CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Nebivolol CF 5 mg tablets
Centrafarm Services B.V., the Netherlands

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/803/001/DC
Registration number in the Netherlands: RVG 33885

Date of first publication: 14 November 2007
Last revision: 26 October 2010

Pharmacotherapeutic group:	beta blocking agents, selective
ATC code:	C07AB12
Route of administration:	oral
Therapeutic indication:	treatment of essential hypertension, and 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:	11 February 2008
Concerned Member States:	AT, BE, DE, EE, FR, IE, IT, LT, LU, LV, PT
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 CF 5 mg tablets from Centrafarm Services B.V. The date of authorisation was on 11 February 2008 in the Netherlands. The product is indicated for the treatment of essential hypertension, and 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 Summary of Product characteristics (SPC).

Nebivolol is a long-acting, cardioselective beta-blocker. Nebivolol consists of a racemic mixture of two enantiomers: D-Nebivolol and L-Nebivolol. Both enantiomers are rapidly resorbed following oral administration, regardless of the absence or presence of food. Nebivolol is extensively metabolized, partly to active hydroxy-metabolites. The metabolism of nebivolol via aromatic hydroxylation is highly dependent on CYP2D6 status. The oral bioavailability of nebivolol is on average 12% in CYP2D6 extensive metabolisers and nearly complete in poor metabolisers. Steady state plasma concentrations of unchanged nebivolol are 23 times higher in poor metabolisers than in extensive metabolisers. The aromatic hydroxyl metabolites have comparable pharmacological and binding features as nebivolol. Other metabolites have no (clinical significant) pharmacological activity. When administered alone, only D-nebivolol but not L-nebivolol has blood-pressure lowering activity. However, the antihypertensive action of D-nebivolol is enhanced by the presence of L-nebivolol.

This application concerns a generic application claiming essential similarity with the innovator product Hypoloc 5 mg tablets, containing 5 mg nebivolol, which has been registered in the Netherlands by Menarini International Operations Luxembourg since 18 October 1995. Another name for the innovator product is Nebilet 5 mg tablets by Berlin Chemie AG or Menarini International Operations Luxembourg. In addition, reference is made to Nebilet/Hypoloc 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 applicant 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.

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 nebivolol hydrochloride, an established active substance. The active substance is not described in the European Pharmacopoeia (Ph.Eur.*) or in a pharmacopoeia of one of the Member States, nor is it described in the USP (Pharmacopoeia in the United States).

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 to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMEA 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.

Quality control of drug substance
The active substance specification is provided by the marketing authorisation holder (MAH), and is considered adequate to control the quality. Batch analytical data demonstrating compliance with this specification have been provided for 3 consecutive batches.

Stability of drug substance
Stability data on the active substance have been provided for 3 batches in accordance with applicable European guidelines demonstrating the stability of the active substance for 6 months without additional temperature conditions. The solid drug substance is susceptible to degradation in light, therefore the active substance should be stored in the original package, i.e. a double PE bag in a HPDE container.

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

Medicinal Product

Composition
Nebivolol CF 5 mg are round, white, biconvex tablets with cross-score, breakable in four equal parts for dosage flexibility. The tablets are packaged into PVC-aluminium blisters packs.

The tablets contain 5.45 mg of the drug substance (nebivolol hydrochloride), which corresponds to 5 mg nebivolol.

The excipients are: povidone K80 (E1201), lactose monohydrate, pregelatinised maize starch, croscarmellose sodium (E468), colloidal anhydrous silica (E551), magnesium stearate (E470B) and crospovidone (E1202).

The excipients, and the quantities of the excipients used, are all common in immediate release tablets.

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

The aim of the development was to obtain a formulation that provides a rapid drug release resulting in plasma concentration profiles corresponding to those of the originator product.

Excipients
The excipients used are common in the manufacture of tablets, and comply with the relevant Ph.Eur. monographs.

Manufacturing process and quality control of the medicinal product
The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for 3 batches in accordance with the relevant European guidelines.

The finished product specifications are adequate to control the relevant parameters for the dosage form. The product specification includes tests for appearance, identity, average mass, uniformity of dosage unit (including broken tablets), disintegration time, assay, degradation (purity), dissolution and microbiological quality. Limits in the specifications have been justified and are considered appropriate for adequate quality control of the product.
Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from the proposed production site(s) have been provided, demonstrating compliance with the specification.

Stability tests on the finished product
Stability data on the product have been provided for 3 batches in accordance with applicable European guidelines demonstrating the stability of the product for 18 months in transparent PVC-aluminium blisters without any special storage conditions. On the basis of the data submitted, the claimed shelf-life of 24 months was granted. Results of the continued studies, at least up to 24 months will be submitted. The drug product is photo stable.
The shelf-life has been changed into 3 years by a type-IB variation (NL/H/0803/001/IB/004). See also table '*Steps taken after finalisation of the initial procedure*' on Page 9.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.2 Non-clinical aspects

This product is a generic formulation of Nebilet/Hypoloc, which is available on the European market. No new pre-clinical data have been submitted, and therefore the application has not undergone pre-clinical assessment. This is acceptable for this type of application.

Environmental risk
The product is intended as a substitute for identical products on the market. The approval of this product will not result in an increase in the total quantity of nebivolol hydrochloride 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 hydrochloride is a well-known active substance with established efficacy and tolerability.

For this generic application, the applicant has submitted one bioequivalence study in which the pharmacokinetic profile of the test product Nebivolol CF 5 mg tablets, by Centrafarm Services B.V., is compared with the pharmacokinetic profile of the reference product Nebilet 5 mg tablets, by Berlin Chemie AG, Germany.

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

Nebivolol hydrochloride should be taken once daily without reference to food intake. Therefore, 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*.

Bioequivalence study
A single-dose, open, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasting conditions in 36 extensive *CYP2D6* metabolisers. According to the guideline for investigation of bioavailability and bioequivalence, only extensive metabolisers (with high activity of *CYP2D6*) were included in the study for safety and pharmacokinetic reasons: in poor metabolisers, the expected plasma levels are higher and thus, the risk for safety concerns may be higher. The bioavailability of the proposed Nebivolol CF 5 mg tablet was compared to the reference product Nebilet 5 mg tablet (Berlin Chemie AG, Germany).

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) of nebivolol following single dose administration under fasting conditions

Treatment	**AUC_{0-t}** ng.h/L	**$AUC_{0-\infty}$** ng.h/L	**C_{max}** ng/L	**t_{max}** h	**$t_{1/2}$** h
Test	4989 ± 2495	5481 ± 2520	1350 ± 580	1.00 ± 0.44 (0.5-3.0)	9.05 ± 2.88
Reference	5030 ± 2378	5494 ± 2393	1450 ± 669	1.00 ± 0.47 (0.5-2.5)	9.27 ± 2.33
***Ratio (90% CI)**	0.97 (0.90-1.04)	0.98 (0.92-1.04)	0.94 (0.83-1.06)	--	--
CV (%)	18	16	31	--	--

$AUC_{0-\infty}$ 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

**ln-transformed values*

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are in agreement with those calculated by the applicant and are within the bioequivalence acceptance range of 0.80 – 1.25. The statistical analysis of the pharmacokinetic data was adequate. Based on the pharmacokinetic parameters, it can be concluded that test Nebivolol CF 5 mg tablet and reference Nebilet 5 mg tablet (Berlin Chemie, Germany) are bioequivalent with respect to rate and extent of absorption of nebivolol, and fulfill the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

The marketed originator product is equivalent in all Member States and therefore bioequivalence studies performed on the test tablet in comparison to the German reference product are accepted. Moreover, the choice of the German reference product in the bioequivalence study has been affirmed by comparison of dissolution results of the reference product in different Member States.

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 hydrochloride was first approved in 1995 in the Netherlands, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of nebivolol hydrochloride 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 applicant 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 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 the approved SPC of the reference products Nebilet/Hypoloc (NL/H/102/103/01) marketed by Berlin Chemie AG or Menarini International Operations Luxembourg.

Readability test

The package leaflet has been evaluated via an user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The readability test has been adequately performed. The test process involved two stages: 1.a pilot test, 2 a final test in an adequate number of participants.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Nebivolol CF 5 mg tablets have a proven chemical-pharmaceutical quality and are generic forms of Nebilet/Hypoloc. Nebilet/Hypoloc 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 SPC is consistent with that of the reference product.

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

The SPC, Package Leaflet and Labelling are in the agreed templates.

The Board followed the advice of the assessors. The Member States, on the basis of the data submitted, considered that bioequivalence has been demonstrated for Nebivolol CF 5 mg with the reference product, and have therefore granted a marketing authorisation. Nebivolol CF is authorised in the Netherlands on 11 February 2008.

There was no discussion in the CMD(h). Agreement between Member States was reached during a written procedure.

A European harmonised birthdate has been allocated for nebivolol and subsequently the internationally approved first data lock point is March 2006. The renewal date is therefore agreed to be 30 November 2009.

The PSUR submission cycle untill then,
PSUR 1: till 30 September 2007
PSUR 2: 1 October 2007 – 31 March 2008
PSUR 3: 1 April 2008 – 31 March 2009
Till the renewal date the PSUR cycle is shortened, because at the end of 2005 the innovator obtained the new indication ‘Chronic heart failure (CHF)’. Thereafter the PSUR submission cycle will be 3 years.

The following post-approval commitments were made during the procedure:

Quality - Drug substance
- Further validation data on the analytical methods used and further evaluation of the limits set, will be provided.

Quality - Drug product
- Process validation data of the first full scale batch will be submitted as soon as available.
- Results of the ongoing stability study at least covering the granted storage period of 2 years will be submitted, including data breakability results at the end of the granted storage period.

Package Leaflet
- The PL will be adapted to the one of the reference product Nebilet after the ongoing harmonization for the latter (MRP variation NL/H/0102/II/022).

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
PL	Package Leaflet
PSUR	Periodic Safety Update Report
RH	Relative Humidity
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	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 procedure	Approval/ non approval	Assessment report attached
Change in pack size of the finished product. Addition of a pack size of 10 tablets. This pack size will only be marketed in Austria and Germany.	NL/H/0803 /001/IA/ 001	IA	3-12-2007	17-12-2007	Approval	N
Change in the name and/or address of the marketing authorisation holder. (PT only).	NL/H/0803 /001/IA/ 002	IA	3-12-2007	17-12-2007	Approval	N
Adaption of the PIL according to the originator, correction of one mistake in the SPC.	NL/H/0803 /001/II/ 003	II	15-4-2008	14-6-2008	Approval	N
Change in the shelf-life of the finished product as packaged for sale.	NL/H/0803 /001/IB/ 004	IB	22-9-2008	13-10-2008	Approval	N
Renewal of the marketing authorisation.	NL/H/0803 /001/R/ 001	Renewal	13-7-2009	14-4-2010	Approval	Y, Annex I
Change in the manufacturing process of the finished product 1.Minor change in the manufacturing process of an immediate release solid oral dosage form or oral solutions. 2.Change in the batch size (including batch size ranges) of the finished product. Up to 10-fold compared to the currently approved batch size.	NL/H/0803 /001/IA/ 005/G	IA/G	10-8-2010	8-9-2010	Non Approval	N
Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product. Secondary packaging site.	NL/H/0803 /001/IA/ 006	IA	22-9-2010	22-10-2010	Approval	N
1. Change in the manufacturing process of the finished product. Minor change in the manufacturing process of an immediate release solid oral dosage form or oral solutions. 2. Minor change in the manufacturing process of an immediate release solid oral dosage form or oral solutions. Change in the batch size (including batch size ranges) of the finished product. Up to 10-fold compared to the currently approved batch size.	NL/H/0803 /001/IA/ 007/G	IA/G	18-10-2010	18-10-2010	Non Approval	N

Annex I – Renewal marketing authorisation (NL/H/0803/001/R/001)

I Recommendation

Based on the review of the data submitted for this renewal application, the benefit/risk balance of Nebivolol CF 5 mg (nebivolol), NL/H/0803/001/R/001, is positive. Therefore, renewal can be granted with unlimited validity.

II Scientific discussion

II.1 Introduction

Nebivolol is a racemate of two enantiomers, SRRR-nebivolol (or d-nebivolol) and RSSS-nebivolol (or l-nebivolol). Nebivolol is a competitive and selective beta-receptor antagonist (SRRR-enatiomer (d-enantiomer)) and it has mild vasodilating properties due to an interaction with the Larginine/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.
The indications are:

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

Below a list of EU Member States/Norway/Iceland, where the product is on the market, is shown.

Country	Authorisation date	Launch date	Trade name	Comments
Austria	A 07/07	05/08	Nebivolol STADA 5 mg Tabletten	NL/H/803/01
Belgium	A 03/08	--	Nebivolol EG 5 mg tablets	NL/H/803/01
Germany	A 07/07 A 07/07	04/08 05/08	Nebivolol STADA 5 mg Tabletten Nebivolol AL 5 mg Tabletten	NL/H/803/01 NL/H/804/01
Estonia	A 04/07	-	Nemirostad 5 mg tabletid	NL/H/803/01
France	A 08/07		Nebivolol EG 5 mg comprimé	NL/H/803/01
Ireland	A 11/07	--	Nebimel 5 mg tablets	NL/H/803/01
Italy	--	--	Nebivolol EG 5 mg compresse.	NL/H/803/01
Lithuania	A 06/07	--	Nemirostad 5 mg tabletes	NL/H/803/01
Luxembourg	--	-	Nebivolol EG 5 mg tablets	NL/H/803//01
Latvia	A 12/07	--	Nemirostad 5 mg tabletes	NL/H/803/01
The Netherlands	A 02/08 A 02/09	-- --	Nebivolol CF 5 mg tabletten Nebilostad 5 mg tabletten	NL/H/803/01 NL/H/804/01
Portugal	A 07/07	--	Nebivolol Ciclum 5 mg comprimidos	NL/H/803/01

The MAH submitted a renewal application for Nebivolol CF tablets. The following documents are assessed in this report:

- Quality Expert Statement for Nebivolol CF (dated and signed May 2009)
- PSUR covering the period 20 April 2004 to 30 September 2007 (dated and signed 22 November 2007)
- PSUR covering the period 01 October 2007 to 31 March 2008 (dated 23 May 2008 and signed)
- PSUR covering the period 01 April 2008 to 31 March 2009 (dated and signed 23 May 2009)
- Summary Bridging Report covering the abovementioned periods (dated and signed May 2009)
- Clinical Expert Statement for Nebivolol CF (dated and signed May 2009)

II.2 Module 1/GMP compliance statements

Manufacturer endproduct and manufaturer responsible for batch release
The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product prior to granting its National authorisation.
For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.
An updated GMP certificate (March 2009) from Centrafarm Services B.V. has been provided.

Manufacturer active ingredient
The applicant submitted a GMP-declaration by the qualified person of the manufacturer of the tablets/manufacturers responsible for batch release. The RMS has no comments regarding this declaration.

Details of contact persons have been provided for the following persons:
• Qualified person in the EEA for pharmacovigilance
• Contact person in the EEA with the overall responsibility for product defects and recalls
• Contact person for scientific service in the EEA in charge of information about the medicinal product

II.3 Quality

In the period between the finalisation of the corresponding DCP for Nebivolol CF 5 mg tablets and present the following change to the quality part of the dossier has been introduced by means of a variation:

- Shelf-life extension from 2 years to 3 years (NL/H/0803/001/IB/004)

In accordance with the CMD(h) *Best Practice Guide on the processing of renewals in the mutual recognition and decentralised procedure* (version November 2008) a quality expert statement has been submitted for Nebivolol CF and Nebilostad confirming:
- That the products are in compliance with the requirements of Directive 2001/83/EC which obliges the MAH "…. *to take account of technical and scientific progress and introduce any changes…*".
- That all changes relating to the quality of the products have been made following applications for variations and that the product conforms to the current CHMP quality guidelines.
  The currently authorised specifications for the active substance and the finished products with the qualitative and quantitative composition have been provided.

There are no outstanding quality commitments.

Comments
The MAH confirms that future reports include the range of dissolution results to document the compliance with the specification NLT 75 % (Q).
The requested data to support the approved storage conditions of *'this medicinal product does not require any special storage conditions*' was provided with variation NL/H/0803/001/IB/004 (shelf life extension). This variation has been approved on 13 October 2008.

II.4 Clinical Efficacy and Safety

II.4.1 Clinical efficacy
No new clinical data have become available during the previous period.
Clinical Safety

II.4.2 Clinical safety - Summary of Cumulative Experience/ Report of Post Marketing Experience 20 April 2004 – 31 March 2009
The PSURs and the SBR (summary bridging report) are included in the assessment of the Nebivolol CF Worksharing (NL/H/PSUR/0029/001).

Clinical Expert Statement
During the period covered by the above-mentioned reports no measures have been taken for safety reasons and the Company Core Safety Information has not been changed.
No serious ADR (Adverse Drug Reaction) reports and 18 non-serious case reports (12 unlisted, 6 listed) have been reported directly to the MAH from spontaneous sources or were received via health authorities.
One serious, unlisted individual case report has been published in the scientific literature.
Neither spontaneous reports nor publications present events that would due to their frequency and/or the nature of the cases in which they occurred signal a new risk.
Based on the data supplied by STADA (MAH at the time of application) the expert comes to the following conclusion: In summary, the evaluated data confirm the balanced safety profile of nebivolol, which is safe and effective in the approved indications. The data do not present or signal a new risk, which is not currently included in the reference safety information.
The clinical expert confirms that no new pre-clinical or clinical data are available in the public domain, which changes or results in a new benefit-risk evaluation. Therefore, the marketing authorization can safely be renewed for an unlimited period, provided that satisfactory responses are given to the preliminary list of questions (Section IV).

II.4.2.1 Conclusion on Safety
Assessment of the documents submitted in scope of the renewal of Nebivolol CF tablets led to the following conclusions: there are no new safety issues, the safety profile of the product has not changed and the renewal can be granted for unlimited validity provided that satisfactory responses are given to the preliminary list of questions (Section IV).

Regarding the next PSUR:

- Nebivolol CF takes part in the PSUR synchronisation project (see appendix 1 for PSUR worksharing AR). The next DLP is March 2012. The next PSUR is expected within 60 days after DLP.

II.5 Product Information

The MAH amended the Product Information (PI) according to the proposed CSP (Core Safety Programme) in the Preliminary Assessment Report of the PSUR work sharing for nebivolol (NL/H/PSUR/0029/001). However there was still some discussion regarding the CSP of nebivolol. The PSUR work sharing for nebivolol (NL/H/PSUR/0029/001) was restarted on 5 March 2010 (day 75). Thus, the latest the work share ended on day 110 (9 April 2010).
The current renewal was restarted and day 85 coincided with day 110 of the PSUR work sharing for nebivolol (NL/H/PSUR/0029/001). This way the CSP could be implemented with the current renewal (NL/H/0803/001/R/001).

Therefore it was requested that the PI will be amended as a result of the PSUR work sharing.

II.5.1 Summary of Product Characteristics
The comments from the member states were taken into account in the PSUR workshare. The E-numbers in section 6.1 have been deleted as requested by.

The MAH was requested to bring sections 4.3-4.9 in line with the CSP on day 85. There were no comments on the other sections of the SPC. See also section V.

II.5.2 Package leaflet and user testing

Package Leaflet
During the DCP the PL was harmonised for this product and is similar to the PIL of the innovator Nebilet. The E-numbers in section 6 have been deleted as requested. As a result of the PSUR worksharing the SPC will probably be changed. The PL should be updated accordingly. See section V.

Assessment of User Testing
A user test has been submitted and assessed during the DCP.

II.5.3 Labelling
Labelling texts were harmonised for this product during the DCP. The pack sizes have been corrected (10 tablets are added).

II.6 Remaining post-approval commitments to be fulfilled by the MAH

All post-approval commitments made at the end of the DCP have been fulfilled.

Taking into account the assessment of the PSUR worksharing, the following post-approval commitments are outstanding:

Area[1]	Description	Due date[2]
Pharmacovigilance	The next PSUR should be submitted after 3 years	March 2012
Pharmacovigilance	The following safety issues should be monitored: - Torsade des Pointes - Cases of serious skin disorders	next PSUR

[1]Areas: Quality, Non-clinical, Clinical, Pharmacovigilance
[2]Due date for the follow-up measure or for the first interim report if a precise date cannot be committed to.

III Overall conclusion and benefit-risk assessment

No new safety issue that warrants regulatory action was identified. The benefit risk balance remains positive.

The renewal can be granted with unlimited validity, provided that the MAH addresses the list of questions in section 8 satisfactory.

The PSUR submission cycle is 3 years. Nebivolol CF takes part in the PSUR synchronisation project of the Heads of Medicine Agencies with a next data lock point of March 2012. The MAH is requested to submit the next PSUR within 60 days following the data lock point of March 2012.

IV List of questions

SPC

1. The MAH is requested to bring sections 4.3-4.9 in line with the CSP on day 85.

PL

2. As a result of the PSUR worksharing the SPC will probably be changed. The PL should be updated accordingly. See section V.

The applicant responded to these issues and brought the product information in line with the CSP for nebivolol, as requested. All outstanding issues have been solved and the renewal was ended positively.

V Amended sections of the SPC and Package leaflet

Red = deleted text
Blue = added text

SPC

Section 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 CF 5 mg 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 < 60 bpm prior to start therapy)
- hypotension (systolic blood pressure < 90 mmHg)
- severe peripheral circulatory disturbances

Section 4.5: Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions

The following interactions apply to beta-adrenergic antagonists in general.

Combinations not recommended:
Class I antiarrhythmics (quinidine, hydroquinidine, cibenzoline, flecainide, disopyramide, lidocaine, mexiletine, propafenone): effect on atrio-ventricular conduction time may be potentiated and negative inotropic effect increased (see section 4.4).

Calcium channel antagonists of verapamil/diltiazem type: negative influence on contractility and atrio-ventricular conduction. Intravenous administration of verapamil in patients with ß-blocker treatment may lead to profound hypotension and atrio-ventricular block (see section 4.4).

Centrally-acting antihypertensives (clonidine, 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 “rebound hypertension”.

Combinations to be used with caution:
Class III antiarrhythmic drugs (Amiodarone): effect on atrio-ventricular conduction time may be potentiated.

Anesthetics - volatile halogenated: concomitant use of beta-adrenergic antagonists and anesthetics may attenuate reflex tachycardia and increase the risk of hypotension (see section 4.4). As a general rule, avoid sudden withdrawal of beta-blocker treatment. The anesthesiologist should be informed when the patient is receiving Nebivolol CF 5 mg.

Insulin and oral antidiabetic drugs: although nebivolol does not affect glucose level, concomitant use may mask certain symptoms of hypoglycemia (palpitations, tachycardia).

Baclofen (antispastic agent), amifostine (antineoplastic adjunct): concomitant use with antihypertensives is likely to increase the fall in blood pressure, therefore the dosage of the antihypertensive medication should be adjusted accordingly.

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

Calcium antagonists of the dihydropyridine type (amlodipine, felodipine, lacidipine, nifedipine, nicardipine, nimodipine, nitrendipine): concomitant use may increase the risk of hypotension, and an increase in the risk of a further deterioration of the ventricular pump function in patients with heart failure cannot be excluded.

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

Non steroidal anti-inflammatory drugs (NSAID): no effect on the blood pressure lowering effect of nebivolol.

Sympathicomimetic agents: concomitant use may counteract the effect of beta-adrenergic antagonists. Beta-adrenergic agents may lead to unopposed alpha-adrenergic activity of sympathicomimetic agents with both alpha- and beta-adrenergic effects (risk of hypertension, severe bradycardia and heart block).

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

Co-administration of cimetidine increased the plasma levels of nebivolol, without changing the clinical effect. Co-administration of ranitidine did not affect the pharmacokinetics of nebivolol. Provided Nebivolol CF 5 mg is taken with the meal, and an antacid between meals, the two treatments can be co-prescribed.

Combining nebivolol with nicardipine slightly increased the plasma levels of both drugs, without changing the clinical effect. Co-administration of alcohol, furosemide or hydrochlorothiazide did not affect the pharmacokinetics of nebivolol. Nebivolol CF does not affect the pharmacokinetics and pharmacodynamics of warfarin.

Section 4.8: Undesirable effects
Adverse events are listed separately for hypertension and CHF because of differences in the background diseases.

Hypertension

The adverse reactions reported, are tabulated below, classified by system organ class and ordered by frequency:

~~*System Organ Class*~~	~~**Common (≥1/100 to < 1/10)**~~	~~**Uncommon (≥1/1,000 to ≤1/100)**~~	~~*Very Rare (≤1/10,000)*~~
~~*Psychiatric disorders*~~		~~*nightmares; depression*~~	
~~Nervous system disorders~~	~~headache, dizziness, paresthesia~~		~~*syncope*~~
~~Eye disorders~~		~~impaired vision~~	
~~Cardiac disorders~~		~~bradycardia, heart failure, slowed AV conduction/AV-block~~	
~~Vascular disorders~~		~~hypotension, (increase of) intermittent claudication~~	
~~Respiratory, thoracic and mediastinal disorders~~	~~dyspnea~~	~~bronchospasm~~	
~~Gastrointestinal disorders~~	~~constipation, nausea, diarrhea~~	~~dyspepsia, flatulence, vomiting~~	
~~Skin and subcutaneous tissue disorders~~		~~pruritus, rash erythematous~~	~~*angioneurotic edema, psoriasis aggravated*~~
~~Reproductive system and breast disorders~~		~~impotence~~	
~~General disorders and administration site conditions~~	~~tiredness, edema~~		

System Organ Class	**Common (*≥1/100 to < 1/10*)**	**Uncommon (*≥1/1,000 to ≤1/100*)**	***Very Rare (≤1/10,000)***	***Not known* (cannot be estimated from the available data)**
Immune system disorders				angioneurotic oedema, hypersensitivity
Psychiatric disorders		nightmares; depression		
Nervous system disorders	headache, dizziness, paresthesia		syncope	
Eye disorders		impaired vision		
Cardiac disorders		bradycardia, heart failure, slowed AV		

		conduction/AV-block		
Vascular disorders		hypotension, (increase of) intermittent claudication		
Respiratory, thoracic and mediastinal disorders	dyspnea	bronchospasm		
Gastrointestinal disorders	constipation, nausea, diarrhea	dyspepsia, flatulence, vomiting		
Skin and subcutaneous tissue disorders		pruritus, rash erythematous	psoriasis aggravated	
Reproductive system and breast disorders		impotence		
General disorders and administration site conditions	tiredness, edema			

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

Chronic heart failure
Data on adverse reactions in CHF patients are available from one placebo-controlled clinical trial involving 1067 patients taking nebivolol and 1061 patients taking placebo. In this study, a total of 449 nebivolol patients (42.1%) reported at least possibly causally related adverse reactions compared to 334 placebo patients (31.5%). The most commonly reported adverse reactions in nebivolol patients were bradycardia and dizziness, both occurring in approximately 11% of patients. The corresponding frequencies among placebo patients were approximately 2% and 7%, respectively.

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

Section 6.1: List of excipients
Povidone K30 ~~(E1201)~~
Lactose monohydrate
Maize starch, pregelatinised
Croscarmellose sodium ~~(E468)~~
Silica, colloidal anhydrous ~~(E551)~~

Magnesium stearate ~~(E470B)~~
Crospovidone ~~(E1202)~~

PIL

Section 2: Before you take Nebivolol CF

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.

Certain medicines cannot be used at the same time, while other drugs require specific changes (in the dose, for example).

Always tell your doctor if you are using or receiving any of the following medicines in addition to Nebivolol CF:
- Medicines for controlling the blood pressure or medicines for heart problems (such as amiodarone, amlodipine, cibenzoline, clonidine, digoxin, diltiazem, disopyramide, felodipine, flecainide, guanfacin, hydroquinidine, lacidipine, lidocaine, methyldopa, mexiletine, moxonidine, nicardipine, nifedipine, nimodipine, nitrendipine, propafenone, quinidine, rilmenidine, verapamil).
- Sedatives and therapies for psychosis (a mental illness) e.g. barbiturates (also used for epilepsy), phenothiazines (also used for vomiting and nausea) e.g. thioridazine.
- Medicines for depression e.g. tricyclic antidepressants, paroxetine, fluoxetine.
- Baclofen (used for the treatment of spastic movement), amifostine (used to treat cancer)
- Medicines used for anaesthesia during an operation.
- Medicines for asthma, blocked nose or certain eye disorders such as glaucoma (increased pressure in the eye) or dilation (widening) of the pupil.

All these drugs as well as nebivolol may influence the bloodpressure and/or
heart function.

- Medicines for treating excessive stomach acid or ulcers (antacid drug), e.g. cimitedine: you should take Nebilvolol STADA during a meal and the antacid drug between meals.
- Insulin or tablets for diabetes. Although nebivolol does not affect glucose level, concomitant use may mask certain symptoms of hypoglycaemia (increased heart beat)

Section 4: Possible Side Effects

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

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

Common side effects (more than 1 person in every 100 treated but less than 1 person in every 10 treated):
- headache
- dizziness
- tiredness
- an unusual itching or tingling feeling (paresthesia)
- diarrhoea
- constipation
- nausea
- shortness of breath
- accumulation of fluid in the body resulting in swelling, particularly of the legs and ankles (edema).

Uncommon side effects (more than 1 person in every 1,000 treated, but less than 1 person in every 100 treated)
- slow heartbeat or other heart complaints

- low blood pressure
- cramp-like leg pains on walking (intermittent claudication)
- abnormal vision
- impotence
- feelings of depression
- digestive difficulties (dyspepsia), gas in stomach or bowel, vomiting
- skin rash, itchiness
- breatlessness such as in asthma, due to sudden cramps in the muscles around the airways (bronchospasm)
- nightmares.

Very rare side effects (fewer than 1 person in every 10,000 treated)
- fainting
- ~~swelling of the lips, eyes or tongue (angioneurotic edema), with possible sudden difficulty breathing~~
- worsening of psoriasis (a skin disease - scaly pink patches).

Not known (cannot be estimated from the available data)
- swelling of the lips, eyes or tongue (angioneurotic edema), with possible sudden difficulty breathing
- allergic reactions

Other side effects seen with drugs that are similar to Nebivolol CF are: hallucinations, mental disorders and confusion, cold fingers and toes sometimes going pale or blue, dry eyes, and a severe disorder of the eyes and mouth.

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

Very common side effects (more than 1 person in every 10 treated)
- slow heart beat
- dizziness

Common side effects (more than 1 person in every 100 but less than 1 person in every 10 treated)
- worsening of heart failure
- low blood pressure (such as feeling faint when getting up quickly)
- inability to tolerate this medicine
- a kind of light heart conduction disorder that affects heart rhythm (1st degree AV-block)
- swelling of the lower limbs (such as swollen ankles).

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

Section 6: Further Information

What Nebivolol CF contains

The active substance is nebivolol. Each tablet contains nebivolol hydrochloride equivalent to 5 mg nebivolol.

The other ingredients are Povidone K30 ~~(E1201)~~; lactose monohydrate; maize starch, pregelatinised; croscarmellose sodium ~~(E468)~~; Silica, colloidal anhydrous ~~(E551)~~; magnesium stearate ~~(E470B)~~ and crospovidone ~~(E1202)~~.

VI Abbreviations used in this Renewal report

ADR	Adverse Drug Reaction
CSP	Core Safety Programme
SBR	Summary Bridging Report