

Public Assessment Report

Decentralised Procedure

**NEBIVOLOL 2.5MG TABLETS
NEBIVOLOL 5MG TABLETS**

Procedure No: UK/H/1548/001-2/DC

UK Licence No: PL 25258/0002-3

GLENMARK GENERICS (EUROPE) LIMITED

LAY SUMMARY

The MHRA granted Glenmark Generics (Europe) Limited Marketing Authorisations (licences) for the medicinal products Nebivolol 2.5 and 5mg Tablets on 25th February 2009. These are prescription-only medicines to treat raised blood pressure (hypertension) and also to treat heart failure, in addition to other therapies, in patients aged 70 years or over.

The active ingredient, nebivolol hydrochloride, is in the class of medicines called beta-blockers. It exerts its effect by widening the blood vessels and reducing the work of the heart.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Nebivolol 2.5 and 5mg Tablets outweigh the risks, hence Marketing Authorisations have been granted.

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Module 1

Product Name	Nebivolol 2.5 and 5mg Tablets
Type of Application	Nebivolol 2.5mg Tablets – Article 10.3 (hybrid) Nebivolol 5mg Tablets – Article 10.1 (generic medicinal product)
Active Substance	Nebivolol hydrochloride
Form	Tablets
Strength	2.5 and 5mg
MA Holder	Glenmark Generics (Europe) Ltd, Laxmi House, 2B Draycott Avenue, Kenton, Middlesex, HA3 0BU
Reference Member State (RMS)	UK
CMS	Belgium, Bulgaria, Czech Republic, Germany, Greece, France, Hungary, Italy, the Netherlands, Poland, Romania, Spain, Sweden and Slovak Republic
Procedure Number	UK/H/1548/001-2/DC
Timetable	Day 210 – 1 st February 2009

Module 2

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Nebivolol 2.5mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2.725 mg nebivolol hydrochloride corresponding to 2.5 mg nebivolol

Excipient: 72.5 mg of lactose monohydrate/tablet

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

Capsule shaped, white biconvex uncoated tablets with breakline on one side and plain on the other side

The tablet can be divided into equal halves.

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 of 70 years or older.

4.2 Posology and method of administration

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.

Hypertension

Adults

The dose is 5 mg (two tablets) daily, preferably at the same time of the day.

The blood pressure lowering effect becomes evident after 1-2 weeks of treatment. Occasionally, the optimal effect is reached only after 4 weeks.

Combination with other antihypertensive agents

Beta –Blockers can be used alone or concomitantly with other antihypertensive agents. To date, an additional antihypertensive effect has been observed only when 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 2.5mg Tablets in these patients is contra-indicated.

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.

Children and adolescents

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

Chronic heart failure (CHF)

The treatment of stable chronic heart failure has to be initiated with a gradual up-titration of dosage until the optimal individual maintenance dose is reached.

Patients should have stable chronic heart failure without acute failure during the past six weeks. It is recommended that the treating physician should be experienced in the management of chronic heart failure.

For those patients receiving cardiovascular drug therapy including diuretics and/or digoxin and/or ACE inhibitors and/or angiotensin II antagonists, dosing of these drugs should be stabilised during the past two weeks prior to initiation of Nebivolol 2.5mg Tablets treatment.

The initial up-titration should be done according to the following steps at 1-2 weekly intervals based on patient tolerability: 1.25 mg 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 up-titration to the maximum tolerated dose is individually adjusted. There is no experience in patients with severe renal insufficiency (serum creatinine $\geq 250 \mu\text{mol/L}$). 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 2.5mg Tablets in these patients is contra-indicated.

Elderly

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

Children and adolescents

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

4.3 Contraindications

Hypersensitivity 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.
- 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 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, 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, 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.

Beta-blockers may rarely cause decreased lacrimation.

The initiation of Chronic Heart Failure 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 interactionPharmacodynamic interactionsCombinations 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 β -blocker treatment may lead to profound hypotension and atrio-ventricular block (see section 4.4).

Centrally-acting antihypertensives (clonidine, guanfacin, moxonidine, methyl dopa, rilmenidine): concomitant use of centrally acting antihypertensive drugs may worsen heart failure by a decrease in the central sympathetic tone (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 2.5mg 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 and sedatives (phenothiazines, tricyclics and barbiturates), organic nitrates as well as other antihypertensive agents: 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. 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, quinidine, terbinafine, bupropion, chloroquine and levomepromazine 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 2.5mg Tablets are taken with the meal, and an antacid between meals, the two treatments can be co-prescribed.

Combining nebivolol with nifedipine 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.

4.6 Pregnancy and lactation

Use in pregnancy

Nebivolol has harmful pharmacological effects on pregnancy and/or the fetus/newborn child. 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 beta-adrenoceptor blockers is necessary, beta₁-selective adrenoceptor blockers are preferable.

Nebivolol 2.5mg 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.

Use in lactation

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 machine 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, one should refrain from driving and other activities requiring alertness. These effects are more likely to occur after initiation of the treatment or after dose increases.

4.8 Undesirable effects

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

<Very common ($\geq 1/10$)>

<Common ($\geq 1/100$ to $< 1/10$)>

<Uncommon ($\geq 1/1,000$ to $< 1/100$)>

<Rare ($\geq 1/10,000$ to $< 1/1,000$)>

<Very rare ($\leq 1/10,000$)>

<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.

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				angioedema and hypersensitivity
Psychiatric disorders		nightmares, depression		
Nervous system disorders	headache, dizziness, paraesthesia		fainting/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	
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 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.

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 be treated in an intensive care ward. Blood glucose levels should be checked. Absorption of any drug residues still present in the gastro-intestinal tract can be prevented by gastric lavage and the administration of activated charcoal and a laxative. Artificial respiration may be required. Bradycardia or extensive vagal reactions should be treated by administering atropine or methylatropine. Hypotension and shock should be treated with plasma/plasma substitutes and, if necessary, catecholamines. The beta-blocking effect can be counteracted by slow intravenous administration of isoprenaline hydrochloride, starting with a dose of approximately 5 µg/minute, or dobutamine, starting with a dose of 2.5 µg/minute, until the required effect has been obtained. In refractory cases isoprenaline can be combined with dopamine. If this does not produce the desired effect either, intravenous administration of glucagon 50-100 µg/kg 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.

5 PHARMACOLOGICAL PROPERTIES**5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Beta blocking agents, selective. ATC code: C07AB 12

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

- It 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 beta1 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: $36 \pm 12.3\%$, 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.

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 2.5mg 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 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.

Distribution

In plasma, both nebivolol enantiomers are predominantly bound to albumin.

Plasma protein binding is 98.1% for SRRR-nebivolol and 97.9% for RS S S-nebivolol. The volume of distribution is between 10.1 and 39.4 l/kg.

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.

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**

Lactose monohydrate
Maize Starch
Croscarmellose Sodium
Hypromellose
Microcrystalline Cellulose
Silica, colloidal anhydrous
Magnesium Stearate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

30 months

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/PVdC/Aluminium blisters
Pack sizes: 14, 28, 30, 50, 100

Aluminium/Aluminium blisters
Pack sizes: 14, 28, 30, 50, 100

Not all pack sizes may be marketed

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

Glenmark Generics (Europe) Ltd
Laxmi House, 2B Draycott Avenue, Kenton
Middlesex, HA3 0BU

8 MARKETING AUTHORISATION NUMBER(S)

PL 25258/0002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25/02/2009

10 DATE OF REVISION OF THE TEXT

25/02/2009

1 NAME OF THE MEDICINAL PRODUCT

Nebivolol 5mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5.45 mg nebivolol hydrochloride corresponding to 5 mg nebivolol
Excipient: 145.0 mg of lactose monohydrate/tablet
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

Circular, white, shallow biconvex uncoated tablets engraved with 'N' and 'L' on either side of the breakline on one side and plain on other side

The tablet can be divided into equal halves.

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 of 70 years or older.

4.2 Posology and method of administrationMethod 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.

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.

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 5mg Tablets in these patients is contra-indicated.

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.

Children and adolescents

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

Chronic heart failure (CHF)

The treatment of stable chronic heart failure has to be initiated with a gradual up-titration of dosage until the optimal individual maintenance dose is reached.

Patients should have stable chronic heart failure without acute failure during the past six weeks. It is recommended that the treating physician should be experienced in the management of chronic heart failure.

For those patients receiving cardiovascular drug therapy including diuretics and/or digoxin and/or ACE inhibitors and/or angiotensin II antagonists, dosing of these drugs should be stabilised during the past two weeks prior to initiation of Nebivolol 5mg Tablets treatment.

The initial up-titration should be done according to the following steps at 1-2 weekly intervals based on patient tolerability: 1.25 mg 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 up-titration to the maximum tolerated dose is individually adjusted. There is no experience in patients with severe renal insufficiency (serum creatinine $\geq 250 \mu\text{mol/L}$). 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 5mg Tablets in these patients is contra-indicated.

Elderly

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

Children and adolescents

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

4.3 Contraindications

Hypersensitivity 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.
- 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 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, 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, 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.

Beta-blockers may rarely cause decreased lacrimation.

The initiation of Chronic Heart Failure 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

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 β -blocker treatment may lead to profound hypotension and atrio-ventricular block (see section 4.4).

Centrally-acting antihypertensives (clonidine, guanfacin, moxonidine, methyl dopa, rilmenidine): concomitant use of centrally acting antihypertensive drugs may worsen heart failure by a decrease in the central sympathetic tone (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 5mg 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 and sedatives (phenothiazines, tricyclics and barbiturates), organic nitrates as well as other antihypertensive agents: 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. 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, quinidine, terbinafine, bupropion, chloroquine and levomepromazine 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 5mg Tablets are 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.

4.6 Pregnancy and lactation

Use in pregnancy

Nebivolol has harmful pharmacological effects on pregnancy and/or the fetus/newborn child. 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 beta-adrenoceptor blockers is necessary, beta₁-selective adrenoceptor blockers are preferable.

Nebivolol 5mg 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.

Use in lactation

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 machine 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, one should refrain from driving and other activities requiring alertness. These effects are more likely to occur after initiation of the treatment or after dose increases.

4.8 Undesirable effects

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

<Very common ($\geq 1/10$)>

<Common ($\geq 1/100$ to $< 1/10$)>

<Uncommon ($\geq 1/1,000$ to $< 1/100$)>

<Rare ($\geq 1/10,000$ to $< 1/1,000$)>

<Very rare ($\leq 1/10,000$)>

<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.

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				angioedema and hypersensitivity
Psychiatric disorders		nightmares, depression		
Nervous system disorders	headache, dizziness, paraesthesia		fainting/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	
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 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.

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 be treated in an intensive care ward. Blood glucose levels should be checked. Absorption of any drug residues still present in the gastro-intestinal tract can be prevented by gastric lavage and the administration of activated charcoal and a laxative. Artificial respiration may be required. Bradycardia or extensive vagal reactions should be treated by administering atropine or methylatropine. Hypotension and shock should be treated with plasma/plasma substitutes and, if necessary, catecholamines. The beta-blocking effect can be counteracted by slow intravenous administration of isoprenaline hydrochloride, starting with a dose of approximately 5 µg/minute, or dobutamine, starting with a dose of 2.5 µg/minute, until the required effect has been obtained. In refractory cases isoprenaline can be combined with dopamine. If this does not produce the desired effect either, intravenous administration of glucagon 50-100 µg/kg 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Beta blocking agents, selective. ATC code: C07AB 12

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

- It 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 beta1 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: $36 \pm 12.3\%$, 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.

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 5mg 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 R_{SSS}-enantiomer are slightly higher than for the S_{RRR}-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.

Distribution

In plasma, both nebivolol enantiomers are predominantly bound to albumin.

Plasma protein binding is 98.1% for S_{RRR}-nebivolol and 97.9% for R_{SSS}-nebivolol. The volume of distribution is between 10.1 and 39.4 l/kg.

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.

- 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**
Lactose monohydrate
Maize Starch
Croscarmellose Sodium
Hypromellose
Microcrystalline Cellulose
Silica, colloidal anhydrous
Magnesium Stearate
- 6.2 Incompatibilities**
Not applicable
- 6.3 Shelf life**
30 months
- 6.4 Special precautions for storage**
This medicinal product does not require any special storage conditions.
- 6.5 Nature and contents of container**
PVC/PVdC/Aluminium blisters
Pack sizes: 14, 28, 30, 50, 100

Aluminium/Aluminium blisters
Pack sizes: 14, 28, 30, 50, 100

Not all pack sizes may be marketed
- 6.6 Special precautions for disposal**
No special requirements
- 7 MARKETING AUTHORISATION HOLDER**
Glenmark Generics (Europe) Ltd
Laxmi House, 2B Draycott Avenue, Kenton
Middlesex, HA3 0BU
- 8 MARKETING AUTHORISATION NUMBER(S)**
PL 25258/0003
- 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
25/02/2009
- 10 DATE OF REVISION OF THE TEXT**
25/02/2009

Module 3

PACKAGE LEAFLET: INFORMATION FOR THE USER

Nebivolol 2.5 mg Tablets Nebivolol 5 mg Tablets Nebivolol

Read all this leaflet carefully before you start taking this medicine:

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What are Nebivolol Tablets and what they are used for
2. Before you take Nebivolol Tablets
3. How to take Nebivolol Tablets
4. Possible side effects
5. How to store Nebivolol Tablets
6. Further information

1. WHAT NEBIVOLOL TABLETS ARE AND WHAT THEY ARE USED FOR

Nebivolol Tablets contains nebivolol which is a selective beta blocker and it dilates blood vessels (vasodilator). It is used for the treatment of raised blood pressure (hypertension).

Nebivolol Tablets are also used to treat chronic heart failure, in addition to other therapies, in patients aged 70 or over

2. BEFORE YOU TAKE NEBIVOLOL TABLETS

Do not take Nebivolol Tablets

- if you are allergic (hypersensitive) to nebivolol or to any of the other ingredients of Nebivolol Tablets (see section 6 of this leaflet),
- if you have low blood pressure (the systolic or "upper" pressure is less than 90 mmHg)
- if you have extremely poor circulation in the arms or legs
- if you have a very slow heartbeat (less than 60 heart beats per minute before having started this medication)
- if you have been diagnosed with conduction disorders in your heart (such as sick sinus syndrome or atrioventricular blockade) and you do not have a functioning pacemaker
- if you have acute heart failure, or you are receiving treatment into a vein (by intravenous 'drip') to help your heart work
- if you have or have had bronchial asthma or chronic obstructive pulmonary disease (COPD)
- if you have severe difficulty in breathing or wheezing
- if you have a tumour of the adrenal gland called pheochromocytoma
- if you have severe liver disease or liver function impairment
- if you have a metabolic acidosis (such as in diabetic patients when the blood sugar has risen too much and blood has become too acidic)

Take special care with Nebivolol Tablets

If you have or develop one of the following conditions:

- heart failure (inability of heart to pump enough blood for body's needs), especially if this is not being treated.
- a mild (first degree) atrioventricular blockade in your heart
- chest pain caused by cramping of the coronary arteries (called Prinzmetal's angina or variant angina)
- poor circulation in the arms or legs, e.g. Raynaud's disease or syndrome, cramp-like pains on walking
- prolonged breathing problems
- diabetes: nebivolol has no effect on blood sugar, but it could mask the signs of a low sugar level (e.g. trembling, fast heartbeat).
- overactive thyroid gland, as nebivolol may mask the signs of an abnormally fast heart rate due to this condition
- allergy, as the allergic reactions may become stronger and more medicines may be needed to treat them
- a skin condition known as psoriasis, as nebivolol may aggravate the symptoms
- dry eyes, as nebivolol may make the eyes drier.

In these cases, your doctor may need to adapt your treatment or check you more often

Children and adolescents

Use in children and adolescents below 18 years old is not recommended.

If you need to have an operation and need an anaesthetic, it is important that you tell the surgeon or dentist that you are taking this medicine.

If you have kidney problems, do not take this medicine for heart failure and inform your doctor.

Taking other medicines

Please tell your doctor or pharmacist if you are using or have recently used any other medicines, including medicines obtained without a prescription.

Always tell your doctor or pharmacist if you are using or receiving any of the following medicines in addition to Nebivolol Tablets as the way nebivolol works or the way the other medicine works may be affected.

- Medicines to treat heart conditions or high blood pressure (amlodarone, amlodipine, atenolol, atenolol, diltiazem, digoxin or other so called digitalis glycosides, diltiazem, disopyramide, felodipine, flecainide, guanfacin, hydroquinidine, lacidipine, lidocaine, methyldopa, mexiletine, moxonidine, nifedipine, nifedipine, nicardipine, nifedipine, nifedipine, organic nitrates, propafenone, quinidine, rilmenidine, verapamil –verapamil should not be injected into a vein)
- Medicines for depression or psychoses (fluoxetine, paroxetine, tricyclic antidepressants, thioridazine, phenothiazines such as levomepromazine)
- Sedative medicines which may be used to treat epilepsy (barbiturates)
- Anti-inflammatory medicines for pain or rheumatism (NSAIDs)
- Diabetic medicines (insulins and oral preparations)
- Medicine for excess acid (cimetidine). You should take Nebivolol Tablets during a meal, and the antacid drug between meals
- Anaesthetics: always inform your anaesthetist that you are on Nebivolol Tablets before being anaesthetized.
- Muscle relaxant (baclofen)
- Medicine that is taken during chemo- or radiation therapy to protect you (amifostine)
- Anti-fungal or to treat yeast infections (terbinafine)
- Medicine that helps in stopping smoking (bupropion)
- Anti-malarials (mefloquine, chloroquine – which is also used for rheumatism)
- Medicines for asthma or to treat a blocked nose.
- Medicine for some eye disorders such as glaucoma (increased pressure in the eye) or dilation of the pupil

Taking Nebivolol Tablets with food and drink

Nebivolol Tablets can be taken before, during or after a meal, but also you can take them without food. The tablet or its parts should be swallowed with some water or another liquid.

Pregnancy and breast-feeding

Pregnancy

Nebivolol Tablets should not be taken during pregnancy unless instructed to do so by a doctor.

Breast-feeding

Breast-feeding is not recommended during administration of Nebivolol Tablets

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

No studies on the effects on the ability to drive and use machines have been performed.

This medicine may cause dizziness or fainting as a result of reduction in blood pressure. If these occur, DO NOT drive or operate machinery. These effects are more likely to occur after initiation of the treatment or after dose increases (see also section 4).

Important information about some of the ingredients of Nebivolol Tablets

This product contains lactose. If your doctor has told you that you have intolerance to some sugars, contact your doctor before taking this medicine.

3. HOW TO TAKE NEBIVOLOL TABLETS

Always take Nebivolol Tablets exactly as your doctor has told you. You should check with your doctor or pharmacist if you are unsure.

Treatment of raised blood pressure (hypertension)

- The usual dose is 5 mg (one 5mg tablet or two 2.5mg tablets) per day
- Elderly patients and patients with a kidney disorder will usually start with 2.5mg (half a 5mg tablet or one 2.5mg tablet) daily.
- It may take up to 4 weeks for this medicine to have full effect.
- If you are aged over 75 years, your doctor may need to monitor you more closely.

Treatment of chronic heart failure

- Your treatment will be started and monitored by an experienced physician.
- Your doctor will start your treatment with 1.25mg (half a 2.5mg tablet) per day.
- This may be increased after 1-2 weeks to 2.5mg (one 2.5mg tablet, or half a 5mg tablet) per day, then to 5mg (two 2.5mg tablets or one 5mg tablet) per day and then to 10mg (four 2.5mg or two 5mg tablets) per day until the correct dose is reached for you.
- The maximum recommended dose is 10mg.
- You will need to be monitored for 2 hours by an experienced physician when you start treatment and every time your dose is increased.
- Your doctor may reduce your dose if necessary, and you should not stop abruptly as this can worsen heart failure.
- Patients with serious kidney problems should not take this medicine.
- If you have liver problems and have been told that your liver does not work properly, you should not take this medicine.

Take your medicine once daily, preferably at about the same time of day.

Your doctor may decide to combine your tablets with other medicine for your condition.

Nebivolol Tablets are not recommended in children and adolescents.

If you take more Nebivolol Tablets than you should

If you accidentally take too many tablets (overdose), you may experience slow heart beat, low blood pressure or other heart problems, or difficulty in breathing or wheezing. Contact your nearest hospital casualty department or tell your doctor or pharmacist immediately.

If you forget to take Nebivolol Tablets

If you forget to take your medicine, but remember to take it after a short time, take the next tablet normally, when it is the time to take it. However, if a long delay has occurred (e.g. all day) skip that dose and take the next dose the next day at the usual time and skip the forgotten dose. Do not take a double or a larger dose to make up for a forgotten dose (s). Repeated skipping is to be avoided.

If you stop taking Nebivolol Tablets

Do not stop taking Nebivolol Tablets without consulting your doctor first. If the medication is terminated abruptly, the patient may experience dangerous worsening of the symptoms. This concerns especially the patients with heart failure.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Nebivolol Tablets can cause side effects, although not everybody gets them.

When Nebivolol Tablets are used for the treatment of raised blood pressure, the possible side effects are:

Common side effects (affects 1 to 10 users in 100) when used for raised blood pressure:

- Headache
- Dizziness
- Tiredness
- An unusual itching or tingling feeling
- Diarrhoea
- Constipation
- Nausea
- Shortness of breath
- Swollen hands or feet

Uncommon side effects (affects 1 to 10 users in 1000) when used for raised blood pressure:

- Slow heartbeat or other heart complaints
- Low blood pressure
- Cramp-like leg pain
- Abnormal vision
- Impotence (difficulty in getting an erection)
- Depressive feelings
- Indigestion, gas in stomach or bowel
- Vomiting
- Skin rash
- Tightening of the chest, difficulty in breathing or wheezing
- Nightmares

Very rare side effects (affects less than 1 user in 10,000):

- Fainting
- Angioedema: swelling of the skin of the face or extremities, lips, tongue, mucous membranes of the throat and airway, resulting in shortness of breath or difficulty to swallow – contact a doctor immediately!
- Psoriasis aggravated

In a clinical study for chronic heart failure, the following side effects were seen:

Very common side effects (affects more than 1 user in 10):

- slow heart beat
- dizziness

Common side effects (affects 1 to 10 users in 100)

- worsening of heart failure
- low blood pressure (such as feeling faint when getting up too quickly)
- inability to tolerate this medicine
- irregular heartbeat
- swelling of the lower limbs (such as swollen ankles)

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE NEBIVOLOL TABLETS

Keep out of the reach and sight of children.

Do not use Nebivolol Tablets after the expiry date which is stated on the carton and on the blister after <EXP>.

The expiry date refers to the last day of that month.

This medicinal product does not require any special storage conditions.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Nebivolol Tablets contain

The active substance is nebivolol.

Each tablet contains 2.5mg of nebivolol equivalent to 2.725mg of nebivolol hydrochloride.

Or

Each tablet contains 5mg nebivolol equivalent to 5.45mg nebivolol hydrochloride

The other ingredients are:

lactose monohydrate; maize starch; croscarmellose sodium; hypromellose; microcrystalline cellulose; silica colloidal anhydrous; magnesium stearate.

What Nebivolol Tablets look like and contents of the pack

Nebivolol 2.5mg Tablets: capsule shaped, white, biconvex uncoated tablets with a breakline on one side and plain on the other side. The tablets can be divided into equal halves.

Nebivolol 5mg Tablets: circular, white, biconvex uncoated tablets engraved with 'N' and 'L' on either side of the breakline on one side and plain on other side. The tablet can be divided into equal halves.

Nebivolol 2.5mg, and 5mg Tablets are available in PVC/PVC/aluminium blisters and aluminium/aluminium blisters of 14, 28, 30, 50, 100 tablets

*Not all pack sizes may be marketed.

Marketing Authorisation Holder

Glenmark Generics (Europe) Ltd,

Laxmi House, 2-B Draycot Avenue,

Kenton, Middlesex, HA3 0BU, UK

Manufacturer

Medicaments a.s., Bělohorská, 39/260, 169 00 Prague 6, Czech Republic

This medicinal product is authorised in the Member States of the EEA under the following names:

Belgium

Nebivolol Glenmark Generics Europe 2.5 mg tabletten

Nebivolol Glenmark Generics Europe 5 mg tabletten

Bulgaria, Hungary, Lithuania, Slovak Republic

Nebicard 2.5 mg

Nebicard 5 mg

Czech Republic, Romania

Nebinorm 2.5 mg

Nebinorm 5 mg

France

NEBIVOLOL GLENMARK GENERICS 2.5 mg, comprimés sécables

NEBIVOLOL GLENMARK GENERICS 5 mg, comprimés sécables

Germany

Nebivolol Glenmark 2.5 mg tabletten

Nebivolol Glenmark 5 mg tabletten

Greece

NEBIVOLOL/GLENMARK

Italy

Nebivolol Glenmark.

Poland

Nebitrix 2.5mg

Nebitrix 5mg

Spain

Nebivolol Glenmark Generics 2.5 mg comprimidos

Nebivolol Glenmark Generics 5 mg comprimidos

Sweden

Nebivolol Glenmark 2.5 mg

Nebivolol Glenmark 5 mg

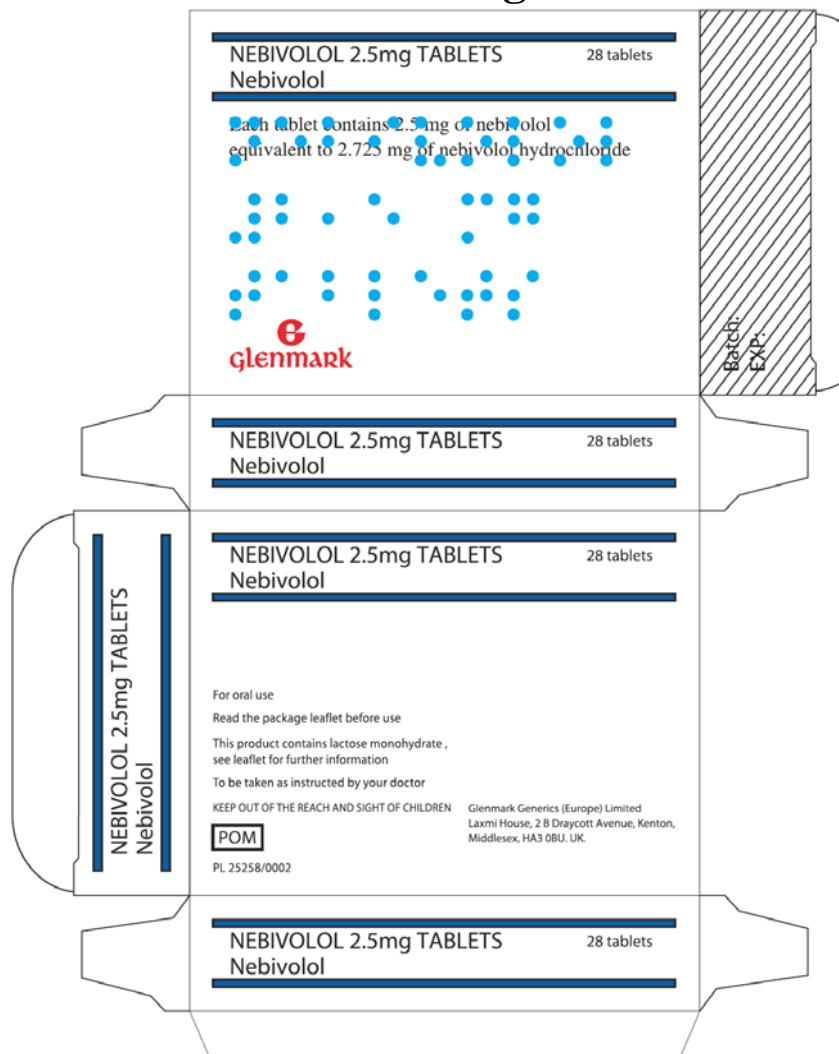
The Netherlands

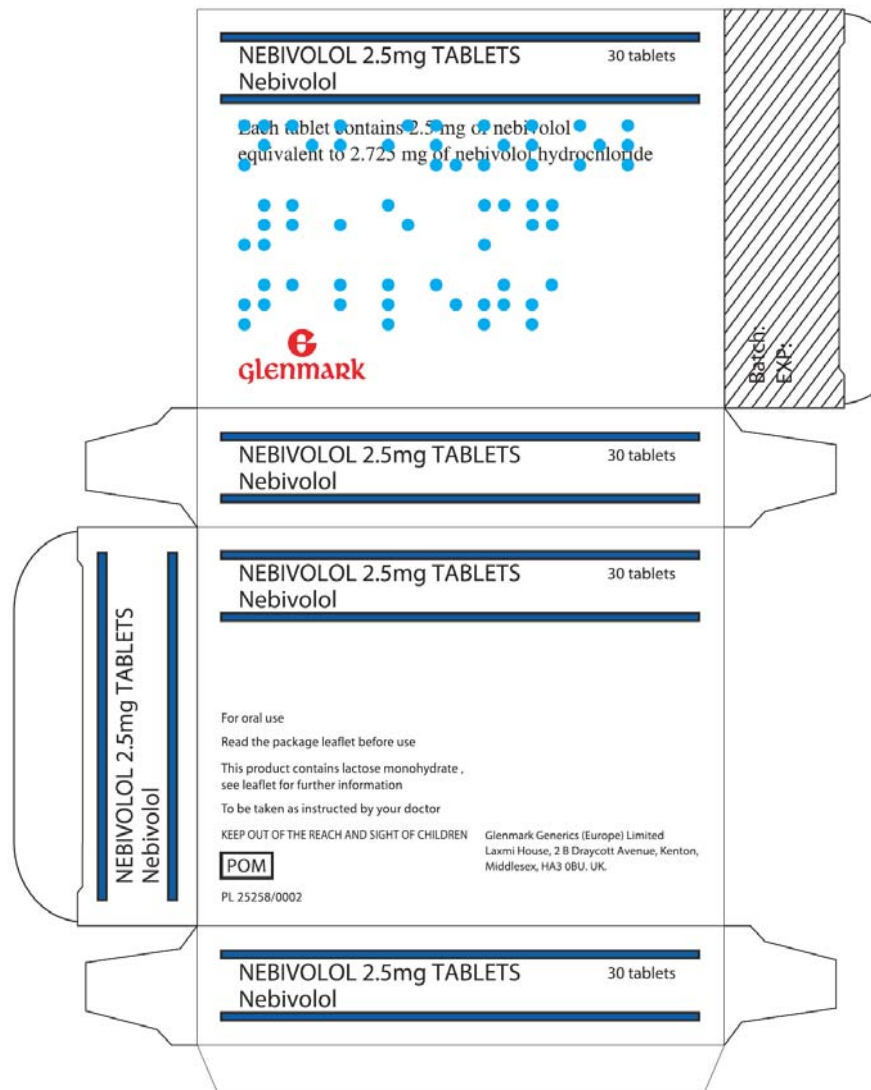
Nebivolol Glenmark 2.5 mg tabletten

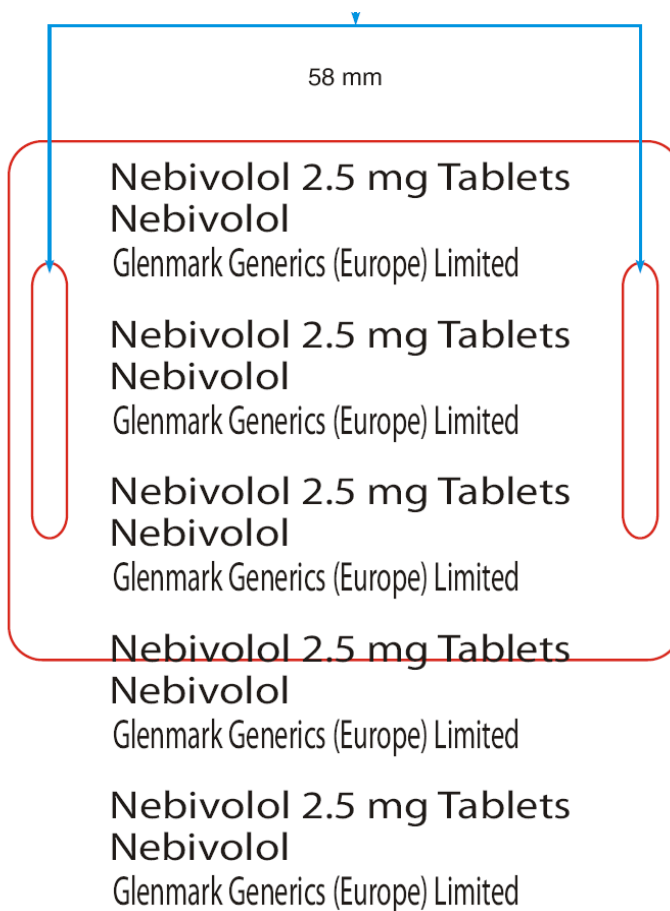
Nebivolol Glenmark 5 mg tabletten

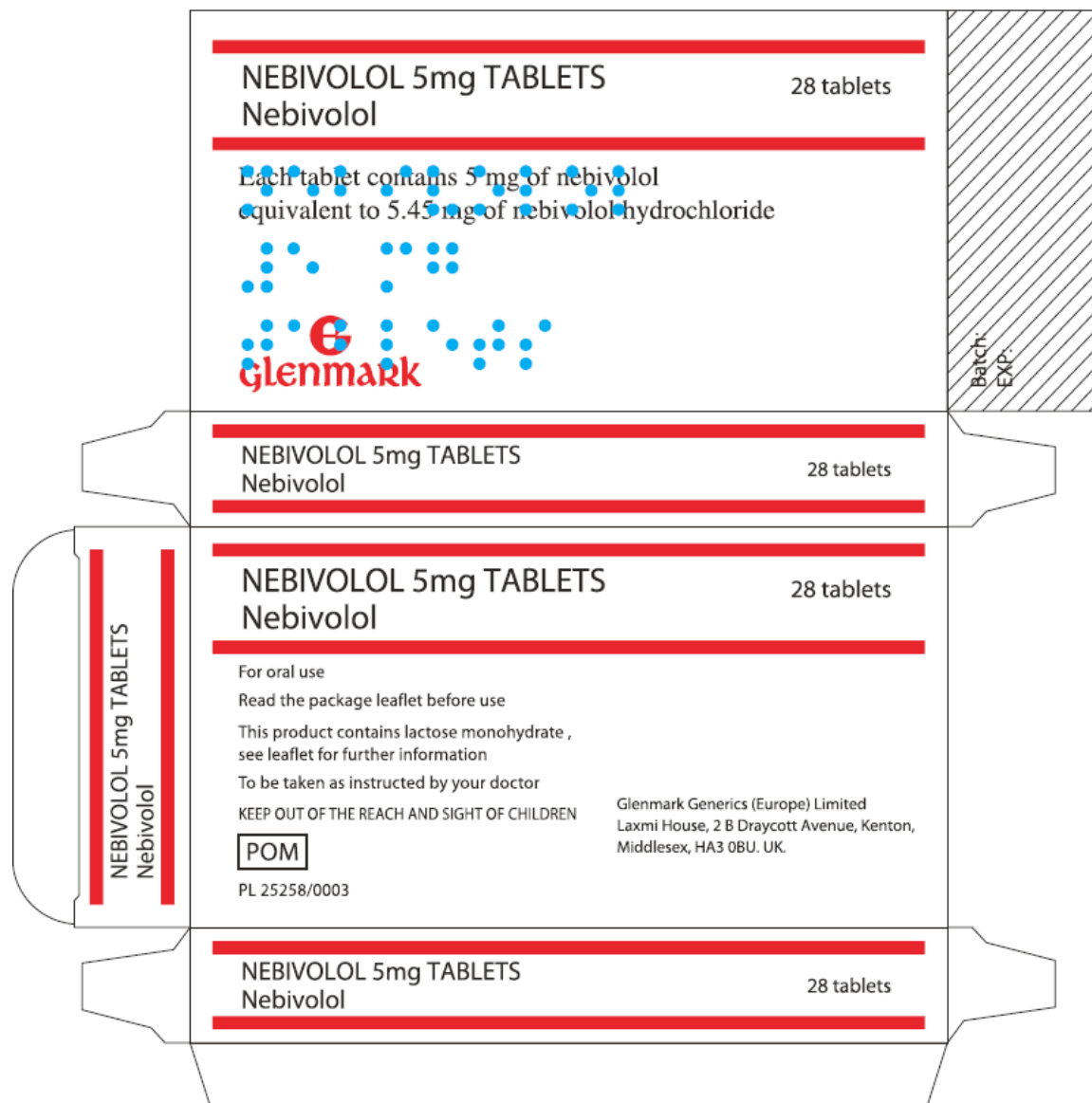
This leaflet was last approved in 01/2009

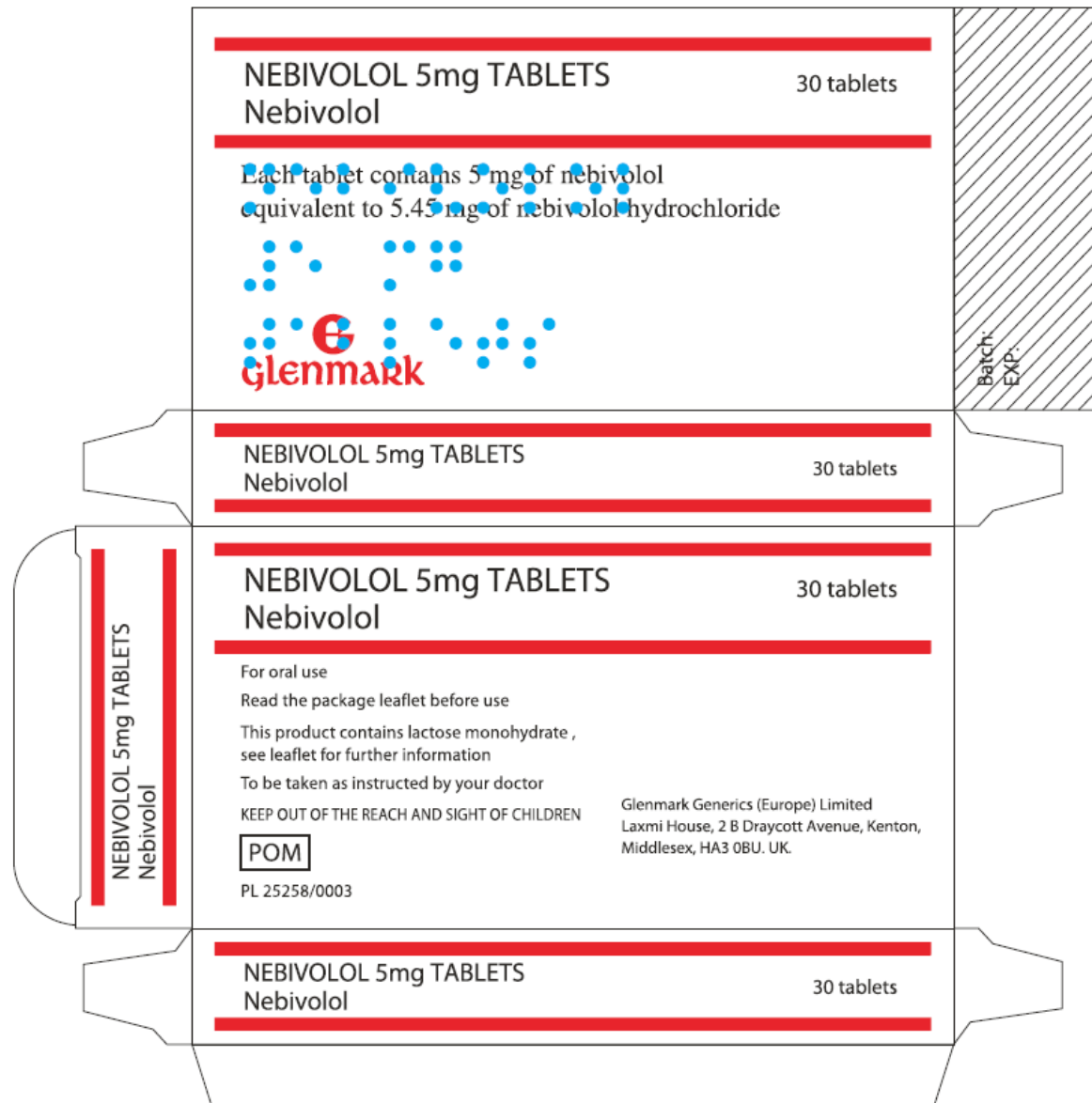
Module 4 Labelling













Module 5

Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the RMS considered that the applications for Nebivolol 2.5 and 5mg Tablets (PL 25258/0002-3; UK/H/1548/001-2/DC) could be approved. The products are prescription-only medicines for the treatment of:

- essential hypertension
- stable mild to moderate chronic heart failure, in addition to standard therapies in elderly patients of 70 years and older.

These applications were submitted using the decentralised procedure (DCP), according to Article 10.3 and 10.1 of 2001/83 EC, as amended, for the 2.5 and 5mg Tablets, respectively. With the UK as RMS, the marketing authorisation holder (Glenmark Generics Europe Limited) was applying for product licences in Belgium, Bulgaria, Czech Republic, Germany, Greece, France, Hungary, Italy, the Netherlands, Poland, Romania, Spain, Sweden and Slovak Republic. The reference medicinal product for both applications is Nebilet 5.0mg Tablets (Menarini International Operations, Luxembourg SA), which has been granted a licence in at least one EU country for at least 10 years.

Nebivolol is third-generation beta-adrenoceptor antagonist with highly selective beta-1 antagonist properties. Nebivolol is a racemate of two enantiomers, SRRR-nebivolol (or d-nebivolol) and RSSS-nebivolol (or l-nebivolol). It combines two pharmacological activities:

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

In therapeutic doses, it reduces heart rate and blood pressure both in normotensive subjects and hypertensive patients. Nebivolol increases the NO-mediated vascular response to acetylcholine (Ach) which is reduced in patients with endothelial dysfunction.

No new preclinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years. No new clinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years. The bioequivalence studies were carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites. For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports issued by an EU regulatory authority.

The decentralised procedure was completed successfully on 1st February 2009. National licences were subsequently granted in the UK on 25th February 2009.

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Nebivolol 2.5mg Tablets Nebivolol 5mg Tablets
Name(s) of the active substance(s) (INN)	Nebivolol hydrochloride
Pharmacotherapeutic classification (ATC code)	Beta-blocking agents, selective (C07A B12)
Pharmaceutical form and strength(s)	2.5 and 5mg Tablets
Reference numbers for the Mutual Recognition Procedure	UK/H/1548/001-2/DC
Reference Member State	United Kingdom
Member States concerned	Belgium, Bulgaria, Czech Republic, Germany, Greece, France, Hungary, Italy, the Netherlands, Poland, Romania, Spain, Sweden and Slovak Republic
Marketing Authorisation Number(s)	PL 25258/0002-3
Name and address of the authorisation holder	Glenmark Generics (Europe) Ltd, Laxmi House, 2B Draycott Avenue, Kenton, Middlesex, HA3 0BU

III SCIENTIFIC OVERVIEW AND DISCUSSION

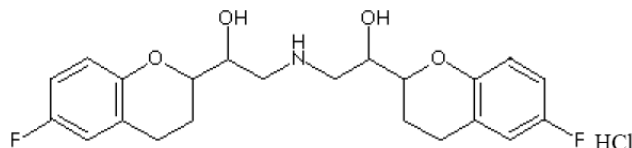
III.1 QUALITY ASPECTS

S. Active substance

INN/Ph.Eur name: Nebivolol hydrochloride

Chemical name: (i) (+)-[2R[1S,5S(S)]]- α , α' -[iminobis(methylene)]bis[6-fluoro-3,4,-dihydro-2H-1-1-benzopyran-2-methanol hydrochloride
(ii) α , α' -(iminodimethylene)bis[6-fluoro-2-chromanmethanol] hydrochloride

Structural formula:



Molecular formula: $C_{22}H_{25}NO_4.HCl$

Appearance: White to off-white crystalline powder that is very slightly soluble in water.

Molecular weight: 441.5

At the time of the grant of the licences for these products, there was no European monograph for nebivolol hydrochloride.

Synthesis of the drug substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant certificates of analysis.

An appropriate specification is provided for the active substance nebivolol hydrochloride, with suitable test methods and limits. The methods of testing and limits for residual solvents are in compliance with current guidelines. Batch analysis data are provided and comply with the proposed specification.

Appropriate proof-of-structure data have been supplied for the active pharmaceutical ingredient. All potential known impurities have been identified and characterised. Suitable certificates of analysis have been provided for all reference standards used.

The active substance is stored in appropriate packaging. Specifications have been provided for all packaging used and are satisfactory. The primary packaging has been shown to comply with current legislation concerning contact with food.

Appropriate stability data have been generated showing the active substance to be a physically and chemically stable drug. A suitable retest period has been set based on stability data submitted for the active substance stored in the proposed packaging.

P. Medicinal Product

Other Ingredients

Other ingredients consist of pharmaceutical excipients lactose monohydrate, maize starch, croscarmellose sodium, hypromellose, microcrystalline cellulose, colloidal anhydrous silica and magnesium stearate.

All excipients comply with their European Pharmacopoeia monograph.

With the exception of lactose monohydrate, none of the excipients contain materials of animal or human origin. The supplier of lactose monohydrate has confirmed that the lactose used is obtained from healthy animals under the same conditions as milk for human consumption. No genetically modified organisms (GMO) have been used in the preparation of these products.

Pharmaceutical Development

The objective of the development programme was to formulate stable, efficacious and tolerable tablets containing nebivolol hydrochloride that can be considered generic medicinal products of Nebilet Tablets (Menarini International Operations, Luxembourg SA).

A satisfactory account of the pharmaceutical development has been provided.

Comparative *in vitro* dissolution profiles and impurity profiles have been provided for the proposed and originator products.

Manufacturing Process

Satisfactory batch formulae have been provided for both strengths of product, along with an appropriate account of the manufacturing process. Supporting validation data have been provided for pilot-scale batches and a suitable validation protocol for scale-up to industrial manufacture.

Finished Product Specification

The finished product specifications proposed for both strengths are acceptable. Test methods have been described and have been adequately validated. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for all working standards used.

Container-Closure System

Both strengths of tablets are packaged in aluminium/polyvinylchloride/polyvinylidene chloride blisters and aluminium/aluminium blisters, both of which are contained in cardboard boxes. Pack sizes for both strengths are 14, 28, 30, 50 and 100 tablets. The marketing authorisation holder does not intend to market all pack sizes at the current time, but has committed to submitting the mock-ups for any pack sizes to the regulatory authorities before marketing them in that country.

Satisfactory specifications and certificates of analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

Stability of the product

Stability studies were performed in accordance with current guidelines on batches of all strengths of finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 30 months, with no specific storage conditions. Suitable post approval stability commitments have been provided to follow-up the batches from the current studies and to place the first three commercial-scale batches of each strength on stability, followed by one batch per year.

Bioequivalence/bioavailability

Satisfactory certificates of analysis have been provided for the test and reference batches used in the bioequivalence study.

Summary of Product Characteristics (SPC), Patient Information Leaflet (PIL), Labels

The SPC, PIL and labels are pharmaceutically acceptable.

A package leaflet has been submitted to the MHRA along with a bridging report for the readability testing of the patient information leaflet, cross-referring to the leaflet for Nebivolol 5mg Tablets (Specifar SA) that was approved by decentralised procedure in May 2008 (DK/H/1012-5/001/DC). Suitable justifications have been provided for bridging to the readability testing for this product and the readability testing results are accepted. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

MAA forms

The MAA forms are pharmaceutically satisfactory.

Expert report

The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion

The grant of marketing authorisations is recommended.

III.2 PRE-CLINICAL ASPECTS

As these applications are for generic medicinal products to Nebilet Tablets, no new preclinical data have been provided and none are required. A Preclinical Expert Report has been provided, which has been written by an appropriately qualified person. It is a suitable summary of the preclinical aspects of the dossier.

III.3 CLINICAL ASPECTS

Pharmacokinetics

In support of these applications, the marketing authorisation holder has submitted the following bioequivalence study:

An open-label, randomised, two-period, two-treatment, two-sequence, single-dose, crossover study to compare the pharmacokinetics of Nebivolol 5mg Tablets (Test) versus Nebilet 5mg Tablets (Reference - Menarini International Operations, Luxembourg SA) in healthy male volunteers under fasted conditions.

Volunteers were dosed with either treatment with blood samples taken measurement of pharmacokinetic parameters pre- and up to 48 hours post dose. The two treatment arms were separated by a 21-day washout period.

The results are presented below for the active substance nebivolol hydrochloride:

	Test	Reference	Ratio (Test/Reference)	90% Confidence Interval (Parametric)
C_{max} (ng/ml)	2.078	1.951	106.5	100.76 – 112.53%
AUC_{0-t} (ng*.hr/ml)	9.125	9.264	98.5	94.56 – 102.61%
$AUC_{0-\infty}$ (ng*.hr/ml)	8.584	8.743	98.2	93.510 – 103.10%

The 90% confidence intervals for nebivolol hydrochloride lie within the acceptance criteria specified in the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98), meaning that bioequivalence has been shown between the test and reference products. As these products meet all the criteria as specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 5mg strength can be extrapolated to the 2.5mg strength tablets.

Pharmacodynamics

No new data on the pharmacodynamics of nebivolol hydrochloride are submitted and none are required for these types of applications.

Efficacy

No new data on the efficacy of nebivolol hydrochloride are submitted and none are required for these types of applications.

Safety

No new data on the safety of nebivolol hydrochloride are submitted and none are required for these types of applications.

SPC, PIL, Labels

The SPCs, PIL and labels are medically acceptable. The SPCs are consistent with the SPC for the originator product.

Conclusion

The grant of marketing authorisations is recommended.

IV OVERALL CONCLUSION AND RISK-BENEFIT ASSESSMENT QUALITY

The important quality characteristics of Nebivolol 2.5 and 5mg Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the risk-benefit balance.

PRECLINICAL

No new preclinical data were submitted and none are required for applications of this type.

EFFICACY

Bioequivalence has been demonstrated between the applicant's Nebivolol 5mg Tablets and the originator products Nebilet 5mg Tablets (Menarini International Operations, Luxembourg SA). As these products meet all the criteria as specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 5mg strength can be extrapolated to the 2.5mg strength tablets.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with those for Nebilet Tablets.

RISK-BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant's products and the innovator products are interchangeable. Extensive clinical experience with nebivolol hydrochloride is considered to have demonstrated the therapeutic value of the compound. The risk-benefit is, therefore, considered to be positive.

Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome