

**PUBLIC ASSESSMENT REPORT
of the Medicines Evaluation Board
in the Netherlands**

**Nebivolol Berolina 5 mg tablets
CDRD Berolina AB, Sweden**

nebivolol (as hydrochloride)

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.

It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.

This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

**EU-procedure number: NL/H/2496/001/DC
Registration number in the Netherlands: RVG 111041**

23 April 2013

Pharmacotherapeutic group:	beta blocking agents, selective
ATC code:	C07AB12
Route of administration:	oral
Therapeutic indication:	treatment of essential hypertension; treatment of stable mild and moderate chronic heart failure in addition to standard therapies in elderly patients > 70 years
Prescription status:	prescription only
Date of authorisation in NL:	2 January 2013
Concerned Member States:	Decentralised procedure with BG, ES
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Nebivolol Berolina 5 mg tablets from CDRD Berolina AB. The date of authorisation was on 2 January 2013 in the Netherlands.

The product is indicated for:

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

A comprehensive description of the indications and posology is given in the SPC.

Mechanism of action and pharmacodynamic effects:

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

- Nebivolol is a competitive and selective beta1-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.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Nebilet 5 mg tablets (NL License RVG 18849) which has been registered in the Netherlands by Menarini International Operations Luxembourg SA since 19 October 1995. This product has been registered in several CMSs through MRP NL/H/0102/001. In addition, reference is made to Nebilet authorisations in the individual member states (reference product).

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. To this end the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Nebilet 5 mg tablets, registered in Germany. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. This generic product can be used instead of its reference product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products, and no paediatric development programme has been submitted, as this is not required for a generic application.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice

The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance

The active substance is neбиволол hydrochloride, an established active substance not described in the European Pharmacopoeia, BP or USP (Ph.Eur.*). The drug substance is a white to off-white powder that is very slightly soluble in water, slightly soluble in methanol and sparingly soluble in dimethyl formamide. Nebivolol hydrochloride contains 4 stereochemic centres and is manufactured as a racemate.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process

Nebivolol hydrochloride is prepared via a five-step synthesis. The quality of the starting materials has been adequately described. The drug substance has been adequately characterized. In general sufficient information has been provided on the synthesis. Also, for the starting material and solvents acceptable specifications have been adopted.

Quality control of drug substance

The drug substance specification from the DMF-holder has been adopted by the MAH. The specification is acceptable in view of the route of synthesis and the various ICH guidelines. Results of batch analysis have been provided of two batches. All results comply with the set specifications.

Stability of drug substance

Stability data has been obtained during storage at 25°C/60%RH (60 months), 30°C/65%RH (12 months), and 40°C/75%RH (6 months). The drug substance was packaged in a simulated commercial packaging. The solid drug substance is stable with respect to degradation, but seems sensitive to light. Based on the stability data provided, the claimed re-test of 60 months can be granted. The proposed storage condition 'Store at 25°C' is not required, but accepted. The drug substance should be stored protected from light.

** Ph.Eur., USP, BP are official handbooks (pharmacopoeias) in which methods of analysis with specifications for substances are laid down by the authorities of the EU, USA, or UK respectively.*

Medicinal Product

Composition

Nebivolol Berolina contains as active substance 5 mg of neбиволол (as hydrochloride), and is a white, round, cross-scored tablet. The tablet can be divided in equal quarter doses.

The tablets are packed in PVC/aluminium blisters.

The excipients are: povidone K30, lactose monohydrate, pregelatinised maize starch, croscarmellose sodium, colloidal anhydrous silica, magnesium stearate, crospovidone

Pharmaceutical development

The development of the product is satisfactory performed and explained. The excipients used are common in the manufacture of tablets. The packaging materials are usual and suitable for the product at issue. Results of batch analysis data and comparative dissolution profiles of the biobatch and reference product batch have been provided. Both products are (almost) completely dissolved (>97%) after 30 minutes. The use of the German reference product Nebilet 5 mg in the bioequivalence study is justified for the markets of the member states involved in this procedure. Results of breakability testing demonstrate compliance with the Ph Eur requirements for halve and quarter tablets. In general, the pharmaceutical development of the product has been adequately performed.

Manufacturing process

The drug product is prepared by a conventional wet granulation process followed by compression. The various steps of the manufacturing process, the process parameters, and the in-process controls have been sufficiently described. Validation data have been provided for three different batch sizes. The results of process validations prove that the fixed mixing times for different batch sizes yield a homogenous mixture of the excipients and the active substance which allow manufacturing of tablets with the desired quality.

Control of excipients

All excipients comply with the Ph.Eur. requirements. These specifications are acceptable.

Quality control of drug product

The product specification includes tests for appearance, identity, average mass, uniformity of dosage units, breakability, disintegration time, hardness, water content, assay, degradation (purity), dissolution and microbiological quality. Uniformity of dosage units is checked for each batch by testing content uniformity in compliance with Ph.Eur. 2.9.40. Batch analysis data have been provided on three batches, demonstrating compliance with the specification.

Stability of drug product

The drug product has been stored at 25°C/60%RH (60 months), 30°C/65%RH (12 months), and 40°C/75%RH (6 months). Overall trends observed are a slight decrease in assay and a slight increase in total impurities at all conditions, and a decrease in hardness at accelerated conditions.

When stored at 40°C/75%RH an increase in degradation products and a decrease in hardness is observed, outside of the specification. It has been demonstrated that the unpacked tablets are not sensitive to light. The proposed shelf-life of 4 years was granted. The storage condition "Do not store above 30°C" is justified.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

Magnesium stearate is manufactured from stearic acid from a vegetable origin. Lactose monohydrate complies with the CPMP "Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human or veterinary medicinal products".

II.2 Non-clinical aspects

This product is a generic formulation of Nebilet, which is available on the European market. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

Environmental risk assessment

The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of nebivolol released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Nebivolol is a well-known active substance with established efficacy and tolerability.

A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Nebivolol Berolina 5 mg (CDRD Berolina AB, Sweden) is compared with the pharmacokinetic profile of the reference product Nebilet 5 mg tablets (Berlin Chemie AG, Germany).

The choice of the reference product

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of reference products.

The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 36 healthy subjects (24 males/12 females) aged 18-42 years. All subjects were selected to be extensive metabolizers of CYP2D6. Each subject received a single dose (5 mg) of one of the 2 nebivolol formulations. The tablet was orally administered under fasted conditions. There were 2 dosing periods, separated by a washout period of 11 or 13 days.

Blood samples were collected pre-dose and at 0.5, 0.75, 1.0, 1.25, 1.5, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0, 24.0, 30.0, 36.0 and 48.0 hours after administration of the products.

In general, this design is considered acceptable. The inclusion of only extensive metabolizers of CYP2D6 is according to the guideline on the investigation of bioequivalence. As extensive metabolizers are expected to have lower plasma levels compared to poor metabolizers, there is a reduced risk for safety concerns. This provided rationale is acceptable.

Analytical/statistical methods

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results

All subjects were confirmed extensive metabolizers of CYP2D6. As there were no drop-out subjects during the study, all were included in pharmacokinetic and statistical analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean \pm SD, t_{\max} (median, range)) of nebivolol under fasted conditions.

Treatment N=36	AUC _{0-t} µg.h/ml	AUC _{0-∞} µg.h/ml	C _{max} µg/ml	t _{max} h	t _{1/2} h
Test	5.0 \pm 2.5	5.5 \pm 2.5	1.4 \pm 0.6	1.0 (0.5-3.0)	--
Reference	5.0 \pm 2.4	5.5 \pm 2.4	1.5 \pm 0.7	1.0 (0.5-2.5)	--
*Ratio (90% CI)	0.97 (0.90-1.04)	--	0.94 (0.83-1.06)	--	--

AUC_{0-∞}	area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours
C_{max}	maximum plasma concentration
t_{max}	time for maximum concentration
t_{1/2}	half-life

**In-transformed values*

The 90% confidence intervals calculated for AUC_{0-t}, AUC_{0-∞} and C_{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the pharmacokinetic parameters of nebivolol under fasted conditions, it can be concluded that Nebivolol Berolina 5 mg and Nebilet 5 mg tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

A total of 4 adverse events were reported by 4 subjects during the study. Of those, 2 subjects were administered the test formulation and 2 administered the reference formulation.

Nebivolol may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of nebivolol. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

Risk management plan

Nebivolol was first approved in 1995, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of nebivolol can be considered to be well established and no product specific pharmacovigilance issues were identified pre or post authorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC

The content of the SPC approved during the decentralised procedure is in accordance with that accepted for the reference product Nebilet.

Readability test

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of a pilot test, followed by two rounds with 10 participants each. In between rounds slight adaptations were made to the final PL to improve clarity. The results of the pilot and two test rounds indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that patients/users are able to act upon the information that it contains. The conclusions are clear, concise and clearly presented. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Nebivolol Berolina 5 mg tablets has a proven chemical-pharmaceutical quality and is a generic form of Nebilet 5 mg tablets. Nebilet is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC is consistent with that of the reference product. The SPC, package leaflet and labelling are in the agreed templates.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Nebivolol Berolina 5 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 26 November 2012. Nebivolol Berolina 5 mg tablets was authorised in the Netherlands on 2 January 2013.

The date for the first renewal will be: 5 November 2017.

There were no post-approval commitments made during the procedure.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C _{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
t _{1/2}	Half-life
t _{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached