Public Assessment Report

Nebivolol 5mg Tablets

Nebivolol hydrochloride

PL 24668/0022
PL 24668/0023

Caduceus Pharma Ltd

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Lay Summary

The MHRA has granted Market Authorisations for the medicinal products Nebivolol 5mg Tablets (PL 24668/0022 and 23) on 6\textsuperscript{th} October 2008. Two separate licences were requested for the products and supported by the same data. These are prescription only medicines for the treatment of high blood pressure as well as heart failure in elderly patients \( \geq 70 \) years.

The active ingredient of the products is nebivolol hydrochloride which acts to reduce the work of the heart.

The products were shown to be generic medical products of the reference product Nebilet 5 mg Tablets (Menarini International Operations Luxembourg S.A.), licensed in Ireland on 20/05/1996. The UK reference product is also Nebilet 5 mg Tablets (PL 16239/0013).
Scientific Discussion

INTRODUCTION

Based on a review of the data on quality, safety and efficacy, the UK granted market authorisations for the medicinal product Nebivolol 5mg Tablets (PL 24668/0022) and a duplicate application Nebivolol 5mg Tablets (PL 24668/0023) on 6/10/2008. The products are prescription-only medicines.

The applications were submitted under Article 10.1 of Directive 2001/83/EC as amended. The original product is Nebilet 5 mg Tablets (Menarini International Operations Luxembourg S.A.), licensed in Ireland on 20/05/1996. The UK reference product is also Nebilet 5 mg Tablets (PL 16239/0013).

The products contain the active ingredient nebivolol hydrochloride which is a competitive β-adrenoceptor antagonist. Nebivolol is used for treatment of essential hypertension and stable, mild and moderate chronic heart failure in addition to standard therapies in elderly patients ≥ 70 years.

PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

Nomenclature

INN: Nebivolol hydrochloride

Chemical names:
(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

Structure

Molecular formula: C_{22}H_{25}F_{2}NO_{4}.HCl  Molecular Mass: 441.5 g/mol

![Chemical Structure](image)

An appropriate specification has been provided.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Nebivolol is stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.
Batch analysis data are provided and comply with the proposed specification.

Satisfactory certificates of analysis have been provided for working standards used by the active substance manufacturer and finished product manufacturer during validation studies.

Appropriate stability data have been generated supporting a retest period of 6 months, with no specific storage instructions.

**DRUG PRODUCT**

**Other ingredients**
The other ingredients are listed below:

- Silica colloidal anhydrous
- Magnesium stearate
- Croscarmellose sodium
- Macrogol 6000
- Lactose monohydrate

All excipients used comply with their respective European Pharmacopoeial monograph. Satisfactory certificates of analysis have been provided for all excipients. Magnesium stearate is of vegetable origin. Lactose monohydrate is derived from milk and a letter from the supplier was provided to state compliance with EMEA/410/01 rev.2

**Dissolution and impurity profiles**
Dissolution and impurity profiles for the drug product were found to be similar to those for the reference products.

**Manufacture**
A description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out on batches of the drug product. The results are satisfactory.

**Finished product specification**
The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

**Container Closure System**
The product is contained in aluminium and PVDC blisters which comply with current guidelines.

**Stability**
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 3 years has been set, which is satisfactory. There are no special storage conditions.
ASSESSOR’S OVERALL CONCLUSIONS ON QUALITY AND ADVICE

A Marketing Authorisation was granted.
PRE-CLINICAL ASSESSMENT

No new pre-clinical data were submitted with these applications and none was required.
MEDICAL ASSESSMENT

General

Nebivolol is a competitive β-antagonist and is used in the treatment of hypertension and heart failure. Both nebivolol enantiomers are rapidly absorbed after oral administration. The absorption of nebivolol is not affected by food. It can be given with or without meals.

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 metabolizing patients 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.

Bioequivalence

Pharmaceutical details

The reference product used in the BE study is Nebilet 5 mg Tablets sourced from the German market. From review of product composition this is an acceptable BE study reference product. The test product was Actavis’ Nebivolol 5 mg Tablets. The test product is considered to be representative of the product proposed for marketing. Satisfactory Certificates of Analysis for the test and reference products were provided.

Essential Similarity

Comparative dissolution and impurity profiles of the Acatvis and originator products were provided and can be considered acceptable.

Bioanalytical methods and validation

Nebivolol was analysed using a LC-MS/MS solid phase extraction method which was not stereoselective, but given that it is acceptable to measure total nebivolol this was satisfactory. The analytical report was provided together with a statement of GLP compliance.

The method was adequately validated and samples were analysed within the long-term storage period validated (72 days at -20 ºC). The validated range was 20-2500 ng/ml, but 5.4% of all samples analysed were re-assayed as they were above the calibration curve. An SOP was provided that covered how re-assays should be performed and the data before and after re-assay were provided together with evidence that diluting up to 20-fold did not affect quantitation of the analyte. Other
relevant SOPs were provided to define method validation and sample analysis parameters; they were acceptable.

**Study Design**

Subjects: 34 females/males randomised (2 drop outs, 1 withdrawal, 31 completed) 31 analysed
Test product: Nebivolol HCl 5 mg tablets
Reference product: Nebilet 5 mg tablets
Dose: single dose, fasting 1 x 5 mg tablet
Washout period: 35 days
Sampling times: 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 24, 36, 48, 72, 96 h and 144 h
AUC

**Results**

**SUMMARY OF RESULTS**

**NEBIVOLOL**

**N = 31**

**Pharmacokinetic Parameters**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Test (Nebivolol (A))</th>
<th>Reference (Nebilet (B))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (pg/h/mL)</td>
<td>SD (pg/h/mL)</td>
</tr>
<tr>
<td>AUC_{0-t}</td>
<td>7464.49</td>
<td>3883.67</td>
</tr>
<tr>
<td>AUC_{0-inf}</td>
<td>7768.87</td>
<td>3903.32</td>
</tr>
<tr>
<td>C_{max}</td>
<td>1467.10</td>
<td>549.50</td>
</tr>
<tr>
<td>Residual area (%)</td>
<td>4.48</td>
<td>1.83</td>
</tr>
<tr>
<td>T_{max}</td>
<td>1.27</td>
<td>0.79</td>
</tr>
<tr>
<td>T_{1/2}</td>
<td>1.25</td>
<td>5.00</td>
</tr>
<tr>
<td>Keq</td>
<td>0.0518</td>
<td>0.0073</td>
</tr>
<tr>
<td>T_{1/2}</td>
<td>13.66</td>
<td>2.02</td>
</tr>
</tbody>
</table>

* Median and interquartile ranges are presented.

**Nebivolol (A) vs Nebilet (B)**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Nebivolol (A)</th>
<th>Nebilet (B)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (pg/h/mL)</td>
<td>Mean (pg/h/mL)</td>
</tr>
<tr>
<td>AUC_{0-t}</td>
<td>108.93%</td>
<td>108.51%</td>
</tr>
<tr>
<td>AUC_{0-inf}</td>
<td>103.61 % to 114.51 %</td>
<td>103.49 % to 113.77 %</td>
</tr>
<tr>
<td>C_{max}</td>
<td>96.30%</td>
<td>87.69 % to 105.76 %</td>
</tr>
</tbody>
</table>

1 Calculated using least-squares means according to the formula: exp(Nebivolol (A) / Nebilet (B) * 100
2 90% Geometric Confidence Interval using ln-transformed data
No predose levels were seen confirming the adequacy of the washout period. All CI\textsubscript{s} within 80-125\% and thus, although the applicant pre-specified wider intervals for $C_{\text{max}}$, they were not used. The area not covered by the measured AUC was consistently $< 15\%$. No critical protocol deviations were noted. The study was performed in line with the relevant clinical guidelines.

The two products can be considered to be bioequivalent.

**Efficacy and Safety**

No new clinical or safety data have been provided and this is acceptable for this type of application.

**Expert Report**

The expert is medically qualified and the expert non-clinical and clinical reports were adequate.

**Summary of Product Characteristics (SPC) and Patient Information Leaflet (PIL)**

The SPC is consistent with the reference product and the PIL reflects the SPC and it has been subjected to readability testing by patient groups and met the required standard.

**Medical Conclusion**

A market authorisation may be granted.
Overall Conclusion and Risk/Benefit Analysis

**Quality**
The important quality characteristics of Nebivolol 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 benefit/risk balance.

**Pre-Clinical**
No new preclinical data were submitted and none are required for applications of this type

**Clinical**
Bioequivalence has been demonstrated between the applicant’s Nebivolol 5mg Tablets and the reference product Nebilet 5mg Tablets. No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with that for the reference product.

**Risk/Benefit Analysis**
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. The risk benefit is, therefore, considered to be positive.
Steps Taken During Assessment

<table>
<thead>
<tr>
<th></th>
<th>Description</th>
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<tbody>
<tr>
<td>1</td>
<td>The MHRA received the application on 14/08/2006.</td>
</tr>
<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the application valid on 03/10/2006.</td>
</tr>
<tr>
<td>3</td>
<td>Following assessment of the application the MHRA requested further information from the applicant regarding the quality assessment on 21/02/2007, 24/04/2008 and 05/08/2008 and on the medical assessment on 21/02/2007 and 24/04/2008.</td>
</tr>
<tr>
<td>4</td>
<td>The applicant provided further information in regard to the quality assessment on 08/04/2008, 27/06/2008 and 22/08/2008 and on the medical assessment on 08/04/2008 and 27/06/2008.</td>
</tr>
<tr>
<td>5</td>
<td>The application was determined on 06/10/2008.</td>
</tr>
</tbody>
</table>
Steps Taken after Assessment

No non-confidential changes have been made to the market authorisation.
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Nebivolol 5mg Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each Nebivolol 5mg Tablet contains 5mg of nebivolol (as hydrochloride)
Excipients: Lactose monohydrate
For a full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM
Tablets.
White, round, biconvex, 9mm diameter tablet, cross-scored on one side and
marked with “N5” on the other side.
The tablet can be divided into equal quarters.

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 old or above.

4.2 Posology and method of administration
Hypertension

Adults
The usual dose is one tablet (5mg) daily, preferably taken at the same time of
the day. Tablets may be taken with meals.
The blood pressure lowering effect may take up to 1-2 weeks of treatment to become evident. Occasionally, the optimal effect is only reached only after 4 weeks.

Beta-blockers can be used alone or concomitantly with other antihypertensive agents. An additional antihypertensive effect has been observed when Nebivolol 5mg Tablets are combined with hydrochlorothiazide 12.5mg-25mg.

Patients with renal insufficiency

The recommended starting dose for patients with renal insufficiency is 2.5mg daily. If needed, the daily dose may be increased to 5mg.

Patients with hepatic insufficiency

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

Elderly

In patients over 65 years, the recommended starting dose is 2.5mg daily. If needed, the daily dose may be increased to 5mg. 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 under the age of 18 years due to a lack of data on safety and efficacy.

Chronic Heart Failure (CHF)

The use of nebivolol for treatment of stable chronic heart failure should involve a gradual increase of dosage until the optimal individual maintenance dose is reached.

Prior to starting treatment, 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, these drugs should be maintained at a stable dose for the two weeks leading up to initiation of nebivolol treatment.

The dose should be increased from the initial dose of 1.25mg daily to 2.5mg and then to 5mg daily and then 10mg daily at intervals of 1-2 weeks based on patient tolerability.
The maximum recommended dose is 10mg nebivolol once daily.

The initiation of therapy and all increases in dose should be carried out under the supervision of an experienced physician over a period of at least 2 hours to ensure that the clinical status (especially as regards blood pressure, heart rate, conduction disturbances, signs of worsening heart failure) remains stable.

The occurrence of adverse events may prevent 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 initial dose increasing 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 led to a transitory worsening of heart failure. If discontinuation is necessary, the dose should be decreased step-wise 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 ≥ 250µmol/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.

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 under the age of 18 years due to a 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.

In addition, as with other beta-blocking agents, nebivolol is contra-indicated in:

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

4.4 Special warnings and precautions for use

Anaesthesia

Continuation of beta blockade reduces the risk of arrhythmias during induction and intubation. If beta blockade is interrupted in preparation for surgery, the beta-adrenergic antagonist should be discontinued at least 24 hours beforehand.

Caution should be observed with certain anaesthetics that cause myocardial depression. The patient can be protected against vagal reactions by intravenous administration of atropine.

Cardiovascular

In general, beta-adrenergic antagonists should not be used in patients with untreated congestive heart failure (CHF), unless their condition has been stabilised.

In patients with 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 suggestive of bradycardia, the dosage should be reduced.
Beta-adrenergic antagonists should be used with caution in the following conditions:

- Peripheral circulatory disorders (Raynaud’s disease or syndrome, intermittent claudication), as aggravation of these disorders may occur upon use of beta blockers.
- First degree heart block, because of the negative effect of beta-blockers on conduction time.
- Prinzmetal’s angina due to unopposed alpha-receptor mediated coronary artery vasoconstriction. Beta-adrenergic antagonists may increase the number and duration of anginal attacks.
- Concomitant treatment with calcium channel antagonists of the verapamil and diltiazem type, with Class I antiarrhythmic drugs, and with centrally acting antihypertensive drugs. For details please refer to section 4.5.

**Metabolic/Endocrinological**
Nebivolol 5mg Tablets 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 aggravate symptoms.

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

**Other**
This medicine contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine. Caution should be exercised when treating patients with a history of psoriasis with beta-adrenergic antagonists as they may increase the sensitivity to allergens and the severity of anaphylactic reactions. The initiation of Chronic Heart Failure treatment with nebivolol necessitates regular monitoring. Treatment discontinuation should not be done abruptly unless clearly indicated.

**4.5 Interaction with other medicinal products and other forms of interaction**

**Pharmacodynamic interactions:**

**Combinations not recommended:**

- Class I anti-arrhythmics (quinidine, hydroquinidine, cibenzoline, flecainide, disopyramide, lidocaine, mexiletine, propafenone) as the effect on atrio-ventricular conduction time may be potentiated and the negative inotropic effect increased (see section 4.4).
• Calcium channel antagonists of verapamil/diltiazem type due to a 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, 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 hypertension.

**Combinations to be used with caution:**

• Class III anti-arrhythmic drugs (Amiodarone) as the effect on atrio-ventricular conduction time may be potentiated.

• Volatile halogenated anaesthetics as concomitant use of beta-adrenergic antagonists and anaesthetics may attenuate reflex tachycardia and increase the risk of hypotension (see section 4.4). Sudden withdrawal of beta-blocker treatment should be avoided if possible. The anaesthesiologist should be informed when the patient is receiving Nebivolol 5mg Tablets.

• Insulin and oral anti-diabetic drugs as, although nebivolol does not affect glucose levels, concomitant use may mask symptoms of hypoglycaemia (palpitations, tachycardia).

**Combinations to be used only after careful consideration:**

• Digitalis glycosides as concomitant use may increase atrio-ventricular conduction time although 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) because concomitant use may increase the risk of hypotension, and cause an increase in the risk of a further deterioration of the ventricular pump function in patients with heart failure.

• Antipsychotics and antidepressants (tricyclics, barbiturates and phenotiazines). Concomitant use may enhance the hypotensive effect of the beta-blockers (additive effect).

• Non steroidal anti-inflammatory drugs (NSAID) are thought to have 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 causing increased risk of hypertension, severe bradycardia and heart block.

**Pharmacokinetic interactions:**

As nebivolol metabolism involves the CYP2D6 isoenzyme, co-administration with substances inhibiting this enzyme, especially paroxetine, fluoxetine, thioridazine and quinidine may lead to increased plasma levels of nebivolol associated with an increased risk of excessive bradycardia and adverse events.

Co-administration of cimetidine increased the plasma levels of nebivolol, without changing the clinical effect. Co-administration of ranitidine did not affect the pharmacokinetics of nebivolol. Provided nebivolol is taken with 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 pharmacological effects that may cause harmful effects on pregnancy and/or the foetus/newborn. In general, beta-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-adrenoreceptor blockers is necessary, beta\textsubscript{1}-selective adrenoreceptor 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 foetal growth should be monitored. In case of harmful effects on pregnancy, alternative treatment should be considered. The newborn infant must be closely monitored. Symptoms of hypoglycaemia and bradycardia are generally to be expected in 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 into human milk. Most beta-blockers, particularly lipophilic compounds like nebivolol and its active metabolites, pass into breast milk although to a variable extent. Therefore breast feeding 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

<table>
<thead>
<tr>
<th>SYSTEM ORGAN CLASS</th>
<th>Common (≥ 1/100 to &lt; 1/10)</th>
<th>Uncommon (≥ 1/1,000 to &lt; 1/100)</th>
<th>Very rare (&lt;1/10,000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychiatric disorders</td>
<td></td>
<td>nightmares, depression</td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>headache, dizziness, paraesthesia</td>
<td></td>
<td>syncope</td>
</tr>
<tr>
<td>Eye disorders</td>
<td></td>
<td>impaired vision</td>
<td></td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td></td>
<td>bradycardia, heart failure, slowed AV conduction/AV-block</td>
<td></td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td>hypotension, (increase of) intermittent claudication</td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td>dyspnoea</td>
<td>bronchospasm</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>constipation, nausea, diarrhoea</td>
<td>dyspepsia, flatulence, vomiting</td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td>pruritus, rash erythematos</td>
<td>angioneurotic oedema, psoriasis aggravated</td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td></td>
<td></td>
<td>impotence</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td>tiredness, oedema</td>
<td></td>
</tr>
</tbody>
</table>

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 nebulol 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 nebulol patients were bradycardia and dizziness, both occurring in approximately 11% of patients. The corresponding frequencies among placebo patients were 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 nebulol patients compared to 5.2% of the placebo patients.

Orthostatic hypotension was reported in 2.1% of nebulol patients compared to 1.0% of placebo patients.

Drug intolerance occurred in 1.6% of the nebulol patients compared to 0.8% of the placebo patients.

First degree atrio-ventricular block occurred in 1.4% of nebulol patients compared to 0.9% of placebo patients.

Oedema of the lower limb were reported in 1.0% of nebulol patients compared to 0.2% of placebo patients.

4.9 Overdose

No data are available on overdosage with Nebivolol 5mg Tablets.

Symptoms of overdose with beta-adrenergic antagonists:

- Bradycardia
- Hypotension
- Bronchospasm
- Acute cardiac insufficiency.

Treatment

In case of overdose or hypersensitivity, the patient should be kept under close supervision. 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 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

Nebivolol is a racemate of two enantiomers, SRRR-nebivolol (or d-nebivolol)
and RSSS-nebivolol (or l-nebivolol). It is a competitive and selective beta-
receptor antagonist, due to the SRRR-enantiomer (d-enantiomer), and also 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, a
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 Nitric Oxide-mediated
vascular response to acetylcholine (ACh) which is reduced in patients with
endothelial dysfunction.

In a mortality–morbidity, placebo-controlled trial performed in 2128 patients
≥ 70 years (median age 75.2 years) with stable chronic heart failure with or
without impaired left ventricular ejection fraction (mean LVEF: 36 ± 12.3%,
with the following distribution: LVEF less than 35% in 56% of patients,
LVEF between 35% and 45% in 25% of patients and LVEF greater than 45% in
19% of patients) followed for a mean time of 20 months, nebivolol, given
concomitantly with standard therapy, significantly prolonged the time to either
the occurrence of death 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 of age, gender, or left ventricular ejection fraction of the population on study. The benefit over all causes of 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 sympathomimetic 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

Both nebivolol enantiomers are rapidly absorbed after oral administration. The absorption of nebivolol is not affected by food. It can be given with or without meals.

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 metabolizing patients 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.

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.

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
No information available.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Silica colloidal anhydrous
Magnesium stearate
Crocarmellose sodium
Macrogol 6000
Lactose monohydrate

6.2 Incompatibilities
Not applicable

6.3 Shelf life
3 years

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions

6.5 Nature and contents of container
Nebivolol 5mg Tablets are provided in Al/PVDC blister packs of 7, 14, 28, 30, 50, 56, 90, 100 or 500 Tablets.

Nebivolol 5mg Tablets are provided in HDPE containers closed with a sealed plastic LDPE cap, containing 7, 14, 28, 30, 50, 56, 90, 100 or 500 Tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
Caduceus Pharma Limited
6th Floor,
94 Wigmore Street,
London
W1U 3RF
UK

8 MARKETING AUTHORISATION NUMBER(S)
PL 24668/0022

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
06/10/2008

10 DATE OF REVISION OF THE TEXT
06/10/2008
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Nebivolol 5mg Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each Nebivolol 5mg Tablet contains 5mg of nebivolol (as hydrochloride)
Excipients: Lactose monohydrate
For a full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM
Tablets.
White, round, biconvex, 9mm diameter tablet, cross-scored on one side and marked with “N5” on the other side.
The tablet can be divided into equal quarters.

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 old or above.

4.2 Posology and method of administration
Hypertension
Adults
The usual dose is one tablet (5mg) daily, preferably taken at the same time of the day. Tablets may be taken with meals.
The blood pressure lowering effect may take up to 1-2 weeks of treatment to become evident. Occasionally, the optimal effect is only reached only after 4 weeks.
Beta-blockers can be used alone or concomitantly with other antihypertensive agents. An additional antihypertensive effect has been observed when Nebivolol 5mg Tablets are combined with hydrochlorothiazide 12.5mg-25mg.

**Patients with renal insufficiency**

The recommended starting dose for patients with renal insufficiency is 2.5mg daily. If needed, the daily dose may be increased to 5mg.

**Patients with hepatic insufficiency**

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

**Elderly**

In patients over 65 years, the recommended starting dose is 2.5mg daily. If needed, the daily dose may be increased to 5mg. 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 under the age of 18 years due to a lack of data on safety and efficacy.

**Chronic Heart Failure (CHF)**

The use of nebivolol for treatment of stable chronic heart failure should involve a gradual increase of dosage until the optimal individual maintenance dose is reached.

Prior to starting treatment, 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, these drugs should be maintained at a stable dose for the two weeks leading up to initiation of nebivolol treatment.

The dose should be increased from the initial dose of 1.25mg daily to 2.5mg and then to 5mg daily and then 10mg daily at intervals of 1-2 weeks based on patient tolerability.

The maximum recommended dose is 10mg nebivolol once daily.

The initiation of therapy and all increases in dose should be carried out under the supervision of an experienced physician over a period of at least 2 hours to
ensure that the clinical status (especially as regards blood pressure, heart rate, conduction disturbances, signs of worsening heart failure) remains stable.

The occurrence of adverse events may prevent 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 initial dose increasing 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 led to a transitory worsening of heart failure. If discontinuation is necessary, the dose should be decreased step-wise 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 ≥ 250µmol/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.

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 under the age of 18 years due to a 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.
In addition, as with other beta-blocking agents, nebivolol is contra-indicated in:

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

4.4 Special warnings and precautions for use

Anaesthesia

Continuation of beta blockade reduces the risk of arrhythmias during induction and intubation. If beta blockade is interrupted in preparation for surgery, the beta-adrenergic antagonist should be discontinued at least 24 hours beforehand.

Caution should be observed with certain anaesthetics that cause myocardial depression. The patient can be protected against vagal reactions by intravenous administration of atropine.

Cardiovascular

In general, beta-adrenergic antagonists should not be used in patients with untreated congestive heart failure (CHF), unless their condition has been stabilised.

In patients with 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 suggestive of bradycardia, the dosage should be reduced.

Beta-adrenergic antagonists should be used with caution in the following conditions:
• Peripheral circulatory disorders (Raynaud’s disease or syndrome, intermittent claudication), as aggravation of these disorders may occur upon use of beta blockers.

• First degree heart block, because of the negative effect of beta-blockers on conduction time

• Prinzmetal’s angina due to unopposed alpha-receptor mediated coronary artery vasoconstriction. Beta-adrenergic antagonists may increase the number and duration of anginal attacks.

• Concomitant treatment with calcium channel antagonists of the verapamil and diltiazem type, with Class I antiarrhythmic drugs, and with centrally acting antihypertensive drugs. For details please refer to section 4.5.

Metabolic/Endocrinological
Nebivolol 5mg Tablets 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 aggravate symptoms.

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

Other
This medicine contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine. Caution should be exercised when treating patients with a history of psoriasis with beta-adrenergic antagonists as they may increase the sensitivity to allergens and the severity of anaphylactic reactions. The initiation of Chronic Heart Failure treatment with nebivolol necessitates regular monitoring. Treatment discontinuation should not be done abruptly unless clearly indicated.

4.5 Interaction with other medicinal products and other forms of interaction
Pharmacodynamic interactions:

Combinations not recommended:

• Class I anti-arrhythmics (quinidine, hydroquinidine, cibenzoline, flecainide, disopyramide, lidocaine, mexiletine, propafenone) as the effect on atrio-ventricular conduction time may be potentiated and the negative inotropic effect increased (see section 4.4).

• Calcium channel antagonists of verapamil/diltiazem type due to a 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 hypertension.

**Combinations to be used with caution:**

- Class III anti-arrhythmic drugs (Amiodarone) as the effect on atrio-ventricular conduction time may be potentiated.

- Volatile halogenated anaesthetics as concomitant use of beta-adrenergic antagonists and anaesthetics may attenuate reflex tachycardia and increase the risk of hypotension (see section 4.4). Sudden withdrawal of beta-blocker treatment should be avoided if possible. The anaesthesiologist should be informed when the patient is receiving Nebivolol 5mg Tablets.

- Insulin and oral anti-diabetic drugs as, although nebivolol does not affect glucose levels, concomitant use may mask symptoms of hypoglycaemia (palpitations, tachycardia).

**Combinations to be used only after careful consideration:**

- Digitalis glycosides as concomitant use may increase atrio-ventricular conduction time although 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) because concomitant use may increase the risk of hypotension, and cause an increase in the risk of a further deterioration of the ventricular pump function in patients with heart failure.

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

- Non steroidal anti-inflammatory drugs (NSAID) are thought to have 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 causing increased risk of hypertension, severe bradycardia and heart block.

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Pharmacokinetic interactions:

As nebivolol metabolism involves the CYP2D6 isoenzyme, co-administration with substances inhibiting this enzyme, especially paroxetine, fluoxetine, thioridazine and quinidine may lead to increased plasma levels of nebivolol associated with an increased risk of excessive bradycardia and adverse events.

Co-administration of cimetidine increased the plasma levels of nebivolol, without changing the clinical effect. Co-administration of ranitidine did not affect the pharmacokinetics of nebivolol. Provided nebivolol is taken with 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 pharmacological effects that may cause harmful effects on pregnancy and/or the foetus/newborn. In general, beta-blockers reduce placental profusion, 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-adrenoreceptor blockers is necessary, beta1-selective adrenoreceptor 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 foetal growth should be monitored. In case of harmful effects on pregnancy, alternative treatment should be considered. The newborn infant must be closely monitored. Symptoms of hypoglycaemia and bradycardia are generally to be expected in 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 into human milk. Most beta-blockers, particularly lipophilic compounds like nebivolol and its active metabolites, pass into breast milk although to a variable extent. Therefore breast feeding 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**

<table>
<thead>
<tr>
<th>SYSTEM ORGAN CLASS</th>
<th>Common (≥ 1/100 to &lt; 1/10)</th>
<th>Uncommon (≥ 1/1,000 to &lt; 1/100)</th>
<th>Very rare (&lt;1/10,000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychiatric disorders</td>
<td>nightmares, depression</td>
<td>Syncope</td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>headache, dizziness, paraesthesia</td>
<td></td>
<td>Syncope</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>impaired vision</td>
<td>Syncope</td>
<td></td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>bradycardia, heart failure, slowed AV conduction/AV-block</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>hypotension, (increase of) intermittent claudication</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>dyspnoea</td>
<td>bronchospasm</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>constipation, nausea, diarrhoea</td>
<td>dyspepsia, flatulence, vomiting</td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>pruritus, rash erythematous</td>
<td>angioneurotic oedema, psoriasis aggravated</td>
<td></td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td>impotence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>tiredness, oedema</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 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 compares to 5.2% of the placebo patients.

Orthostatic hypotension was reported in 2.1% of nebivolol patients compared to 1.0% of placebo patients.

Drug intolerance occurred in 1.6% of the nebivolol patients compared to 0.8% of the 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 were reported in 1.0% of nebivolol patients compared to 0.2% of placebo patients.

4.9 Overdose

No data are available on overdosage with Nebivolol 5mg Tablets.

Symptoms of overdose with beta-adrenergic antagonists:

- Bradycardia
- Hypotension
- Bronchospasm
- Acute cardiac insufficiency.

Treatment

In case of overdose or hypersensitivity, the patient should be kept under close supervision. 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 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

Nebivolol is a racemate of two enantiomers, SRRR-nebivolol (or d-nebivolol) and RSSS-nebivolol (or l-nebivolol). It is a competitive and selective beta-receptor antagonist, due to the SRRR-enantiomer (d-enantiomer), and also 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, a 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 Nitric Oxide-mediated vascular response to acetylcholine (ACh) which is reduced in patients with endothelial dysfunction.

In a mortality–morbidity, placebo-controlled trial performed in 2128 patients ≥70 years (median age 75.2 years) with stable chronic heart failure with or without impaired left ventricular ejection fraction (mean LVEF: 36 ± 12.3%, with the following distribution: LVEF less than 35% in 56% of patients, LVEF between 35% and 45% in 25% of patients and LVEF greater than 45% in 19% of patients) followed for a mean time of 20 months, nebivolol, given concomitantly with standard therapy, significantly prolonged the time to either the occurrence of death 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 of age, gender, or left ventricular ejection fraction of the population on study. The benefit over all causes of
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 sympathomimetic 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
Both nebivolol enantiomers are rapidly absorbed after oral administration. The absorption of nebivolol is not affected by food. It can be given with or without meals.

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 metabolizing patients 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.

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.
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
No information available.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Silica colloidal anhydrous
Magnesium stearate
Croscarmellose sodium
Macrogol 6000
Lactose monohydrate

6.2 Incompatibilities
Not applicable

6.3 Shelf life
3 years

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions

6.5 Nature and contents of container
Nebivolol 5mg Tablets are provided in Al/PVDC blister packs of 7, 14, 28, 30, 50, 56, 90, 100 or 500 Tablets.

Nebivolol 5mg Tablets are provided in HDPE containers closed with a sealed plastic LDPE cap, containing 7, 14, 28, 30, 50, 56, 90, 100 or 500 Tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.
Any unused product or waste material should be disposed of in accordance with local requirements.

UKPAR Caduceus Pharma Ltd, Nebivolol 5mg Tablets
7  MARKETING AUTHORISATION HOLDER
Caduceus Pharma Limited
6th Floor,
94 Wigmore Street,
London
W1U 3RF
UK

8  MARKETING AUTHORISATION NUMBER(S)
PL 24668/0023

9  DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
06/10/2008

10 DATE OF REVISION OF THE TEXT
06/10/2008
Labels and Leaflets
PACKAGE LEAFLET: INFORMATION FOR THE USER

Nebivolol 5mg Tablets
(nebivolol hydrochloride)

Read all of 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 get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Nebivolol 5mg Tablets are and what they are used for
2. Before you take Nebivolol 5mg Tablets
3. How to take Nebivolol 5mg Tablets
4. Possible side effects
5. How to store Nebivolol 5mg Tablets
6. Further Information

1. WHAT NEBIVOLOL 5mg TABLETS ARE AND WHAT THEY ARE USED FOR

Nebivolol 5mg Tablets belong to a group of medicines known as beta blockers. They work by blocking the activity of specific proteins in the heart, lungs, pancreas, liver, and blood circulation system.

Nebivolol 5mg Tablets are used to treat:
- high blood pressure (hypertension)
- chronic heart failure in patients aged 70 years or older.

2. BEFORE YOU TAKE NEBIVOLOL 5mg TABLETS

Do not take Nebivolol 5mg Tablets if:
- you are allergic or sensitive to nebivolol or any of the other ingredients of Nebivolol 5mg Tablets, your symptoms are the same as yours.
- you have low blood pressure or poor circulation in the arms or legs.
- you have a very slow heart beat (less than 60 beats per minute).
- you have certain serious heart rhythm problems.
- you have the condition heart failure which has just occurred or which has recently become worse.
- you have asthma or wheezing (now or in the past).
- you have been told by your doctor that you have a tumour in your adrenal gland which is located on top of the kidney (the medical term for this is an unwatered pheochromocytoma).
- you have metabolic acidosis such as diabetic ketoacidosis.

If you are unsure, contact your doctor.

Take special care with Nebivolol 5mg Tablets:
Tell your doctor before you start to take this medicine if:
- you notice that your heart rate is abnormally slow or you experience shortness of breath or dizziness.
- you have ischaemic heart disease such as angina (chest pains).
- you have been told you suffer from any of the following conditions:
  - Poor blood circulation which makes the toes and fingers numb and pale (Raynaud's disease).
  - A type of chest pain due to spontaneously occurring heart camp (called Prinzmetal angina).
  - Pain, tension and weakness in the legs when walking which is relieved by rest (intermittent claudication).
  - A persistent obstruction of your airway such as chronic bronchitis.
  - Diabetes, as it can hide the warning signs of low sugar levels.
  - Overactivity of the thyroid gland (hyperthyroidism).
  - A skin condition known as psoriasis.
  - Impairment of the electrical conduction of signals in the heart (First degree heart block).
  - You are being treated with any other drugs which lower your blood pressure.
- 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.

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

The following medicines may interact with nebivolol by decreasing or increasing its effects:
- Calcium channel blockers, used to treat high blood pressure or other heart problems, such as verapamil, diltiazem, amiodipine, felodipine, lacidipine, nifedipine, nicardipine, nisoldipine and nitrendipine. It is particularly important that verapamil is not injected into a vein during treatment with nebivolol.
- Chlorpheniramine, meclofenamine, methylphenidate and rimonidine, are used to treat high blood pressure.
- Quinidine, hydroquinidine, amiodarone, ecarbazole, flecainide, disopyramide, lidocaine, mexiletine and propafenone, which are used to treat cardiac arrhythmias (irregular heartbeat).
- Barbiturates and phenothiazine, which are used to treat anxiety.
- Amithryptiline, trazadone, paroxetine, fluoxetine and thioridazine, which are used to treat depression.
- Asthma medications, medications to block the nasal passage (e.g. pseudoephedrine) or for certain eye disorders such as glaucoma (increased pressure in the eye) or dilation of the pupil.
- Medicines for diabetes (insulin and medicines for oral use).
- Anaesthetics. Always inform your anaesthetist that you are on nebivolol before being anaesthetized.
- Antacids (e.g. cimetidine), which are used to treat excessive stomach acid. If you are being treated for excessive stomach acid, you should take nebivolol during a meal, and the antacid drug between meals.
- Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) such as ibuprofen and diclofenac, which are used to treat certain types of pain and inflammation.

Taking Nebivolol 5mg Tablets with food and drink
Nebivolol can be taken with or without food unless you take antacids (see: Taking other medicines). The tablet should be swallowed with a glass of water or other liquid.

Pregnancy and breast-feeding
Nebivolol should not be used during pregnancy unless clearly necessary. It is not recommended for use while breast-feeding.

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

Driving and using machines
Nebivolol may cause fatigue and/or dizziness and if you are affected you should not drive or use any machines or tools.

Important information about some of the ingredients of Nebivolol Tablets
This medicine contains lactose if you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3. HOW TO TAKE NEBIVOLOL 5mg TABLETS

Always take Nebivolol 5mg Tablets exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Treatment of high blood pressure (hypertension)
The usual dose is one tablet (5mg) daily, although elderly patients and patients with kidney problems may begin treatment on a lower dose.

The blood pressure lowering effect may take up to 1-2 weeks of treatment to become evident. Occasionally, the optimal effect is only reached after 4 weeks.

UKPAR Caduceus Pharma Ltd, Nebivolol 5mg Tablets 40
Treatment of chronic heart failure

The usual initial dose is 1.25 mg daily. This may be increased after 1-2 weeks to half a tablet daily (2.5 mg) and then to 1 tablet daily (5 mg). This may be further increased to a maximum recommended dose of 2 tablets daily (10 mg).

Your doctor may reduce your dose if necessary. Every time your dose is changed, your doctor will monitor you for approximately two hours.

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

Children and Adolescents

There are limited data in children and hence nebivolol 5 mg Tablets are not recommended in children and adolescents under 18 years of age.

If you take more nebivolol 5mg Tablets than you should

If you accidentally take too much nebivolol, tell your doctor immediately or go to your nearest accident and emergency department.

If you forget to take Nebivolol 5mg Tablets

If you forget to take a dose, take one as soon as you remember, unless it is almost time for your next dose. Then go on as before. Do not take a double dose to make up for a forgotten dose.

If you stop taking Nebivolol 5mg Tablets

You should not stop treatment abruptly as this can worsen heart failure. Your doctor will reduce your dose of nebivolol gradually.

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 5mg Tablets can cause side effects, although not everybody gets them.

Hypertension

The side effects reported in people taking nebivolol for hypertension are listed below:

Common Side Effects (that affect more than 1 person in every 100 treated but fewer than 1 person in every 10 treated):
- Headache
- Dizziness
- Tiredness
- An unusual itching or tingling feeling
- Diarrhoea
- Constipation
- Nausea (feeling sick)
- Shortness of breath
- Swollen hands or feet

Uncommon Side Effects (that affect more than 1 person in every 1000 but fewer than 1 person in 100):
- Slow heartbeat or other heart complaints
- Low blood pressure
- Cramp-like leg pains on walking
- Abnormal vision
- Impotence
- Depressive feelings
- Indigestion
- Gas in stomach or bowel
- Vomiting
- Skin rash
- Tightness in the throat
- Nightmares
- Itching

Very rare side effects (that affect fewer than 1 person in every 10,000 treated):
- Fainting
- Worsening of psoriasis (a skin disease - scaly pink patches)
- Rapid onset swelling, especially around the lips, eyes, or of the tongue with sudden difficulty breathing (angioedema).

The following side effects have been reported only in some isolated cases during nebivolol treatment:
- Whole-body allergic reaction, with generalised skin erosion (hypersensitivity reactions)

Chronic Heart Failure

The side effects reported in people taking nebivolol for chronic heart failure are listed below:

Very Common Side Effects (that affect more than 1 person in every 10 treated):
- Slow heartbeat
- Dizziness

Common Side Effects (that affect more than 1 person in every 100 treated but fewer than 1 person in every 10 treated):
- Worsening of heart failure
- Low blood pressure (with symptoms such as feeling faint when you get up quickly)
- Inability to tolerate the medicine
- Irregular heartbeat
- Swollen legs, ankles, or feet

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

5. HOW TO STORE NEBIVOLOL 5mg TABLETS

Keep out of the reach and sight of children.

This medicinal product does not require any special storage conditions.

Do not use Nebivolol 5mg Tablets after the expiry date which is stated on the carton after Exp. The expiry date refers to the last day of that month.

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 5mg Tablets contain

The active substance is nebivolol hydrochloride corresponding to 5mg nebivolol.

The other ingredients are silica colloidial anhydrous, magnesium stearate, croscarmellose sodium, macrogol 6000, and lactose monohydrate.

What Nebivolol 5mg Tablets looks like and contents of the pack

Round, white, biconvex tablets with a cross-score on one side and marked “N5” on the other. The tablets can be divided into equal quarters.

Pack sizes:
Nebivolol 5mg Tablets are provided in either blister packs or HDPE containers of 7, 14, 28, 30, 56, 55, 90, 100, or 500 Tablets.

[Not all pack sizes may be marketed. Only marketed pack sizes will appear on printed version]

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder
Caduceus Pharma Limited, 6P Floor, 94 Wigmore Street, London, W1U 3RF, UK

Manufacturer
Actavis M. Reykjavikvergur 78, 15-220 Hafnarfjörður, Iceland

Or*
Actavis Ltd, B.8016 Bulebel Industrial Estate, Ziażun ZIN 1001, Malta

[Only the manufacturer which released the batch will appear on the printed version]

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