SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Nebimel 5 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains nebivolol hydrochloride equivalent to 5 mg of nebivolol.

Excipient with known effect: 167.05 mg lactose monohydrate/tablet (see section 4.4 and 6.1).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

White, round, cross-scored tablet.

The tablet can be divided in equal quarter 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 ≥ 70 years.

4.2 Posology and method of administration

1. When used for the indication hypertension:

Adults
The dose is one tablet (5 mg) daily, preferably at the same time of the day. Tablets may be taken with meals.

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 nebivolol 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 nebivolol in these patients is contra-indicated (see section 4.3).

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.

Paediatric population
No studies have been conducted in children and adolescents. Therefore, use in children and adolescents is not recommended.

2. When used for the indication chronic heart failure (CHF):

The treatment of stable chronic heart failure has to 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. 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 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, to be increased to 2.5 mg nebivolol 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 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 nebivolol, 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 nebivolol is generally a long-term treatment.

The treatment with nebivolol 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 uptitration to the maximum tolerated dose is individually adjusted. There is no experience in patients with severe renal insufficiency (serum creatinine $\geq$ 250 μmol/L). Therefore, the use of nebivolol in these patients is not recommended.

Patients with hepatic insufficiency
Data in patients with hepatic insufficiency are limited. Therefore the use of nebivolol in these patients is contraindicated (see section 4.3).

Elderly
No dose adjustment is required since uptitration to the maximum tolerated dose is individually adjusted.

Paediatric population
No studies have been conducted in children and adolescents. Therefore, use in children and adolescents is not recommended.

Method of administration:

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 i.v. inotropic therapy.

In addition, as with other beta-blocking agents, nebivolol is contraindicated 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 of therapy)
- hypotension (systolic blood pressure < 90 mmHg)
- severe peripheral circulatory disturbances

4.4 Special warnings and precautions for use

See also section 4.8.

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 alpha-receptor mediated coronary artery vasoconstriction: beta-adrenergic antagonists may increase the number and duration of angina 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, for details please refer to 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.

The initiation of CHF treatment with nebivolol necessitates regular monitoring. For the posology and method of administration, please refer to section 4.2. Treatment discontinuation should not be done abruptly unless clearly indicated. For further information please refer to section 4.2.

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.

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, guanfacine, moxonidine, methyldopa, rilmenidine): concomitant use of centrally acting antihypertensive drugs may worsen heart failure by a decrease in the central sympathetic tonus (reduction of heart rate and cardiac output, 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 nebivolol.

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 the antihypertensive medication should be adjusted accordingly.

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

Calcium antagonists of the 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 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 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 Nebimel 5 mg 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. Nebimel 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. If treatment with beta-adrenoceptor blockers is necessary, $beta_1$-selective adrenoceptor blockers are preferable.

Nebivolol should not be used during pregnancy unless clearly necessary. If treatment with nebivolol is considered necessary, the uteroplacental blood flow and the foetal growth should be monitored. In case of harmful effects on pregnancy or the foetus alternative treatment should be considered. The newborn infant must be closely monitored. Symptoms of hypoglycaemia and bradycardia are generally to be expected within the first 3 days.

Breastfeeding:
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.

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. 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 cased 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 (cannot be estimated from the available data)
Immune system disorders				angioneurotic oedema, hypersensitivity
Psychiatric disorders		nightmares; depression		
Nervous system disorders	headache, dizziness, paraesthesia		syncope	
Eye disorders		impaired vision		
Cardiac disorders		bradycardia, heart failure, slowed AV conduction/AV-block		
Vascular disorders		hypotension, (increase of) intermittent claudication		
Respiratory, thoracic and mediastinal disorders	dyspnoea	bronchospasm		
Gastrointestinal disorders	constipation, nausea, diarrhoea	dyspepsia, flatulence, vomiting		
Skin and subcutaneous tissue disorders		pruritus, rash erythematous	psoriasis aggravated	urticaria
Reproductive system and breast disorders		impotence		
General disorders and administration site conditions	tiredness, oedema			

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

Chronic heart failure:
Data on adverse reactions in CHF patients are available from one placebo-controlled clinical trial involving 1067 patients taking nebivolol and 1061 patients taking placebo. In this study, a total of 449

nebivolol patients (42.1 %) reported at least possibly causally related adverse reactions compared to 334 placebo patients (31.5 %). The most commonly reported adverse reactions in nebivolol patients were bradycardia and dizziness, both occurring in approximately 11 % of patients. The corresponding frequencies among placebo patients were approximately 2 % and 7 %, respectively.

The following incidences were reported for adverse reactions (at least possibly drug-related) which are considered specifically relevant in the treatment of chronic heart failure:
- Aggravation of cardiac failure occurred in 5.8 % of nebivolol patients compared to 5.2 % of placebo patients.
- Postural hypotension was reported in 2.1 % of nebivolol patients compared to 1.0 % of placebo patients.
- Drug intolerance occurred in 1.6 % of nebivolol patients compared to 0.8 % of placebo patients.
- First degree atrio-ventricular block occurred in 1.4% of nebivolol patients compared to 0.9 % of placebo patients.
- Oedema of the lower limb was reported by 1.0 % of nebivolol patients compared to 0.2 % of placebo patients.

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

No data are available on overdosing with nebivolol.

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

Treatment:
In case of overdosing 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 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 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 and pharmacodynamic effects
Nebivolol is a racemate of two enantiomers, SRRR-nebivolol (or d-nebivolol) and RSSS-nebivolol (or l-nebivolol). It combines two pharmacological activities:

- Nebivolol is a competitive and selective beta-receptor antagonist: this effect is attributed to the SRRR-enantiomer (d-enantiomer).
- 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 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.

Clinical efficacy and safety

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 reduction 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 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.

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. 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 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 RSSS-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 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

Povidone K30
Lactose monohydrate
Maize starch, pregelatinised
Croscarmellose sodium
Silica, colloidal anhydrous
Magnesium stearate
Crospovidone

6.2 Incompatibilities

Not applicable

6.3 Shelf life

5 years.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

Tablets are provided in blister (PVC/aluminium blister).

Pack sizes of 7, 10, 14, 28, 30, 50, 56, 84, 98, 100, 500 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Clonmel Healthcare Ltd
Waterford Road
Clonmel
Co. Tipperary

8. MARKETING AUTHORISATION NUMBER(S)

PA0126/165/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16 November 2007

Date of last renewal: 30 November 2009

10. DATE OF REVISION OF THE TEXT

April 2015