Public Assessment Report

Scientific discussion

Nortriptyline Blackrock 10 mg and 25 mg film-coated tablets

(nortriptyline hydrochloride)

NL/H/3462/001-002/DC

Date: 3 November 2017

This module reflects the scientific discussion for the approval of Nortriptyline Blackrock 10 mg and 25 mg film-coated tablets. The procedure was finalised on 3 October 2016. For information on changes after this date please refer to the ‘steps taken after finalisation’ at the end of this PAR.
**List of abbreviations**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASMF</td>
<td>Active Substance Master File</td>
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<tr>
<td>CEP</td>
<td>Certificate of Suitability to the monographs of the European Pharmacopoeia</td>
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<tr>
<td>CHMP</td>
<td>Committee for Medicinal Products for Human Use</td>
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<tr>
<td>CMD(h)</td>
<td>Coordination group for Mutual recognition and Decentralised procedure for human medicinal products</td>
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<tr>
<td>CMS</td>
<td>Concerned Member State</td>
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<tr>
<td>EDMF</td>
<td>European Drug Master File</td>
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<td>EDQM</td>
<td>European Directorate for the Quality of Medicines</td>
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<td>EEA</td>
<td>European Economic Area</td>
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<tr>
<td>ERA</td>
<td>Environmental Risk Assessment</td>
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<td>ICH</td>
<td>International Conference of Harmonisation</td>
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<td>MAH</td>
<td>Marketing Authorisation Holder</td>
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<td>Ph.Eur.</td>
<td>European Pharmacopoeia</td>
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<td>PL</td>
<td>Package Leaflet</td>
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<tr>
<td>RH</td>
<td>Relative Humidity</td>
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<tr>
<td>RMP</td>
<td>Risk Management Plan</td>
</tr>
<tr>
<td>SmPC</td>
<td>Summary of Product Characteristics</td>
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<tr>
<td>TSE</td>
<td>Transmissible Spongiform Encephalopathy</td>
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</tbody>
</table>
I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Nortriptyline Blackrock 10 mg and 25 mg film-coated tablets, from Blackrock Pharmaceuticals.

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

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Nortrilen 10 and 25 mg, film-coated tablets (NL RVG 03285) 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 Blackrock 10 mg and 25 mg are white, round film-coated tablets and contain respectively 10 or 25 mg nortriptyline hydrochloride. The 25 mg strength has a score line on one side, which is only for facilitate swallowing of the product and not to divide into equal halves.

The film-coated tablets are packed in Aluminium-PVC/PVDC Opaque blisters.

The excipients are: lactose monohydrate, maize starch, dibasic calcium phosphate, polysorbate 80, magnesium stearate, polyvinyl alcohol (partially hydrolysed), titanium dioxide, talc, macrogol and lecithin (E322).

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. It is sparingly soluble in water and soluble in ethanol (96%) and methylene chloride. Nortriptyline hydrochloride does not contain a chiral centre and only one polymorphic form is 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 produced in five steps. The route of synthesis is adequately described and the proposed starting materials are acceptable. During the manufacturing process no class I solvents are used. The specifications of the starting materials are acceptable.

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. with additional requirements for residual solvents and particle distribution. Batch analytical data demonstrating compliance with this specification have been provided for 3 validation and 3 production batches. All batches comply with the proposed specification.
Stability of drug substance
Stability data on the active substance have been provided for 3 production batches stored at 40°C /75% RH (6 months) and 30°C/65% RH (24 months). No significant trends or changes were observed. Based on the data submitted, a retest period could be granted of 48 months without any special 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 choice of excipients are justified and their functions explained. No polymorphs are known.
The formulation development studies have been adequately described. A bioequivalence study has been performed using the 25 mg strength test product and the reference product Nortrilen 25 mg film-coated tablets. For the 10 mg strength a bio waiver was requested. The comparative dissolution profiles in pH 1.2, pH 4.5, pH 6.8 and QC medium (water) have been obtained using a paddle apparatus at 75 rpm as well as at 50 rpm. The similarity of the test and reference product profiles has been shown for pH 1.2, pH 4.5 and pH 6.8 using 75 rpm and 50 rpm. However, in QC medium (500 ml water, 75 rpm), similarity has not been shown. In view of the data using 900 ml / 50 rpm, there was no objection.

Manufacturing process
The manufacturing process has been validated according to relevant European guidelines. The process consist of wet granulation, blending, compression, coating and packaging steps and is described in sufficient detail. Process validation data on the product have been presented for 3 full scaled batches.

Control of excipients
The excipients comply with Ph.Eur. monographs except the ready mixture for coating. An in-house specification for this mixture has been provided and the individual components comply with the Ph.Eur. 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, identity, uniformity of mass, disintegration, dissolution, assay, degradation, uniformity of dosage units and microbial purity. 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 3 full 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 3 full scaled batches stored at 25°C/60% RH (12 months) and 40°C/75% RH (6 months). Data of three pilot scaled batches at 25°C/60% RH (18 months), 30°C/65% RH (18 months) and 40°C/75% RH (6 months) have also been provided. The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the proposed packaging. Out of specification results are observed at accelerated conditions in the pilot scaled batches, but not in full scaled batches. A discussion on the observed differences in pilot and full scaled batches has been provided. For setting the shelf-life period only the full scale batch results are taken into account. The photostability studies showed that the product is sensitive to light. On basis of the data submitted, a shelf life was granted of 24 months when stored in the original packaging in order to protect from light.

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 for lactose monohydrate and magnesium stearate and are 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 Blackrock 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 Blackrock 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 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 Blackrock 25 mg film-coated tablets (Blackrock Pharmaceuticals, UK) 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 studies is justified. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver

To support a biowaiver for the 10 mg strength based on the bioequivalence study with the highest strength of 25 mg the MAH has demonstrated comparable in vitro dissolution data for the 10 mg and 25 mg strengths of the test product under experimental dissolution conditions as per guidance at pH 1.2, 4.5 and 6.8. As the two strengths of the test products meet all the criteria specified in the Guideline, the results and conclusions of the bioequivalence studies on the 25mg strength can be extrapolated to the 10mg strength.
Bioequivalence study

Design

A single-dose, open-label, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in healthy male subjects, aged 20-43 years. Each subject received a single dose (25 mg) of one of the two nortriptyline hydrochloride formulations. The tablet was orally administered with 240 ml water after. There were 2 dosing periods, separated by a washout period of 21 days.

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

The design of the study is acceptable. As nortriptyline can be taken regardless of food, a study under fasting conditions is acceptable. The half-life of nortriptyline is about 26 hours (for normal metabolisers). Therefore plasma sampling until 72 hours after dosing is allowed and a wash-out period of 21 days would be sufficient, also for poor metabolisers.

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 did not report to the clinic for the second period of the study and was considered a drop-out. Therefore, a total of 27 subjects were eligible for pharmacokinetic analysis.

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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>( \text{AUC}_{0-t} ) ( \text{ng} \cdot \text{h/mL} )</th>
<th>( \text{AUC}_{0-\infty} ) ( \text{ng} \cdot \text{h/mL} )</th>
<th>( \text{C}_{\text{max}} ) ( \text{ng/mL} )</th>
<th>( t_{\text{max}} ) ( \text{h} )</th>
<th>( t_{1/2} ) ( \text{h} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>550 ± 226</td>
<td>852 ± 656</td>
<td>13.7 ± 3.9</td>
<td>7.0</td>
<td>3.5 – 12.0</td>
</tr>
<tr>
<td>Reference</td>
<td>545 ± 205</td>
<td>800 ± 465</td>
<td>13.7 ± 3.8</td>
<td>8.0</td>
<td>4.5 – 12.0</td>
</tr>
</tbody>
</table>

\( *\text{Ratio (90\% CI)} \)

| Test      | 1.00             | 0.96 - 1.05     | 1.00            | 0.95 - 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
\( C_{\text{max}} \) maximum plasma concentration
\( t_{\text{max}} \) time for maximum concentration
\( t_{1/2} \) half-life

\( *\text{ln-transformed values} \)

Conclusion on bioequivalence study

The 90\% confidence intervals calculated for \( \text{AUC}_{0-t} \) and \( \text{C}_{\text{max}} \) are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Nortriptyline Blackrock 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 Blackrock.
- Summary table of safety concerns as approved in RMP

<table>
<thead>
<tr>
<th>Important identified risks</th>
<th>Suicide/suicidal thoughts or clinical worsening</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Withdrawal symptoms (including neonatal ones)</td>
</tr>
<tr>
<td></td>
<td>Cardiovascular disorders (myocardial infarction, cardiac arrhythmias and stroke)</td>
</tr>
<tr>
<td></td>
<td>Serotonergic syndrome in concomitant use with MAO-inhibitors</td>
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<tr>
<td></td>
<td>Increased risk of bone fractures</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Important potential risks</th>
<th>Use in pregnancy and lactation</th>
</tr>
</thead>
</table>

| 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**

The package leaflet 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. Questions (14 in total) were asked about all parts of the leaflet, key safety issues were addressed. Two test rounds were held with 10 participants each. After the first test round no amendments were considered necessary. The results show that the package leaflet 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 Blackrock 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.

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 Blackrock with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 3 October 2016.
## STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Type of modification</th>
<th>Date of start of the procedure</th>
<th>Date of end of the procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached</th>
</tr>
</thead>
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