COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Nortriptyline Double-e Pharma 10 mg and 25 mg, film-coated tablets (nortriptyline hydrochloride)

NL License RVG: 127406 & 127407

Date: 23 March 2023

This module reflects the scientific discussion for the approval of Nortriptyline Double-e Pharma 10 mg and 25 mg, film-coated tablets. The marketing authorisation was granted on 12 September 2022. 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
EMA	European Medicines Agency
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
RMS	Reference Member State
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 Double-e Pharma 10 mg and 25 mg, film-coated tablets, from Double-E Pharma Limited.

The product is indicated for the treatment of major depressive disorder episodes in adults.

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 products Nortrilen 10 mg (RVG 03285) and 25 mg (RVG 03286) film-coated tablets, registered since 26 November 1964 in the Netherlands by Lundbeck B.V. (Netherlands).

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

II. QUALITY ASPECTS

II.1 Introduction

Nortriptyline Double-e Pharma are film-coated tablets:

- The 10 mg strength are round, biconvex, white film-coated tablets, debossed with "10" on one side, containing 10 mg nortriptyline equivalent to 11.38 mg nortriptyline hydrochloride.
- The 25 mg strength are round, biconvex, orange film-coated tablets, scored on one side and debossed with "25" on the other side, containing 25 mg nortriptyline equivalent to 28.46 mg nortriptyline hydrochloride. The score line is meant to break the tablet to make it easier to swallow and not to divide the tablet into equal doses.

The tablets are packed in high-density polyethylene (HDPE) bottles or PVC-PVDC/Aluminium blisters.

The excipients are:
Tablet core (both strengths) - pregelatinised starch (E1422), magnesium stearate (E470b), lactose monohydrate, monocalcium phosphate (E341)
Tablet coating (both strengths) - hypromellose (E464), macrogol 8000 (E1521), macrogol 400 (E1521)
Additionally, the coating of the 25 mg strength contains sunset yellow FCF (E110).

The two tablet strength cores are dose proportional.

II.2 Drug Substance

The active substance is nortriptyline hydrochloride, an established active substance described in the European Pharmacopoeia. The active substance is a crystalline powder and is sparingly soluble in water. It exists in two different polymorphic forms, not affecting the bioavailability of the product. For this product, polymorphic form α is consistently produced.

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 active substance is manufactured in five steps from amitriptyline. The active substance has been sufficiently characterised and acceptable specifications have been adopted for the starting material, solvents and reagents. The active substance has been adequately characterised and the manufacturing process is described in sufficient detail.

Quality control of drug substance

The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. Batch analytical data demonstrating compliance with this specification have been provided for two batches by the drug product manufacturer. For a third batch, reference is made to the ASMF.

Stability of drug substance

Stability data on the active substance have been provided for 19 production scaled batches in accordance with applicable European guidelines demonstrating the stability of the active substance at 25°C/60% RH (up to 60 months) and 40°C/75% RH (up to 6 months). Based on the data submitted, a retest period could be granted of 5 years when stored under the stated 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 main development studies were performed on: particle size distribution, polymorphism, hygroscopicity, solubility, forced degradation, compatibility of the excipients and a design of experiments study about parameters of granulation and tabletting processes. Comparative dissolution has been studied at three pH levels, in support of bioequivalence and the biowaiver of strengths (see section *IV.2 Pharmacokinetics*). The

choice for the finalised dissolution method for routine control has been justified. A bioequivalence study was performed with the 25 mg strength and a biowaiver is claimed for the 10 mg strength. The test batch used in the bioequivalence study was manufactured according to the finalised composition and manufacturing process at a representative scale. Bioequivalence has been demonstrated and the biowaiver of strength is acceptable from a quality and pharmacokinetic point of view. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The tablets are manufactured by wet granulation. Process validation data on the product has been presented for two pilot scale batches of common blend and of each tablet strength. The product is manufactured using conventional manufacturing techniques. Process validation for full-scale batches will be performed post authorisation.

Control of excipients

The excipients comply with Ph.Eur. requirements. The 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, average mass, resistance to crushing, uniformity of dosage units, disintegration, dissolution, assay, related substances, water content and microbial purity. The release and shelf-life requirements are identical. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. An adequate nitrosamines risk assessment has been provided, containing detailed information regarding the risk of nitrosamine formation in the substance, excipients, manufacturing process and packaging. In absence of nitrosating agents in the finished product and considering that the drug product is a solid state pharmaceutical form, the risk of nitrosamine formation during the drug product storage is adequately described.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from two pilot scale batches 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 on two pilot scaled batches of each strength, stored at 25°C/60% RH for 18 months and 40°C/75% RH for 6 months. The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in Alu-PVC/PVDC blister packs or HDPE bottles. No clear trends or changes were observed in any of the tested parameters at both storage conditions in any of the batches. The impurities remained below the proposed limits throughout the stability studies.

Photostability studies were performed in accordance with ICH recommendations and showed the product is stable when exposed to light. During the stability studies no significant changes in the drug product were observed.

On basis of the data submitted, a shelf-life of 30 months is acceptable with the storage condition: "without any special storage requirements."

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
A declaration for lactose monohydrate has 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 Double-e Pharma 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 Double-e Pharma 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 MEB agreed that no further clinical studies are required, other than the 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 Double-e Pharma 25 mg film-coated tablets (Double-E Pharma Limited, The Netherlands) is compared with the pharmacokinetic profile of the reference product Nortrilen 25 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 study results and composition. The formula and preparation of the bioequivalence batch was identical to the formula proposed for marketing.

Biowaiver

The following conditions are met to justify a biowaiver of strength for the 10 mg product, in line with the EMA Bioequivalence guideline:

- 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. All tablets were dissolved for more than 85% within 15 minutes.

Bioequivalence studies

Design

A single-dose, randomised, open-label, three-period, three-sequence, three-treatment, three-way crossover bioequivalence study was carried out under fasted conditions in 30 healthy subjects (13 male/ 17 female), aged 32-73 years. Nortriptyline Double-e Pharma 25 mg film-coated tablets was compared to Nortrilen 25 mg film-coated tablets (RVG 03286) (Lundbeck B.V., The Netherlands) and to Nortriptyline 25 mg tablets (King Pharmaceuticals Ltd., Ireland). Only the comparison to the Dutch reference product is presented below, because only these pivotal results were assessed for this national procedure.

Each subject received a single dose (25 mg) of one of the three nortriptyline hydrochloride formulations. The tablet was orally administered with 240 mL water after an overnight fast of at least ten hours. There were three dosing periods, separated by a washout period of 21 days.

Blood samples were collected pre-dose and at 1, 2, 3, 4, 5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 10, 11, 12, 14, 20, 24, 36, 48 and 72 hours after administration of the products.

Nortriptyline hydrochloride may be taken without reference to food intake. The SmPCs of the new product and the innovator do not specify if nortriptyline hydrochloride tablets should be taken with or without food. 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. The design of the study is acceptable.

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 was withdrawn from the study due to non-compliance at the period 3 check-in. The results of this subject from the first two periods were included in the pharmacokinetic analysis. Thus, all 30 subjects were included in the analysis of the test product versus the Dutch reference product.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of nortriptyline hydrochloride, 25 mg, under fasted conditions.

Treatment N=30	**AUC_{0-72} (ng.h/mL)**	**C_{max} (ng/mL)**	**t_{max} (h)**
Test	620.0 (±241.6)	18.2 (±5.5)	7.25 (4.00-20.00)
Reference (Nortrilen)	593.8 (±218.1)	17.8 (±5.4)	7.00 (5.00 -12.00)
***Ratio (90% CI)**	1.03 (0.98 – 1.07)	1.01 (0.95 – 1.07)	-

AUC_{0-72}	Area under the plasma concentration-time curve from time zero to the last measured plasma concentration at time t = 72 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-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 Double-e Pharma 25 mg film-coated tablets is considered bioequivalent with Nortrilen 25 mg film-coated tablets.

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).

The results of the study for the 25 mg strength can be extrapolated to the 10 mg strength, according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

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 Double-e Pharma.

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

Important identified risks	None
Important potential risks	None
Missing information	None

The MEB 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 25 mg strength product is similar to the pharmacokinetic profile of this strength's reference product. A biowaiver was granted for the 10 mg strength. Risk management is adequately addressed. These generic medicinal products can be used instead of the reference products.

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 leaflet comes in two variations, namely in a booklet form which accompanies the bottle and a regular leaflet form which accompanies the blister. Because the regular leaflet has a bigger font and therefore will be easier to read, it was decided that testing the bottle booklet is sufficient to cover the readability of both formats of the otherwise identical leaflet.

The language used for the purpose of user testing the PL was Dutch. The test consisted of two rounds with ten 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 Double-e Pharma 10 mg and 25 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Nortrilen 10 mg 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.

The MEB, on the basis of the data submitted, considered that essential similarity has been demonstrated for Nortriptyline Double-e Pharma with the reference product, and have therefore granted a marketing authorisation. Nortriptyline Double-e Pharma was authorised in the Netherlands on 12 September 2022.

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
-	-	-	-	-	-