IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Nortriptyline Chanelle Medical 25 mg film-coated tablets
NORTRIPTYLINE HYDROCHLORIDE
PA0688/063/002

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

CONTENTS

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Nortriptyline Chanelle Medical 10 mg and 25 mg film-coated tablets, from Chanelle Medical on 24/10/2019 for the following indication:
For the treatment of major depressive episodes in adults.

This application for a marketing authorisation was submitted in accordance with Article 10.1 of Directive 2001/83/EC and is referred to as a generic application.
The application was assessed through a decentralised procedure in which the HPRA acted as RMS (reference member state) and the UK was the only concerned member state (CMS) in the procedure.

The product is authorised for pharmacy only supply as a prescription only medical product which may not be renewed (A).

The Summary of Product Characteristics for (SmPC) for this medicinal product is available on the HPRA's website at www.hpra.ie

Name of the product	Nortriptyline Chanelle Medical 10mg & 25mg film-coated Tablets
Name(s) of the active substance(s) (INN)	Nortriptyline Hydrochloride
Pharmacotherapeutic classification (ATC code)	N06AA10
Pharmaceutical form and strength(s)	10mg & 25mg film-coated Tablets
Marketing Authorisation Number(s) in Ireland (PA)	PA688/063/001-002
Marketing Authorisation Holder	Chanelle Medical
MRP/DCP No.	IE/H/0587/001-002/DC
Reference Member State	IE
Concerned Member State	UK

II. QUALITY ASPECTS

II.1. Introduction

This application is for Nortriptyline Chanelle Medical 10mg & 25mg film-coated tablets.

II.2 Drug substance

The active substance is nortriptyline hydrochloride, an established active substance described in the European Pharmacopoeia, and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP)

The active substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition

Nortriptyline Chanelle Medical 10 mg film-coated tablets contain 10 mg nortriptyline (as hydrochloride).

Nortriptyline Chanelle Medical 25 mg film-coated tablets contain 25 mg nortriptyline (as hydrochloride).

The excipients in the medicinal product are listed in section 6.1 of the SmPC.
A visual description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European and ICH guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients)

All ingredients comply with Ph. Eur. or are adequately controlled by the manufacturer's specifications.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for tablets, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site(s) have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that the packaging complies with Ph. Eur. and EU legislation for use with foodstuffs requirements.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Nortriptyline Chanelle Medical 10mg & 25mg film-coated tablets.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This active substance is a generic formulation of Allegron Tablets on the European market. No new preclinical data have been submitted.

The pharmacodynamic, pharmacokinetic and toxicological properties of nortriptyline are well known. As nortriptyline is a widely used, well-known active substances, and this is a generic application, the applicant has not provided additional nonclinical studies and further studies are not required. The overview provided based on literature review is thus appropriate.

III.2 Ecotoxicity/environmental risk assessment

Since Nortriptyline Chanelle Medical 10mg & 25mg film-coated Tablets 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.3 Discussion on the non-clinical aspects

The pharmacodynamic, pharmacokinetic and toxicological properties of nortriptyline are well known. As nortriptyline is a widely used, well-known active substances, and this is a generic application, the applicant has not provided additional nonclinical studies and further studies are not required. The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology provided is adequate. Non-clinical findings are adequately represented in the appropriate sections of the SmPC.

IV. CLINICAL ASPECTS

IV.1 Introduction

Nortriptyline hydrochloride is a well-known active substance with established efficacy and tolerability.

This decentralised application for a marketing authorisation for Nortriptyline Chanelle Medical 10 mg and 25 mg film-coated tablets containing the active substance Nortriptyline hydrochloride was submitted to HPRA in accordance with Article 10.1 of Directive 2001/83/EC.

The content of the SmPC approved during the decentralised procedure is in accordance with that accepted for the reference product Allegron Tablets 10mg and 25mg film coated tablets marketed by King Pharmaceuticals, registered since 30/03/1998. Further, the content of the SmPC has also taken account of recent decentralised nortriptyline generics – e.g. UK/H/6634/01-03/DC and UK/H/6990/001/DC.

For this generic application, a bioequivalence study is not presented in line with the Note for guidance on Bioavailability and bioequivalence-CPMP/EQP/QWP/1401/98, as these applications are based on a Biopharmaceutics Classification System BCS class I biowaiver.

IV.2 Pharmacokinetics

The pharmacokinetics of nortriptyline hydrochloride are well established. No new data has been submitted.
The pharmacokinetics of nortriptyline hydrochloride have been adequately discussed by the applicant and the overview is based on published literature. This is acceptable.

IV.3 Pharmacodynamics

The applicant has not submitted any new pharmacodynamic data in accordance with EC article 10.1 (a) (iii) of directive 2001/83/EC which is considered acceptable for this type of application.The pharmacodynamics of nortriptyline hydrochloride have been adequately discussed by the applicant and the overview is based on published literature.

IV.4 Clinical Efficacy

No new clinical studies have been conducted by the applicant to support this application for marketing authorisation which is acceptable for this application type based on the justification provided by the applicant.

For this generic application, a bioequivalence study is not presented in line with the Note for guidance on Bioavailability and bioequivalence-CPMP/EQP/QWP/1401/98, as these applications are based on a Biopharmaceutics Classification System BCS class I biowaiver.

The applicant provided the requested clinical and quality justification to support the biowaiver approach.

There is a precedent for the acceptance of a BCS-based biowaiver for this active substance and a similar approach has been accepted in other DCP procedures where nortriptyline generics have been successfully authorised (ref PAR for procedure nos. UK/H/5843/001-03/DC).
Based on the totality of the data provided by the applicant, the applicant justification for the use of a BCS class biowaiver approach was accepted.

IV.5 Clinical Safety

No additional safety studies were conducted for this procedure which is acceptable for this application type. The safety profile of nortriptyline hydrochloride has been adequately discussed by the applicant and the overview is based on published literature.
No post-marketing data is available.

Risk Management Plan
The risk management plan proposed by the applicant, including the proposed pharmacovigilance activities and risk minimisation measures is considered acceptable. The approved summary of safety concerns is outlined in the table below:

Important identified risks	• Suicide/suicidal thoughts or clinical worsening • Withdrawal symptoms (including neonatal) • 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	N/A

Routine risk minimisation measures and routine pharmacovigilance activities were proposed to address the safety concerns outlined above and this is considered acceptable.

The Applicant should submit Periodic Safety Update Reports (PSUR) Periodic Safety Update Reports (PSUR) in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

IV.6 Discussion on the clinical aspects

Nortriptyline hydrochloride is a well-known active substance with established efficacy and tolerability.

The clinical pharmacology, efficacy and safety of the active substance are well known and have been adequately discussed in the clinical overview for this type of application.

For this generic application, a bioequivalence study is not presented in line with the Note for guidance on Bioavailability and bioequivalence-CPMP/EQP/QWP/1401/98, as these applications are based on a Biopharmaceutics Classification System BCS class I biowaiver.however the applicant has justified this by clarifying that the criteria for a BCS-based biowaiver have been fulfilled.
A number of points for clarification in relation to the biowaiver were raised during the procedure and the applicant has provided satisfactory responses to justify their approach.
The proposed excipients are considered standard for the dosage form in line with the current EU guidance.
There is a precedent for the acceptance of a BCS-based biowaiver in this instance and a similar approach has been accepted in other DCP procedures where nortriptyline generics have been successfully authorised (ref PAR for procedure nos. UK/H/5843/001-03/DC).

Routine risk minimisation measures and routine pharmacovigilance activities were proposed to address the safety concerns and this is considered acceptable.

The Applicant is requested to submit Periodic Safety Update Reports (PSUR) Periodic Safety Update Reports (PSUR) in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

V. OVERALL CONCLUSIONS

The active substance, nortriptyline hydrochloride, is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established efficacy and safety profile.

Nortriptyline Chanelle Medical 10 mg and 25 mg film-coated tablets are a generic formulation of the reference product Allegron Tablets 10mg and 25mg film coated tablets marketed by King Pharmaceuticals, registered in the UK since 30/03/1998.

This decentralised application for a marketing authorisation for Nortriptyline Chanelle Medical 10 mg and 25 mg film-coated tablets was submitted to HPRA in accordance with Article 10.1 of Directive 2001/83/EC. This is a generic application of the reference product Allegron Tablets 10mg and 25mg film coated tablets marketed by King Pharmaceuticals, registered in the UK since 30/03/1998.

For this marketing authorisation, reference is made to the clinical experience with the reference product Allegron Tablets 10mg and 25mg film coated tablets marketed by King Pharmaceuticals.
The content of the SmPC approved during the decentralised procedure is in accordance with that accepted for the reference product Allegron Tablets 10mg and 25mg film coated tablets marketed by King Pharmaceuticals, registered since 30/03/1998. Further, the content of the SmPC has also taken account of recent decentralised nortriptyline generics – e.g. UK/H/6634/01-03/DC and UK/H/6990/001/DC.

For this generic application, a bioequivalence study is not presented in line with the Note for guidance on Bioavailability and bioequivalence-CPMP/EQP/QWP/1401/98, as these applications are based on a Biopharmaceutics Classification System BCS class I biowaiver.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The HPRA, on the basis of the data submitted, considered that Nortriptyline Chanelle Medical 10 mg and 25 mg film-coated tablets demonstrated adequate evidence of efficacy for the approved indication, as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

Following MRP/DCP procedure:

Not applicable.

VI. REVISION DATE

VII. UPDATES