium stearate
8	Colloidal anhydrous silica
9	Croscarmellose sodium

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions. Store below 30°C. Protect from light and moisture. Keep out of the reach and sight of children.

6.5 Nature and contents of container

10 tablets packed in one ALU-PVC blister; 3 such blisters packed in one carton with package insert. Pack size: 30 tablets.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

ZAIN PHARMA LTD.

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P.O. Box: 100167-00101, Nairobi, Kenya.

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