COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Nortriptyline Mylan 10 mg and 25 mg, film-coated tablets

(nortriptyline hydrochloride)

NL/H/4190/001-002/DC

Date: 22 July 2019

This module reflects the scientific discussion for the approval of Nortriptyline Mylan 10 mg and 25 mg, film-coated tablets. The procedure was finalised at 10 January 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 Nortriptyline Mylan 10 mg and 25 mg, film-coated tablets, from Mylan B.V.

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 and 25 mg, film-coated tablets (NL License RVG 03285 & 03286) which has been registered in The Netherlands by Lundbeck B.V. since 26 November 1964.

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

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

II. QUALITY ASPECTS

II.1 Introduction

Nortriptyline Mylan 10 mg and 25 mg are white, round, film-coated tablets, debossed respectively with '10' or '25' on one side. The tablets contain respectively 10 or 25 mg nortriptyline hydrochloride.

The film-coated tablets are packed in Clear PVC-PVDC/Aluminium blisters or HDPE bottles with screw cap .

The excipients are:
Tablet core - lactose monohydrate, maize starch, microcrystalline cellulose (E460) and magnesium stearate (E470b)
Film-coating - hypromellose (E464), titanium dioxide (E171) and macrogol

II.2 Drug Substance

The active substance is Nortriptyline hydrochloride, an established active substance described in the European Pharmacopoeia (Ph.Eur.). It is a white or almost white powder and sparingly soluble in water, soluble in ethanol (96%) and methylene chloride. The active

substance is not chiral and therefore there are no stereochemical issues. Nortriptyline hydrochloride displays polymorphism, which is adequately controlled.

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 considered adequate to control the quality and meets the requirements of the CEP with additional requirements for particle size and microbial limits. In addition, the specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance

The active substance is stable for two 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 the packaging and manufacturing process are justified in relation to the innovator. A bioequivalence study has been performed versus the reference product. The test product batch of the highest strength used in the bioequivalence study was manufactured according to the finalised composition and manufacturing process. Comparative dissolution studies at 3 pHs with the innovator product as well as the lower strength have generally been adequately performed to support the bioequivalence study and the biowaiver of additional strength respectively. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The tablets are manufactured by wet granulation. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three pilot scaled batches of both strengths. 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. 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 description, identification, average weight, water content, content uniformity, assay, dissolution, dibenzosuberone, microbial limits and related substances. The release and shelf-life limits are identical. 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 from three pilot scaled batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product have been provided for three pilot scaled batches of each strength stored at 25°C/60%RH (24 months) and 40°C/75%RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light. No changes are seen for any of the tested stability indicating parameters. On basis of the data submitted, a shelf life was granted of 36 months when stored in the blisters or bottles without any special precautions for storage.
In addition, in-use stability data has been provided demonstrating that the product remains stable for 120 days following first opening of the container.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
TSE/BSE risk free certificates from the drug substance manufacturer and the excipient manufacturers 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 Mylan 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 Nortriptyline Mylan 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 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 Nortriptyline Mylan 25 mg, film-coated tablets (Mylan B.V., NL) is compared with the pharmacokinetic profile of the reference product Nortrilen 25 mg, film-coated tablets (Lundbeck B.V., NL).

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

Biowaiver
A biowaiver request for the additional 10 mg strength is being applied for.

The following requirements for granting a biowaiver for additional strength(s) are met:

- the pharmaceutical products are manufactured by the same manufacturing process,
- the qualitative composition of the different strengths is the same
- Dissolution data showing that all batches at all three pH, 92% or more is dissolved at 15 minutes.

Overall, a biowaiver for the additional strength 10 mg can be granted as all requirements for a biowaiver for additional strength are fully fulfilled.

Bioequivalence study

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 34 healthy male subjects, aged 21-40 years. Each subject received a single dose (25 mg) of one of the 2 nortriptyline 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 28 days.

Blood samples were collected at pre-dose and at 1, 2, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 9.00, 10, 12, 16, 24, 36, 48 and 72 hours after administration of the products.

The design of the study is acceptable.

Nortriptyline may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption. 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

One subject withdrew from the study. Therefore, a total of 33 subjects completed the study and were eligible for pharmacokinetic analysis.

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

Treatment N=33	AUC_{0-72} (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)
Test	589 ± 157	16.4 ± 3.9	6.5 (3.5– 10)
Reference	589 ± 138	16.5 ± 4.1	6.0 (3.5 – 10)

***Ratio (90% CI)**	1.00 (0.95– 1.04)	1.00 (0.94 – 1.05)	--

$AUC_{0-\infty}$ 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

**In-transformed values*

Conclusion on bioequivalence study

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

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 Mylan.

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	- Suicide/Suicidal thoughts or clinical worsening - Withdrawal symptoms - Cardiovascular disorders (myocardial infarction, cardiac arrhythmias and stroke) - Serotonergic syndrome in concomitant use with MAO-inhibitors - Increased risk of bone fractures
Important potential risks	- Use during pregnancy and lactation
Missing information	- Use in paediatric population

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

The package leaflet (PL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of: a pilot test with 2 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Nortriptyline Mylan 10 mg and 25 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Nortrilen 10 and 25 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 Mylan with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 10 January 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
NL/H/4190/1-2/IA/001/G	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of human medicinal products intended to implement the outcome of a procedure concerning PSUR or PASS, or the outcome of the assessment done by the competent authority under Articles 45 or 46 of Regulation 1901/2006; implementation of wording agreed by the competent authority	Yes	11 May 2019	Approved	-