Public Assessment Report

UKPAR

Nortriptyline 10 mg and 25 mg Film-coated Tablets

(nortriptyline hydrochloride)

UK Licence No: PL 21880/0150-0151

MEDREICH PLC
LAY SUMMARY
Nortriptyline 10 mg and 25 mg Film-coated Tablets
(nortriptyline hydrochloride)

This is a summary of the Public Assessment Report (PAR) for Nortriptyline 10 mg and 25 mg Film-coated Tablets (PL 21880/0150-0151). These medicinal products will be referred to as Nortriptyline Tablets in the remainder of this report, for ease of reading.

This summary explains how Nortriptyline Tablets were assessed and their authorisations recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use these products.

For practical information about using Nortriptyline Tablets, patients should read the package leaflet or contact their doctor or pharmacist.

What are Nortriptyline Tablets and what are they used for?
Nortriptyline Tablets are ‘generic medicines’. This means that Nortriptyline Tablets are similar to ‘reference medicines’ authorised in the the European Union (EU) called Allegron 10 mg and 25 mg Tablets (PL 14385/0001-0002; King Pharmaceuticals Limited).

Nortriptyline Tablets are used in the treatment of symptoms of depression. Nortriptyline Tablets may also be used for the treatment of bedwetting in children 6 years and older.

How do Nortriptyline Tablets work?
The active substance in Nortriptyline Tablets, nortriptyline hydrochloride, is a tricyclic antidepressant which works by elevating the mood in patients with depression.

How are Nortriptyline Tablets used?
Nortriptyline Tablets are taken by mouth. These medicinal products can only be obtained on prescription from a doctor.

The usual adult dose is 25 mg three or four times daily or the dose may be given once a day, usually at night. The dose should begin at a low level, 10 mg, 3-4 times daily, for example and be increased gradually as required. The maximum dose is 150 mg per day.

The usual dose in elderly is 30 to 50 mg/day in divided doses. Treatment may start with 10 mg three times a day.

The usual dose in adolescent patients is 30 to 50 mg/day in divided doses. Treatment may start with 10 mg three times a day. Lower dosages are recommended for outpatients than for patients in hospital who will be under close supervision.

Following remission maintenance treatment may be needed longer term. This should be at the lowest dose that stops the symptoms of depression coming back.

The dose of Nortriptyline Tablets for children (for bed-wetting only):

<table>
<thead>
<tr>
<th>Age (Years)</th>
<th>Weight</th>
<th>Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>kg</td>
<td>lb</td>
</tr>
</tbody>
</table>
The dose should be given thirty minutes before bedtime. The maximum length of treatment should be three months. Another course of treatment should not be started until a full physical examination has been made.

For further information on how Nortriptyline Tablets are used, refer to the Summaries of Product Characteristics or package leaflet available on the MHRA website.

**What benefits of Nortriptyline Tablets have been shown in studies?**

As Nortriptyline Tablets are generic medicines, studies in patients have been limited to tests to determine that they are bioequivalent to Allegron 10 mg and 25 mg Tablets (King Pharmaceuticals Limited). Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

**What are the possible side effects of Nortriptyline Tablets?**

Because Nortriptyline Tablets are generic medicines and are bioequivalent to Allegron 10 mg and 25 mg Tablets, their benefits and possible side effects are taken as being the same as those of the reference medicines.

For the full list of all side effects reported with Nortriptyline Tablets, see section 4 of the package leaflet available on the MHRA website.

**Why was Nortriptyline Tablets approved?**

It was concluded that, in accordance with EU requirements, Nortriptyline Tablets have been shown to have comparable quality and to be bioequivalent to Allegron 10 mg and 25 mg Tablets. Therefore, the MHRA decided that, as for Allegron 10 mg and 25 mg Tablets, the benefits of Nortriptyline Tablets are greater than its risks and recommended that they can be approved for use.

**What measures are being taken to ensure the safe and effective use of Nortriptyline Tablets?**

A risk management plan has been developed to ensure that Nortriptyline Tablets are used as safely as possible. Based on this plan, safety information has been included in the Summaries of Product Characteristics and the package leaflet for Nortriptyline Tablets, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously as well.

**Other information about Nortriptyline Tablets**

Marketing Authorisations were granted in the UK on 26th March 2015.

The full PAR for Nortriptyline Tablets follows this summary.

For more information about treatment with Nortriptyline Tablets, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in May 2015.
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I  INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) granted MEDREICH PLC Marketing Authorisations for the medicinal products Nortriptyline 10 mg and 25 mg Film-coated Tablets (PL 21880/0150-0151). The products are prescription-only medicines (POM) indicated for the relief of symptoms of depression. It may also be used for the treatment of some cases of nocturnal enuresis.

These applications were submitted under Article 10(1) of Directive 2001/83/EC, as amended cross-referring to Allegron 10 mg and 25 mg Tablets, which were originally authorised to Eli Lilly & Company Limited (PL 00006/5002R-5003R) on 14th February 1983. These reference licences underwent change of ownership procedures to the currently Marketing Authorisation Holder, King Pharmaceuticals Limited (PL 14385/0001-0002), on 30th March 1998.

Nortriptyline is a tricyclic antidepressant with actions and uses similar to those of amitriptyline. It is the principal active metabolite of amitriptyline.

A bioequivalence study was submitted to support these applications comparing the applicant’s test product Nortriptyline 25 mg tablets (manufacturer: Medreich Limited, India) with the reference product Allegron 25 mg Tablets (King Pharmaceuticals Ltd, County Donegal, IE) under fasting conditions. The applicant has stated that the bioequivalence study was conducted in compliance with Good Clinical Practice (GCP) requirements.

With the exception of the bioequivalence study, no new non-clinical or clinical data were submitted, which is acceptable given that these applications were based on being generic medicinal products of the originator products that have been in clinical use for over 10 years.

No new or unexpected safety concerns arose during the review of information provided by the Marketing Authorisation Holder and it was, therefore, judged that the benefits of taking Nortriptyline 10 mg and 25 mg Film-coated Tablets outweigh the risks and Marketing Authorisations were granted.
II QUALITY ASPECTS

II.1 Introduction
Each film-coated tablet contains 10 mg or 25 mg of nortriptyline hydrochloride, as active ingredient. The excipients present are lactose monohydrate, anhydrous calcium hydrogen phosphate, maize starch, magnesium stearate, hypromellose and macrogol (PEG 6000). The 25 mg strength additionally contains sunset yellow (E110) and titanium dioxide (E171). Appropriate justification for the inclusion of each excipient has been provided.

All excipients comply with their respective European/British Pharmacopoeia monographs with the exception of sunset yellow (E110) which complies with an in-house specification. Satisfactory Certificates of Analysis have been provided for these excipients.

The only excipient used that contains material of animal or human origin is lactose monohydrate. The applicant has provided a declaration that the milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that for human consumption. In addition, the supplier has confirmed that no ruminant material other than calf rennet is used during the production of lactose monohydrate. Confirmation has also been given that the magnesium stearate used in the tablets is of vegetable origin.

The finished product is packed either in clear aluminium polyvinylchloride (PVC) blisters containing 10, 30 and 100 tablets or in high density polyethylene (HDPE) container with polypropylene screw on cap with a pack size of 100 tablets.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components.

II.2 Drug Substance

INN: Nortriptyline hydrochloride
Chemical name(s): 3-(10,11-Dihydro-5H-dibenz[a,d][7]annulen-5-ylidene)-N-methylpropan-1-amine hydrochloride

Structural formula:

![Structural formula of nortriptyline hydrochloride]

Molecular formula: C_{19}H_{21}N, HCl
Molecular mass: 299.8 g/mol
Appearance: white to off-white powder.
Solubility: Sparingly soluble in water and soluble in ethanol (96 per cent) and in methylene chloride.

Nortriptyline hydrochloride is the subject of an active substance master file (ASMF).

Synthesis of the drug substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification
tests are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

An appropriate specification is provided for the drug substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Certificates of Analysis for all working standards have been provided.

Batch analyses data are provided that comply with the proposed specification.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging used to store the drug substance. Confirmation has been provided that the primary packaging complies with current guidelines concerning materials in contact with food.

Appropriate stability data have been provided, supporting a suitable retest period when the drug substance is stored in the packaging proposed.

II.3. Medicinal Product Pharmaceutical Development

The objective of the development programme was to formulate safe, efficacious, film-coated tablets containing nortriptyline hydrochloride that are bioequivalent to Allegron 10 mg and 25 mg Tablets (King Pharmaceuticals Ltd).

A satisfactory account of the pharmaceutical development has been provided. Comparative impurity and in-vitro dissolution profiles have been provided for the proposed and originator products.

Manufacture of the products

Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing processes. The manufacturing processes have been validated and have shown satisfactory results. Process validation data on three commercial scale batches have been provided. The results are satisfactory.

Finished Product Specifications

The finished product specifications are acceptable. The test methods have been described and have been adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for all working standards used.

Stability of the Products

Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. The data from these studies support a shelf-life of 2 years for the blister pack and HDPE container with no special storage conditions. Once the tablet container is opened the tablets should be used within 60 days. These are satisfactory.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects

There are no objections to the approval of these applications from a pharmaceutical point of view.
III NON-CLINICAL ASPECTS

III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of nortriptyline hydrochloride are well-known, no new non-clinical studies are required and none have been provided. An overview based on the literature review is, thus, appropriate.

The applicant’s non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

III.2 Pharmacology
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.3 Pharmacokinetics
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.4 Toxicology
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.5 Environmental Risk Assessment (ERA)
Since these products are 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.6 Discussion on the non-clinical aspects
No new non-clinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years.

There are no objections to the approval of these applications from a non-clinical point of view.

IV CLINICAL ASPECTS

IV.1 Introduction
The clinical pharmacology of nortriptyline hydrochloride is well-known. With the exception of data from the bioequivalence study detailed below, no new pharmacodynamic or pharmacokinetic data are provided and none are required for these applications.

No new efficacy or safety studies have been performed and none are required for this type of applications. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of nortriptyline hydrochloride.

IV.2 Pharmacokinetics
In support of these applications, the applicant has submitted a single dose bioequivalence study under fasting conditions comparing the test product with the reference product.

This was an open label, two treatment, two period, two sequence, single dose, cross-over bioequivalence study comparing the pharmacokinetics of the applicant’s test product, Nortriptyline 25 mg tablets manufactured by Medreich Limited, India, versus the reference product, Allegron 25 mg Tablets (MAH: King Pharmaceuticals Ltd, County Donegal, IE), in 30 healthy adult male subjects under fasting conditions.
Serial blood sampling pre-dose and at 1,000, 2,000, 3,000, 5,000, 5,333, 5,667, 6,000, 6,500, 7,000, 7,500, 8,000, 8,500, 9,000, 10,000, 12,000, 16,000, 24,000, 36,000, 48,000 and 72,000 hours post-dose was carried out in each period. The washout period between treatments was 22 hours.

**Results**

Ratio and 90% Confidence Intervals of Test versus Reference for Nortriptyline (N=30)

<table>
<thead>
<tr>
<th>PK Parameter</th>
<th>Ratio (T/R) %</th>
<th>90% Confidence Interval (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (ng/ml)</td>
<td>103.54</td>
<td>98.19% – 109.17%</td>
</tr>
<tr>
<td>$AUC_{0-72}$ (ng.hr/ml)</td>
<td>104.69</td>
<td>101.22% – 108.28%</td>
</tr>
</tbody>
</table>

**Conclusion**

The 90% confidence intervals for $C_{\text{max}}$ and $AUC_{0-72}$ were within the acceptance criteria of 80.00-125.00%. Bioequivalence has been shown for the test formulation (Nortriptyline 25 mg tablets) and the reference formulation (Allegron 25 mg Tablets) under fasting conditions.

As the 10 mg and 25 mg strength products meet all the criteria specified in the “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98 Rev.1 Corr*), the results of the study for 25 mg tablets can be extrapolated to the other strength i.e. 10 mg Film-coated Tablets. Therefore, bioequivalence has been shown between the 10 and 25 mg strengths of the test products and their respective reference products.

**IV.3 Pharmacodynamics**

No new pharmacodynamic data were submitted and none were required for applications of this type.

**IV.4 Clinical efficacy**

No new efficacy data were submitted and none were required for applications of this type.

**IV.5 Clinical safety**

Six adverse events were reported during the study which three of those were considered related to the study products. Among the three adverse events (AEs), two were considered related to the test product and one to the reference product. All AEs were mild in intensity and resolved completely without sequelae. There were no serious AE in the study. No new safety data were submitted and none were required for applications of this type.

**IV.6 Risk Management Plan (RMP)**

The Marketing Authorisation Holder (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 10 mg and 25 mg Film-coated Tablets.
A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, is listed below:

<table>
<thead>
<tr>
<th>Safety concern</th>
<th>Routine risk minimisation measures</th>
<th>Additional risk minimisation measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use in patients with cardiovascular disorders</td>
<td>The risks of cardiovascular disorders (low/high blood pressure, myocardial infarction, stroke, heart block and palpitations) associated with the use of the drug product, particularly in patients with pre-existing cardiovascular disorders, and those taking medicines for these disorders are described in the SPC Sections 4.3, 4.4, 4.5, 4.8, and the PIL Sections 2, 4, and appropriate advice is provided to the prescriber to minimise these risks.</td>
<td>None</td>
</tr>
<tr>
<td>Use in patients with severe liver disease</td>
<td>The risks of liver impairment associated with the use of the drug product in patients, particularly in patients with severe liver disease, and those taking concomitant medicines metabolised in the liver are</td>
<td>None</td>
</tr>
<tr>
<td>Safety concern</td>
<td>Routine risk minimisation measures</td>
<td>Additional risk minimisation measures</td>
</tr>
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<td>described in the SPC Sections 4.2, 4.3, 4.5, 4.8, and the PIL Section 2, 4, and appropriate advice is provided to the prescriber to minimise these risks.</td>
<td>None</td>
</tr>
<tr>
<td>Use in patients with mania</td>
<td>The risks of exacerbation of mania symptoms associated with the use of the drug product, particularly in patients with mania are described in the SPC Sections 4.3, 4.4, 4.8 and the PIL Section 2, 4, and appropriate advice is provided to the prescriber to minimise these risks.</td>
<td>None</td>
</tr>
<tr>
<td>Use in nursing mothers</td>
<td>The risks (1) associated with the use of the drug product in nursing mothers, and (2) risks to the breast-fed babies associated with the use of the drug product are described in the SPC Section 4.3 and the PIL Section 2, and appropriate advice is provided to the prescriber to minimise these risks.</td>
<td>None</td>
</tr>
<tr>
<td>Use in children less than 6 years of age</td>
<td>The risks (1) associated with the use of the drug product in children, especially less than 6 years of age, and (2) associated with the prolonged use of the drug product (more than three months) for nocturnal enuresis are described in the SPC Sections 4.2, 4.3, 4.4, and the PIL Sections 2, 3. Appropriate advice is provided to the prescriber to minimise these risks.</td>
<td>None</td>
</tr>
<tr>
<td>Suicide/suicidal thoughts or clinical worsening of depression</td>
<td>The risks (1) of suicide/suicidal thoughts associated with the use of the drug product, particularly in the patients with depression and previous history of suicide-related events, and (2) of worsening of the depression, especially during the initial stage</td>
<td>None</td>
</tr>
<tr>
<td>Safety concern</td>
<td>Routine risk minimisation measures</td>
<td>Additional risk minimisation measures</td>
</tr>
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<td></td>
<td>of the treatment are described in the SPC Sections 4.4, 4.5, 4.8, and the PIL Section 2. Appropriate advice is provided to the prescriber to minimise these risks.</td>
<td></td>
</tr>
<tr>
<td>Arrhythmias</td>
<td>The risks of arrhythmias associated with the use of the drug product, especially in the patients with arrhythmias, cardiovascular disorders, and altered thyroid levels are described in the SPC Sections 4.3, 4.4, 4.8, and the PIL. Sections 2, 4, and appropriate advice is provided to the prescriber to minimise these risks.</td>
<td>None</td>
</tr>
<tr>
<td>Concomitant use with monoamine oxidase inhibitors/sympathomimetic agents</td>
<td>The risks associated with the concomitant use of the drug product with monoamine oxidase inhibitors/sympathomimetic agents are described in the SPC Section 4.5 and the PIL Section 2, and appropriate advice is provided to the prescriber to minimise these risks.</td>
<td>None</td>
</tr>
<tr>
<td>Concomitant use with anaesthetics</td>
<td>The risks associated with the concomitant use of the drug product with anaesthetics are described in the SPC Section 4.4 and the PIL Section 2, and appropriate advice is provided to the prescriber to minimise these risks.</td>
<td>None</td>
</tr>
<tr>
<td>Discontinuation/withdrawal symptoms</td>
<td>The risks of withdrawal symptoms (like insomnia, nausea, and headache) associated with the discontinuation of the drug product are described in the SPC Sections 4.4, 4.8 and the PIL Section 3, 4 and appropriate advice is provided to the prescriber to minimise these risks.</td>
<td>None</td>
</tr>
<tr>
<td>Safety concern</td>
<td>Routine risk minimisation measures</td>
<td>Additional risk minimisation measures</td>
</tr>
<tr>
<td>------------------------------------------------------------------------------</td>
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</tr>
<tr>
<td>Use in patients with schizophrenia</td>
<td>The risks of exacerbation of psychotic symptoms associated with the use of the drug product, particularly in patients with schizophrenia are described in the SPC Sections 4.4, 4.8 and the PIL. Section 2, 4 and appropriate advice is provided to the prescriber to minimise these risks.</td>
<td>None</td>
</tr>
<tr>
<td>Use in patients with history of epilepsy</td>
<td>The risks of seizures associated with the use of the drug product, particularly in patients with history of epilepsy are described in the SPC Sections 4.4, 4.8, and the PIL. Section 2, 4 and appropriate advice is provided to the prescriber to minimise these risks.</td>
<td>None</td>
</tr>
<tr>
<td>Use in elderly patients</td>
<td>The risks of agitation, confusion, cardiotoxicity, and postural hypotension associated with the use of the drug product in elderly patients are described in the SPC Sections 4.2, 4.4, 4.8, and the PIL. Sections 3, 4, and appropriate advice is provided to the prescriber to minimise these risks.</td>
<td>None</td>
</tr>
<tr>
<td>Use in patients with certain conditions (narrow-angle glaucoma and prostatic hypertrophy)</td>
<td>The risks of visual disorders and urinary retention associated with the use of the drug product in patients with certain conditions (narrow-angle glaucoma and prostatic hypertrophy) are described in the SPC Sections 4.4, 4.8, and the PIL. Section 2, 4 and appropriate advice is provided to the prescriber to minimise these risks.</td>
<td>None</td>
</tr>
<tr>
<td>Agranulocytosis and aplastic anaemia</td>
<td>The risks of agranulocytosis and aplastic anaemia associated with the use of the drug product are described in the SPC Section 4.8 and the PIL Section 4, and</td>
<td>None</td>
</tr>
<tr>
<td>Safety concern</td>
<td>Routine risk minimisation measures</td>
<td>Additional risk minimisation measures</td>
</tr>
<tr>
<td>------------------------</td>
<td>-----------------------------------------------------------------------------------------------------</td>
<td>---------------------------------------</td>
</tr>
<tr>
<td></td>
<td>appropriate advice is provided to the prescriber to minimise these risks.</td>
<td></td>
</tr>
<tr>
<td>Hepatitis</td>
<td>The risk of hepatitis associated with the use of the drug product is described in the SPC Section 4.8 and the PIL Section 4, and appropriate advice is provided to the prescriber to minimise this risk.</td>
<td>None</td>
</tr>
<tr>
<td>Toxicity in overdose</td>
<td>The risks like vomiting, dizziness, cardiac disorders, seizures, confusion associated with overdose of the drug product are described in the SPC Section 4.9 and the PIL Section 3, and appropriate advice is provided to the prescriber to minimise these risks.</td>
<td>None</td>
</tr>
<tr>
<td>Paralytic ileus</td>
<td>The risk of paralytic ileus associated with the use of the drug product is described in the SPC Section 4.8 and the PIL Section 4, and appropriate advice is provided to the prescriber to minimise this risk.</td>
<td>None</td>
</tr>
<tr>
<td>Important potential risks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use in patients with diabetes</td>
<td>The risks of altered sugar levels associated with the use of the drug product, particularly in the patients with diabetes are described in the SPC Sections 4.4, 4.8, and the PIL Section 2, 4 and appropriate advice is provided to the prescriber to minimise these risks.</td>
<td>None</td>
</tr>
<tr>
<td>Bone fracture</td>
<td>The risk of bone fractures associated with the use of the drug product, particularly in the patients above 50 years of age is described in the SPC Section 4.8 and the PIL Section 4, and appropriate advice is provided to the prescriber to minimise this</td>
<td>None</td>
</tr>
</tbody>
</table>
### IV.7 Discussion on the clinical aspects

With the exception of the bioequivalence study, no new clinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years.

Bioequivalence has been demonstrated between the applicant’s product Nortriptyline 25 mg tablets and the reference product, Allegron 25 mg Tablets (King Pharmaceuticals Ltd), under fasting conditions. As the 10 mg and 25 mg strength products meet all the criteria specified in the “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98 Rev.1 Corr**), the results of the study for 25 mg tablets can be extrapolated to the other strength i.e. 10 mg Film-coated Tablets. Therefore, bioequivalence has been shown between the 10 and 25 mg strengths of the test products and their respective reference products.

The grant of Marketing Authorisations is recommended for these applications.

### 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. The language used for the purpose of user testing the patient information leaflet (PIL) was English.

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

The quality of the products is acceptable, and no new non-clinical or clinical concerns have been identified. Bioequivalence has been demonstrated between the applicant’s product and the reference product. Extensive clinical experience with nortriptyline hydrochloride is considered to have demonstrated the therapeutic value of the compound. The benefit risk is, therefore, considered to be positive.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The approved labelling for Nortriptyline 10 mg and 25 mg Film-coated Tablets is presented below:
Table of content of the PAR update
Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
</thead>
</table>