COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Nortriptyline Milstein 50 mg, tablets

(nortriptyline hydrochloride)

NL Licence RVG 116782

Date: 19 August 2019

This module reflects the scientific discussion for the approval of Nortriptyline Milstein 50 mg, tablets. The marketing authorisation was granted on 31 May 2018. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
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 Medicines Evaluation Board (MEB) of the Netherlands has granted a marketing authorisation for Nortriptyline Milstein 50 mg, tablets from Milstein C.V.

The product is indicated for treatment of episodes of major depression.

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

This national procedure concerns a generic application claiming essential similarity with the innovator product Nortrilen 50 mg film-coated tablets (NL Licence RVG 11407), which has been registered in the Netherlands by Lundbeck B.V. since 14 May 1987.

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

II. QUALITY ASPECTS

II.1 Introduction

Nortriptyline Milstein 50 mg is a white to off-white, round, biconvex tablet debossed 'NO' on one side and '50' on the other side.

Each tablet contains as active substance nortriptyline hydrochloride corresponding to 50 mg nortriptyline.

The film-coated tablets are packed in a HDPE bottle with a polypropylene cap.

The excipients are: lactose monohydrate, maize starch and magnesium stearate

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 sparingly soluble in water, soluble in ethanol and methylene chloride. The active substance does not contain a chiral centre nor is polymorphism reported.

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 specification of the MAH is set conform the Ph.Eur. monograph and CEP. Additional requirements are included for assay, a residual solvent and particle size. The specification is acceptable. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three full-scale batches.

Stability of drug substance
The MAH provided stability data on more than 10 batches of the drug substance. The active substance was stored at long-term conditions (25°C±2°C/60±5% RH) up to 60 months, at accelerated conditions (40°C±2°C/75±5% RH) up to 6 months and at intermediate stability conditions (30°C±2°C/75±5% RH) up to 48 months. Results remain stable over time, no specific changes are noted in assay or degradation products. All results are compliant with the specification. Sufficient stability data is provided to support the proposed re-test of 60 months. No storage conditions are considered necessary.

II.3 Medicinal Product

Pharmaceutical development
The pharmaceutical development of the product is adequately described. In support of this national application, the applicant has submitted a bioequivalence study using the Dutch reference product 50 mg Nortrilen and the proposed 50 mg test product. The discriminative nature of the dissolution method is sufficiently shown. Dissolution data show that at 15 minutes, for the test batch over 85% is dissolved.

Manufacturing process
The manufacturing process consists of sifting, mixing, granulation, drying, lubrication and compression of tablets. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for two full-scale batches.

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

Quality control of drug product
The product specification includes tests for description, identification, water, dissolution, related substances, assay, uniformity of dosage units and microbial tests. Release and shelf-

life specification are identical except for the limits for impurities measured per HPLC method. All limits and parameters are acceptable and in line with various European guidelines and requirements. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on three pilot-scale batches, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product has been provided five batches stored at 25°C/60% RH (3-18 months) and 40°C/75% RH (3-6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in HDPE bottles with PP cap. The product is stable under both conditions. Only a slight increase is noted in impurities. The claimed shelf-life of 30 months can be granted based on the provided data. The storage claim (none) is acceptable. Photostability studies demonstrate that the product is not sensitive to light. Stability data demonstrating that the product remains stable after first opening shows that the product is stable throughout its intended period of use.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

Lactose monohydrate is the only excipient of animal origin. 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 MEB considers that Nortriptyline Milstein 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 Milstein 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 MEB 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 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 Milstein 50 mg film-coated tablets (Milstein C.V., the Netherlands) 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 studies is justified. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

<u>Bioequivalence studies</u>
Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 60 healthy male subjects, aged 18-40 years. Each subject received a single dose (50 mg) of one of the 2 nortriptyline hydrochloride formulations. The tablet was orally administered with 240 ml water after an overnight fast of 10 hours. There were 2 dosing periods, separated by a washout period of 28 days.

Blood samples were collected pre-dose and at 0.5, 1, 2, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10, 12, 16, 20, 24, 36, 48, 72, 96, 120, 144 and 168 hours after administration of the products.

The design of the bioequivalence study is acceptable. The wash-out period was 28 days, which is more than 5 half-lives of nortriptyline (half-life of 16 to 38 hours). In addition,

nortriptyline was not quantifiable in all subjects pre-dosing in the 2nd period of the study. Cmax is reached ~5 hour after dosing and the sampling around this period is sufficient.
The sampling period was long enough and the sampling scheme was adequate to estimate the pharmacokinetic parameters. The bioequivalence study was performed under fasted conditions which was adequate as nortriptyline may be taken regardless of food.

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
Two subjects were withdrawn from the study due to adverse events (abdominal pain and vomiting), one in Period I after dosing and one in Period II after dosing. Three subjects dropped out, because they did not report to the facility for period II check-in due to personal reasons. Fifty-five subjects finished both study periods and were included in the statistical analysis.

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

Treatment N=55	**AUC_{0-t}** (ng.h/ml)	**$AUC_{0-\infty}$** (ng.h/ml)	**C_{max}** (ng/ml)	**t_{max}** (h)	**$t_{1/2}$** (h)
Test	1367 ± 544	1453 ± 639	27.00 ± 6.36	6.5 (2.0-10.0)	--
Reference	1402 ± 623	1505 ± 735	28.25 ± 7.31	6.0 (3.0-20.0)	--
***Ratio (90% CI)**	0.98 (0.95-1.01)	--	0.96 (0.92-0.99)	--	--
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 AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Nortriptyline Milstein 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).

Safety
No severe, serious or life-threatening adverse events were reported during the course of the study. A total of 43 adverse events were reported by 28 subjects during the study and post study laboratory safety evaluation; 1 adverse event occurred during period I while, 7 adverse events occurred during period II and 35 adverse events occurred during post study laboratory safety evaluation. A total of 2 adverse events were noted with test treatment and a total of 6 adverse events were noted with reference treatment during the study periods. Thirty eight (38) adverse events were mild in intensity and five (5) adverse events were moderate in intensity. The relationship of 40 adverse events to the study drug was thought to be possible, the relationship of 2 adverse events to the study drug was thought to be probable and the relationship of 1 adverse event to the study drug was thought to be unlikely.

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 Milstein.

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

Important identified risks	Suicide/suicidal thoughts or clinical worsening Withdrawal symptoms (including neonatal ones) 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 in pregnancy and lactation
Missing information	None

The MEB agrees 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 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 Milstein 50 mg, tablets has a proven chemical-pharmaceutical quality and is a generic form of Nortrilen 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.

The MEB, on the basis of the data submitted, considered that essential similarity has been demonstrated for Nortriptyline Milstein with the reference product, and has therefore granted a marketing authorisation. Nortriptyline Milstein 50 mg, tablets was authorised in the Netherlands on 31 May 2018.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Type of modification	Product Information affected	Date of end of the procedure	Approval/ non approval	Summary/Justification for refuse
MA transfer/change in product name	IB	Y	13-8-2018	Approval	--
Change in test procedure for the finished product	IA	N	9-9-2018	Approval	--
Change in test procedure for the finished product	IA	N	4-5-2019	Approval	--
Correction of typographical errors in the PL.	Art. 61(3) notification	Y	3-5-2019	Approval	--
Adjustment of SmPC and PL according the outcome of PSUSA/ 00002192/201803	IA	Y	25-4-2019	Approval	--
Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product	IA	N	15-5-2019	Approval	--