COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Nebivolol ARX 5 mg tablets

(nebivolol hydrochloride)

NL/H/4589/001/DC

Date: 20 November 2019

This module reflects the scientific discussion for the approval of Nebivolol ARX 5 mg tablets. The procedure was finalised on 24 September 2019. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Nebivolol ARX 5 mg tablets from Amarox Limited.

The product is indicated for:

- 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.

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

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 S.A. since 19 October 1995. This product has been registered in several CMSs through MRP NL/H/0102/001.

The concerned member states (CMS) involved in this procedure were France, Germany, Italy and Spain.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Nebivolol ARX 5 mg is a white to off-white, round, biconvex tablets, debossed with cross score line on one side and 'H' on the other side. The tablet can be divided into four equal doses. Each tablet contains 5 mg of nebivolol (as nebivolol hydrochloride).

The tablets are packed in PVC/PVdC-aluminium blisters.

The excipients are: lactose monohydrate, maize starch, croscarmellose sodium (E468), hypromellose (type 2910, 5cps) (E464), polysorbate 80 (E433), microcrystalline cellulose (E460), colloidal anhydrous silica (E551) and magnesium stearate (E572)

II.2 Drug Substance

The active substance is nebivolol hydrochloride, an established active substance for which a Ph.Eur. monograph is not available yet. Nebivolol HCl is a white to off-white crystalline powder, non hygroscopic, sparingly soluble in dimethylformamide, slightly soluble in methanol and very slightly soluble in water and practically insoluble in 0.1 M HCl. . Nebivolol HCl is a racemate and exhibits polymorphism, as it exists in crystalline form and partially amorphous form-T1. The crystalline form is manufactured.

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 HCl is produced by a 4-step chemical synthesis starting from two well characterized starting materials. The substance used for manufacture of the drug product is micronized. An exhaustive characterisation of the active substance has been performed. Potential impurities are addressed, including residual solvents in line with the European guidelines.

Quality control of drug substance

The active substance specification has been established in-house by the MAH. The specifications are acceptable in view of the relevant Ph.Eur. monographs and relevant European guidelines. The drug product manufacturer applies the same specification as the ASMF holder, plus two additional tests: particle size distribution and microbiological quality. The analytical methods and their validation are adequately described in the ASMF and in the drug substance part of the dossier provided by the drug product manufacturer.
Batch analytical data demonstrating compliance with the drug substance specification have been provided by the ASMF holder for three full-scale batches produced and by the drug product manufacturer for four full-scale batches.

Stability of drug substance

Stability studies have been performed on six full-scale batches of nebivolol HCl by the ASMF holder. The stability studies are carried out under ICH conditions. The tested parameters are considered to indicate stability sufficiently, and the HPLC method used is demonstrated to be stability indicating. Based on the stability data provided, the claimed re-test of 5 years is justified. No specific storage conditions are needed. The drug product manufacturer applies the same storage condition and retest period as stated by the ASMF holder.

II.3 Medicinal Product

Pharmaceutical development

The same pharmaceutical form, strengths and excipients as for the reference product have been chosen. The characteristics of drug substance which are important for the performance and manufacturability of drug product are discussed, as well as the compatibility with the excipients. The limit chosen for particle size distribution of the active substance is in line with the results of the batches used to manufacture the biobatch. The stability of the crystalline form of the active substance is sufficiently demonstrated.

The process and formulation development studies are adequately performed and presented in sufficient detail. The critical process parameters are identified and the values settled in the development studies are in line with the ones included in the manufacturing process description and validation reports.

Study results are provided which demonstrate that the tablets can be consequently divided in four equal parts. The SmPC indicates as minimal dosage 1.25 mg, which is a quarter of a tablet. The reference product and other registered generics can also be divided into four doses.

The development of the QC method for dissolution is discussed and is in line with the relevant guideline. The discriminatory power of the method is demonstrated.

The dissolution profile of the biobatch has been compared with that of the reference product and found to be similar, with the exception of the test at pH 4.5. However the results of the bioequivalence study, confirming bioequivalence, prevail. The chosen biobatch is acceptable from a pharmaceutical point of view, in line with the Guideline on Investigation of bioequivalence.

Manufacturing process

The manufacturing process consists of the following steps: granulation, blending and compression. The dossier includes a flow-chart and description of the process including process controls. The manufacturing process has been validated according to relevant European guidelines. Process validation data on the product has been presented for four batches of the minimal proposed batch size. The product is manufactured using conventional manufacturing techniques.

Control of excipients

All of the excipients comply with a Ph. Eur. monograph and are well-known excipients broadly used in similar pharmaceutical forms. Several functionality related characteristics are tested, next to the mandatory tests according to the relevant Ph. Eur. monographs. The specifications are acceptable.

Quality control of drug product

The product specification includes tests for appearance, identity, assay, related substances, dissolution, uniformity of dosage units, average weight, water content, hardness, friability, breakability, microbial quality. The specification at release and shelf-life are adequate and in line with Guideline ICH Q6A. The analytical methods have been adequately described and

validated. The methods for related substances and assay are proven to be stability indicating, by means of forced degradation studies.
Batch analytical data from the proposed production site have been provided for four (minimal) commercial scale batches, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided on four full-scale batches packaged in the proposed commercial packaging and stored at 25°C/60% RH (up to 36 months for three batches and up to 18 months for one batch) and 40°C/75% RH (up to 6 months). The conditions and planned time points used in the stability studies are according to the stability guideline. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light.
The available results show no trends or significant change in results, at all tested conditions.
A shelf life of 24 months has been granted without any special storage condition.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Certificates from the suppliers of all components are included, stating that the substances contain no material of animal origin, with the exception of lactose monohydrate, for which a statement of origin of the materials is included. The product has no risk of BSE/TSE contamination.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Nebivolol ARX has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Nebivolol ARX is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Nebilet, which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. 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.

IV. CLINICAL ASPECTS

IV.1 Introduction

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, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Nebivolol ARX 5 mg (Amarox Limited, UK) is compared with the pharmacokinetic profile of the reference product Nebilet 5 mg (Berlin Chemie AG, Germany).

The choice of the reference product in the bioequivalence study has been justified.
The formula and preparation of the bioequivalence batch are identical to the formula proposed for marketing.

Bioequivalence studies
Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 56 healthy male subjects, aged 19-44 years. Each subject received a single dose (5 mg) of one of the 2 nebivolol formulations. The tablet was orally administered with 240 ml water after (an overnight fast of at least 10 hours There were 2 dosing periods, separated by a washout period of 16 days.

Blood samples were collected pre-dose and at 0.33, 0.67, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.25, 3.5, 3.75, 4, 4.33, 4.67, 5, 5.5, 6, 8, 10, 12, 16, 24, 36 and 48 hours after administration of the products.

The design of the study is acceptable. A single dose study using 5 mg tablet is appropriate to support the application for the proposed immediate-release product. The conduct of the study under fasting conditions is appropriate as the proposed product can be taken with or without food.
Nebivolol chloride is a racemic mixture of two enantiomers: R-SSS-nebivolol (l-nebivolol) and S-RRR-nebivolol (d-nebivolol). A washout period of 16 days is adequate to prevent carry-over

effects as this is more than 5x the half-life (i.e. about 10 hours for fast metabolisers and 3-5 times longer in slow metabolisers) of the nebivolol enantiomers.

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
56 (+2 extra subjects) were enrolled in the study. One withdrew consent before dosing of period 1 and was replaced with extra subject 1. Among the 56 subjects dosed, five subjects were withdrawn from the study for the following reasons:

- three subjects did not report to the facility during Period 2 admission.
- one subject had a positive alcohol breath test during Period 2 admission.
- one subject was withdrawn from the study due to an adverse event.

Hence, 51 subjects completed both periods of the study and the data from all of these subjects were included in the pharmacokinetic and statistical analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax (median, range)) of R-SSS nebivolol under fasted conditions

Treatment N=51	**AUC_{0-t}** (ng.h/ml)	**$AUC_{0-\infty}$** (ng.h/ml)	**C_{max}** (ng/ml)	**t_{max}** (h)	**$t_{1/2}$** (h)
Test	8.872 ± 12.523	12.464 ± 28.690	1.334 ± 0.397	1.00 (0.67– 6.00)	--
Reference	7.776 ± 9.179	10.285 ± 20.944	1.280 ± 0.415	1.00 (0.67 – 4.33)	--
***Ratio (90% CI)**	1.07 (1.04–1.11)	1.08 (1.04–1.11)	1.05 (0.99 – 1.11)	--	--
CV (%)	--	--	--	--	--

$AUC_{0-\infty}$ 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
CV coefficient of variation

**ln-transformed values*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax (median, range)) of S-RRR nebivolol under fasted conditions

Treatment N=51	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)	$t_{1/2}$ (h)
Test	6.432 ± 10.128	7.634 ± 14.400	0.950 ± 0.439	1.00 (0.67 – 6.00)	--
Reference	5.982 ± 8.438	6.900 ± 11.165	0.924 ± 0.461	1.00 (0.67 – 4.33)	--
***Ratio (90% CI)**	1.03 (1.00 – 1.06)	1.02 (0.98 – 1.06)	1.03 (0.98 – 1.09)	-	--
CV (%)	--	--	--	--	--

$AUC_{0-\infty}$ 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
CV coefficient of variation

**ln-transformed values*

Conclusion on bioequivalence study

The 90% confidence intervals calculated for AUC0-t, AUC0-∞ and Cmax of the two enantiomers are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Nebivolol ARX 5 is considered bioequivalent with Nebilet 5 mg.

Safety

Three (3) mild-moderate adverse events (2 after reference and 1 after test product) were reported by 3 subjects during the conduct of the study. No serious or clinically significant adverse event occurred during the conduct of the study.

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).

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Nebivolol ARX.

Table 3. Summary table of safety concerns as approved in RMP

Important identified risks	None

Important potential risks	None
Missing information	None

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Nebilet. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet (PL) has not been evaluated via a user consultation study. The MAH submitted a bridging report for the content and a separate bridging report for the layout. The content of the PL (i.e. safety information) is generally in line with the PL for Nebilet 5 mg. The proposed design/layout for the PL is similar to the PL for PT/H/0515 (levetiracetam 750 mg film-coated tablets). The justification for bridging and the bridging reports are accepted for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Nebivolol ARX 5 mg tablets has a proven chemical-pharmaceutical quality and <are/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 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 ARX 5 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 24 September 2019.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse