COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Nebivolol Accord 2.5 mg and 5 mg tablets (nebivolol hydrochloride)

NL/H/5187/001-002/DC

Date: 17 January 2022

This module reflects the scientific discussion for the approval of Nebivolol Accord 2.5 mg and 5 mg tablets. The procedure was finalised at 18 November 2021. 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 Accord 2.5 mg and 5 mg tablets, from Accord Healthcare B.V.

The product is used for the following 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.

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/H/0102/001) which has been registered in the European Union by since 1995 (original product) by Berlin-Chemie, Menarini, Germany (for NL/H/5187/001/DC) and Menarini, Luxembourg (for NL/H/5187/002/DC). Additionally, a new strength is applied for, the 2.5 mg tablets as a hybrid application.

The concerned member state (CMS) involved in this procedure was Cyprus for the 2.5 mg tablets and Austria, Cyprus, Denmark, Finland, Ireland and Italy for the 5 mg tablets.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC for 5mg and Article 10(3) of Directive 2001/83/EC for 2.5mg.

II. QUALITY ASPECTS

II.1 Introduction

Nebivolol Accord 2.5 mg tablets:
Round, white, biconvex, uncoated tablets, marked with 'NE2' on one side and plain on the other side.

Nebivolol Accord 5 mg tablets:
Round, white, convex, cross-scored tablets (snap-tab cross-score), marked with 'NE3' on other side. The tablet can be divided into equal quarters.

The tablets contain as active substance 2.725 mg or 5.45 mg of nebivolol hydrochloride respectively, equivalent to 2.5 mg and 5 mg of nebivolol.

The tablets are packed in clear PVC/PVDC aluminium and PVC/PE/PVDC aluminium blisters.

The excipients are colloidal silica – hydrated (E551), magnesium stearate (E572), croscarmellose sodium (E468), macrogol (E1521) and lactose.

The two tablet strengths are dose proportional.

II.2 Drug Substance

The active substance is Nebivolol, an established active substance not described in the any Pharmacopoeia although a draft USP monograph is available. The active substance is a white to off-white crystalline powder and is insoluble in water, sparingly soluble in dimethyl formamide and slightly soluble in methanol. Nebivolol hydrochloride has been shown to have the prior art form, and was shown to be stable over time. Nebivolol has four chiral centres and is a mixture of two isomers. Control of the eight other possible isomers has been described.

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

The synthesis of nebivolol as performed by the manufacturer consists of five stages starting from the starting material. The five stages comprises of five chemical transformations and one separation of diastereomers. No class 1 solvents have been used in the synthesis of nebivolol hydrochloride. The drug substance might be micronized on the request of the drug product manufacturer. The active substance has been adequately characterized and acceptable specifications have been adopted for the starting material, solvents and reagents.

Quality control of drug substance

The active substance specification is established in house and is in line with the draft USP monograph and general guidelines. The drug substance is tested for the following parameters by the drug product manufacturer: description, solubility, identification, chloride content, melting range, loss on drying, sulphated ash, related substances, stereo-isomer purity, assay residual solvents, polymorph, particle size and content of the starting materials. The

specification is acceptable in view of the route of synthesis and the various European guidelines.

Batch analytical data demonstrating compliance with the drug substance specification have been provided for nine batches.

Stability of drug substance

Stability data on the active substance have been provided for three small scale batches stored at 25°C/60% RH (60 months) and 40°C/75% RH (six months), as well as one micronized batch stored for 60 months at 25°C/60% RH. In addition data up to nine months at 25°C/60% RH and up to six months at 40°C/75% RH have been provided for three large scale batches. No clear up- or downward trends have been observed for all batches as well as the micronized batch. The batches were stored in double polyethylene bags, inner clear outer black, in triple laminated bag, kept in a HDPE container. This is all in accordance with applicable European guidelines and demonstrates the stability of the active substance for 60 months. Based on the data submitted, a retest period could be granted of 60 months with no special temperature restrictions in the storage conditions.

II.3 Medicinal Product

Pharmaceutical development

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

The development of the product has been described, the choice of excipients is justified and their functions explained. The aim of this development was to obtain a formulation which is stable, robust and has comparable dissolution as the reference product. Based on the information available for the reference product a formulation was set and further optimized for the levels of croscarmellose sodium and magnesium stearate. The pharmaceutical development of the product has been adequately performed, and the choice of packaging materials and manufacturing process have been justified. The batch used in the bioequivalence study is acceptable, as it was manufactured according to the finalized composition and manufacturing process, at the intended commercial scale and at the proposed site. Furthermore, the test batch has a comparable quality as the reference product Nebilet. The requested biowaiver of strengths is acceptable, dissolution studies at three pH's were performed an showed comparable dissolution in all three media.

Manufacturing process

Nebivolol tablets are manufactured by the following steps: Granulation, compression and packaging. The granulation steps is divided in API mixing, sifting blending, sifting and blending. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three commercial scale batches of each strength. The product is manufactured using conventional manufacturing techniques.

Control of excipients
The excipients comply with Ph. Eur. requirements. These specifications are acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for description, average weight, identification, water content, friability, resistance to crushing, disintegration time, dissolution, uniformity of dosage units, related substances, assay, microbial examination, and, only for the 5 mg tablets, subdivision of tablets. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. The release and shelf-life specification have different limits for the tests for water content, resistance to crushing and related substances The proposed specification is acceptable. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on three commercial scale batches, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided on three full scale batches of each strength stored at 25°C/60% RH (24 months) and 40°C/75% RH (six months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in clear PVC/PVDC- aluminium blister, or clear PVC/PE/PVDC ultrasafe-aluminium blister. Photostability studies were performed in accordance with ICH Q1B recommendations and showed that the products are stable when exposed to light. The proposed shelf-life of 24 months is acceptable without special temperature storage conditions. It has been sufficiently shown that the product is photostable and not sensitive to moisture, therefore it is not required to include a storage condition to protect from light and/or moisture.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Scientific data and/or certificates of suitability issued by the EDQM for lactose 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.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Nebivolol Accord 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 Accord 2.5 mg and 5 mg is intended for hybrid and generic substitution respectively, 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 one bioequivalence study, in which the test product Nebivolol 5 mg tablets are compared against the reference product Nebilet 5 mg tablets.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Nebivolol 5 mg tablets (Intas Pharmaceuticals Limited, India) is compared with the pharmacokinetic profile of the reference product Nebilet 5 mg tablets (Menarini International Operations, Luxemburg). The d- and l- enantiomer were separately measured to test bioequivalence.

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of the EU reference product.
The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver

Based on the bioequivalence study using Nebivolol 5 mg tablets, a waiver for the additional strength 2.5 mg is being applied for based on the following requirements stated in the BE guideline:

a) All the strengths i.e. 2.5 mg and 5 mg of proposed pharmaceutical products are manufactured by the same manufacturer using the same manufacturing process,
b) The qualitative composition of the Nebivolol tablets 2.5 mg is same as that of Nebivolol tablets 5 mg.
c) The composition of the all strengths i.e. 2.5 mg and 5 mg are quantitatively proportional i.e. the ratio between the amount of each excipient to the amount of active substance(s) is same among 2.5 mg and 5 mg strengths.
d) The in-vitro dissolution profile is similar under identical conditions for the additional strengths i.e. 2.5 mg and the strength of batch used in the bioequivalence studies i.e. 5 mg.
e) Nebivolol demonstrates linear pharmacokinetics over the therapeutic dose range of 2.5-20 mg.

This is considered adequate, and the biowaiver for the 2.5 mg tablets is therefore approvable.

Bioequivalence studies

Design

An open-label, randomized, two-treatment, two-period, two-sequence, single-oral dose, crossover, bioequivalence study was carried out under fasted conditions in 56 healthy male subjects, aged 18-41 years. Each subject received a single dose (5 mg) of one of the two nebivolol formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least ten hours. There were two dosing periods, separated by a washout period of 27 days.

Blood samples were collected pre-dose and at 0.167, 0.33, 0.5, 0.75, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.5, 5, 5.5, 6, 8, 10, 12, 16, 24, 36, 48 and 72 hour after administration of the products.

The design of the study is acceptable.

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.

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
Out of a total of 56 subjects, 53 were eligible for pharmacokinetic analysis. One subject was withdrawn due to medical grounds. One subject withdrew on his own accord and one subject was withdrawn due to protocol non-compliance.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of d-nebivolol (5 mg) under fasted conditions.

Treatment N=53	**AUC_{0-72} (ng.h/ml)**	**C_{max} (ng/ml)**	**t_{max} (h)**
Test	6385 ± 11639	547 ± 454	1.33 (0.75 – 5.50)
Reference	6195 ± 11342	581 ± 431	1.33 (0.75 – 6.00)
***Ratio (90% CI)**	1.028 (0.9697 – 1.0888)	0.909 (0.8555 – 0.9658)	--
AUC_{0-72} area under the plasma concentration-time curve from time zero to 72 hours **C_{max}** maximum plasma concentration **t_{max}** time for maximum concentration			

**ln-transformed values*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of l-nebivolol (5 mg) under fasted conditions.

Treatment N=53	**AUC_{0-72} (ng.h/ml)**	**C_{max} (ng/ml)**	**t_{max} (h)**
Test	11264 ± 22331	978 ± 575	1.0 (0.50 – 6.02)
Reference	11060 ± 21669	1070 ± 522	1.0 (0.52 – 6.00)
***Ratio (90% CI)**	1.005 (0.9660 – 1.0454)	0.891 (0.8414 – 0.9426)	--
AUC_{0-72} area under the plasma concentration-time curve from time zero to 72 hours **C_{max}** maximum plasma concentration **t_{max}** time for maximum concentration			

*ln-transformed values

Conclusion on bioequivalence study:

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Nebivolol Accord is considered bioequivalent with Nebilet.

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 Accord.

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

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Nebivolol Berolina 5 mg tablets (NL/H/2496/001/DC) for key safety messages and Solifenacin succinate 5/10 mg film-coated tablets for design/layout. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Nebivolol Accord 2.5 mg and 5 mg tablets have a proven chemical-pharmaceutical quality and are respectively hybrid and generic and forms 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 concerned member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Nebivolol Accord with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 18 November.

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