COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Nortriptyline BB 10 mg, 25 mg and 50 mg film-coated tablets (nortriptyline hydrochloride)

NL/H/5159/001-003/DC

Date: 25 January 2022

This module reflects the scientific discussion for the approval of Nortriptyline BB 10 mg, 25 mg and 50 mg film-coated tablets. The procedure was finalised on 17 March 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 Nortriptyline BB 10 mg, 25 mg and 50 mg film-coated tablets, from Brown & Burk IR Limited.

The product is indicated for the treatment of Major Depressive Episodes in adults.

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 Nortrilen 10 mg, 25 mg and 50 mg, film-coated tablets (NL RVG 03285, 03286 and 11407) which has been registered in The Netherlands by Lundbeck B.V. since 26 November 1964 (10 and 25 mg strength) and 14 May 1987 (50 mg strength).

The concerned member state (CMS) involved in this procedure was United Kingdom (Northern Ireland).

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

II. QUALITY ASPECTS

II.1 Introduction

Nortriptyline 10 mg is a white to off-white coloured, round, biconvex, film-coated tablet debossed with 'NT' on one face and other face plain. Each tablet contains 25 mg nortriptyline hydrochloride.

Nortriptyline 25 mg is a orange coloured, round, biconvex, film-coated tablets debossed with 'N' and 'T' on either side of breakline on one face and other face plain. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses. Each tablet contains 25 mg of nortriptyline hydrochloride.

Nortriptyline 50 mg is a white to off-white coloured, round, biconvex, film-coated tablet debossed with 'N50' on one face and other face plain. Each tablet contains 50 mg of nortriptyline hydrochloride

The tablets are packed in Alu-Alu, Alu-PVC/PE/PVDC blister packs or HDPE containers.

The excipients are:

Tablet core - lactose monohydrate, maize starch, calcium hydrogen phosphate (E341), magnesium stearate (E470b).

Coating
For 10 mg & 50 mg - hypromellose (464), glycerol (E422).
For 25 mg - hypromellose (E464), glycerol (E422), sunset yellow FCF aluminum lake (E110).

The three tablet strengths are dose proportional.

II.2 Drug Substance

The active substance is nortriptyline hydrochloride, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white or almost white powder and sparingly soluble in water. The active substance is not chiral and therefore there are no stereochemical issues. Nortriptyline hydrochloride exists in two polymorphic forms, which are Form-α and β. For this procedure, Form-α is consistently produced.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specification is in line with the CEP. The specification is acceptable in view of the route of synthesis and the various European guidelines. An acceptable justification for not including microbial control in the specification of the drug substance has been provided. Batch analytical data demonstrating compliance with this specification have been provided for one batch.

Stability of drug substance
The active substance is stable for 36 months/years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

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 choice of excipients is justified and their functions explained. The choices of packaging and manufacturing process are adequately justified based on the dosage form. Comparative dissolution at three pHs has been successfully studied in support of bioequivalence and the biowaiver of strengths. The dissolution method has been sufficiently justified. A commitment to provide a comparative dissolution profile testing on the first three production batches has been enclosed. The optimal composition and manufacturing process parameters have been adequately investigated. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The drug product is manufactured by a wet granulation process which consists of mixing, granulation, lubrication, compression and film-coating. The manufacturing process has been validated according to relevant European guidelines. Process validation data on the product have been presented for two minimum scale batches of each strength in accordance with the relevant European guidelines. The product is manufactured using conventional manufacturing techniques. Process validation for full scaled batches will be performed post authorisation.

Control of excipients

The excipients comply with Ph.Eur. and in-house requirements and their 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 appearance, identification, water content, uniformity of dosage units, dissolution, assay, related substances and microbial limits. Limits in the specification 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 ontwo minimum scaled batches of each strength from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product has been provided for two minimum scaled batches of each strength stored at 25°C/60%RH (18 months) and 40°C/75%RH (6 months) in accordance with applicable European guidelines. On basis of the data submitted, a shelf life was granted of 24 months. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light. No specific storage conditions need to be included in the SmPC or on the label.

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.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Nortriptyline BB has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitment was made:

- The MAH commits to perform comparative dissolution profile study on the first three production batches as and when these batches are manufactured and the relevant documents will be made available at the manufacturing site for the inspectorate upon request.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Nortriptyline BB 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 Nortrilen 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

Nortriptyline hydrochloride 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, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Nortriptyline BB 50 mg film-coated tablets (Brown & Burk IR Limited, Ireland) is compared with the pharmacokinetic profile of the reference product Nortrilen 50 mg, film-coated tablets (Lundbeck B.V., The Netherlands).

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

Biowaiver

The MAH has requested a biowaiver for the lower strengths 10 and 25 mg, based on the provided bioequivalence study with the 50 mg formulation. The following conditions have been met:

- the pharmaceutical products are manufactured by the same manufacturing process,
- the qualitative composition of the different strengths is the same,
- the composition of the strengths are quantitatively proportional,
- appropriate *in vitro* dissolution data confirm the adequacy of waiving additional *in vivo* bioequivalence testing.

Therefore, a biowaiver has be granted.

Bioequivalence study

Design

A randomised, two-treatment, two-sequence, two-period, two-way, crossover, single-dose, oral bioequivalence study was carried out under fasted conditions in 42 healthy subjects, aged 22-43 years. Each subject received one dose (50 mg) of one of the two nortriptyline hydrochloride formulations. The tablet was orally administered with water after 10 hours of fasting. There were two dosing periods, separated by a washout period of 14 days.

Blood samples were collected pre-dose and at 0.5, 1, 2, 3, 3.5, 4, 4.33, 4.67, 5, 5.33, 5.67, 6, 6.33, 6.67, 7, 7.5, 8, 8.5, 9, 9.5, 10, 12, 14, 16, 24, 36, 48 and 72 hours after administration of the products.

The design of the study is acceptable. Nortriptyline hydrochloride may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of nortriptyline hydrochloride. 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
Four subjects were withdrawn/discontinued: one subject was withdrawn during wash-out in Period I on its own accord, one subject withdrew voluntarily after before dosing in Period II, and two subjects did not report for check-in at period II. Therefore, 38 subjects were eligible for pharmacokinetic analysis.

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

Treatment N=38	**AUC_{0-72h} (ng/ml/h)**	**C_{max} (ng/mL)**	**t_{max} (h)**
Test	1427.57 ± 492.44	43.97 ± 19.84	6.0 (4-12)
Reference	1375.82 ± 491.74	43.41±19.09	4.67 (4.33-12)
***Ratio (90% CI)**	1.01 (0.99-1.04)	1.00 (0.96-1.04)	-
AUC_{0-72h} Area under the plasma concentration curve from administration to 72 hours. **C_{max}** Maximum plasma concentration **t_{max}** Time until C_{max} is reached			

**ln-transformed values*

Conclusion on bioequivalence study:
The 90% confidence intervals calculated for AUC_{0-72h} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Nortriptyline BB is considered bioequivalent with Nortrilen.

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 Nortriptyline BB.

Table 2. 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 Nortrilen. 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 Nortrilen 10 mg, 25 mg & 50 mg film-coated tablets (RVG 03285, RVG 03286 & RVG 11407) and Nortriptyline Mylan 10 mg, 25 mg and 50 mg film-coated tablets (Procedure number: NL/H/4190/001-002/DC & NL/H/42071001 /DC). Furthermore the PL design and layout is similar with that of Atorvastatin 10 mg, 20 mg, 40 mg & 80 mg film-coated tablets. 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

Nortriptyline BB 10, 25 and 50 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Nortrilen, 10, 25 and 50 mg, film-coated tablets. Nortrilen 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 Nortriptyline BB with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 17 March 2021.

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
NL/H/5159/ 1-3/IB/001	Type IB, C.I.z – Changes (Safety/Efficacy) to Human and Veterinary Medicinal Products - Other variation	SmPC, PL	24-11-2021	Approved	