IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

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 Astilin 10 mg and 25 mg, film-coated tablets, from Ascot Laboratories Ltd on 1st November 2019 for:

-the treatment of major depressive disorder in adults

-the treatment of neuropathic pain in adults

-the prophylactic treatment of chronic tension type headache (CTTH) in adults

-the prophylactic treatment of migraine in adults

-the treatment of nocturnal enuresis in children aged 6 years and above when organic pathology, including spina bifida and related disorders, have been excluded and no response has been achieved to all other non-drug and drug treatments, including antispasmodics and vasopressin-related products. This medicinal product should only be prescribed by a healthcare professional with expertise in the management of persistent enuresis.

This application for a marketing authorisation was submitted as a national application in accordance with Article 10a of Directive 2001/83/EC and is referred to as a well-established use application.

This is a prescription-only medicinal product.

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	Astilin 10 mg and 25 mg, film-coated tablets
Name(s) of the active substance(s) (INN)	AMITRIPTYLINE HYDROCHLORIDE
Pharmacotherapeutic classification (ATC code)	N06AA09
Pharmaceutical form and strength(s)	10 mg and 25 mg, film-coated tablets
Marketing Authorisation Number(s) in Ireland (PA)	PA2101/002/001-002
Marketing Authorisation Holder	Ascot Laboratories Ltd

II. QUALITY ASPECTS

II.1. Introduction

This application is for Astilin 10 mg film-coated tablets.

II.2 Drug substance

The active substance is amitriptyline 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

Astilin 10 mg film-coated tablets contain 11.32 mg of amitriptyline 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 relevant European guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients)

All ingredients comply with Ph. Euror 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 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 Astilin 10 mg film-coated tablets.

III. NON-CLINICAL ASPECTS

III.1 Introduction

As the pharmacodynamics, pharmacokinetic and toxicological properties of amitriptyline 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 Ecotoxicity/environmental risk assessment

An Environmental Risk Assessment has not been performed as this product is intended for generic substitution and therefore will not result in an increase of risk to the environment during use, storage and disposal.

III.6 Discussion on the non-clinical aspects

The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate. Non-clinical findings of relevance to the prescriber are adequately mentioned in the appropriate sections of the SmPC.

IV. CLINICAL ASPECTS

IV.1 Introduction

This application is based on well-established use and therefore the clinical dossier is based upon published literature.

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

IV.2 Pharmacokinetics

The applicant provided an adequate overview of the pharmacokinetics.

Absorption:
Oral administration of tablets results in maximum serum levels in about 4 hours.

Distribution:
The apparent volume of distribution estimated after intravenous administration is 1221 L±280 L; range 769-1702 L (16±3 L/kg).
The plasma protein binding is about 95%.
Amitriptyline and the main metabolite nortriptyline pass across the placental barrier.

Biotransformation:
In vitro the metabolism of amitriptyline proceeds mainly by demethylation (CYP2C19, CYP3A4) and hydroxylation (CYP2D6) followed by conjugation with glucuronic acid. Other isozymes involved are CYP1A2 and CYP2C9.

Elimination
The elimination half-life amitriptyline after oral administration is about 25 hours (24.65±6.31 hours; range 16.49-40.36 hours).
The excretion proceeds mainly with urine. The renal elimination of unchanged amitriptyline is insignificant (about 2%).

Elderly patients
Longer half-lives and decreased oral clearance values due to a reduced rate of metabolism have been demonstrated in elderly patients.

Reduced hepatic function
Hepatic impairment may reduce hepatic extraction resulting in higher plasma levels and caution should be exercised when dosing these patients.

Reduced renal function
Renal failure has no influence on the kinetics.

IV.3 Pharmacodynamics

The pharmacodynamics of amitriptyline hydrochloride has been adequately discussed by the applicant and has been based on published literature.

Mechanism of action
Amitriptyline is a tricyclic antidepressant and an analgesic. It has marked anticholinergic and sedative properties. The antidepressant and analgesic effects usually set in after 2-4 weeks; the sedative action is not delayed.

IV.4 Clinical Efficacy

The efficacy of amitriptyline has been demonstrated in treatments of the following indications in adults:
-Major Depressive Disorder
-Neuropathic Pain
-Chronic tension type headache prophylaxis
-Migraine prophylaxis

The efficacy of amitriptyline has been demonstrated for treatments of nocturnal enuresis in children aged 6 years and above.

IV.5 Clinical Safety

The applicant has given an adequate overview of the safety of amitriptyline hydrochloride.

Pharmacovigilance System
The marketing authorisation holder (MAH) submitted a summary of the Pharmacovigilance System, including confirmation of the availability of an EU Qualified Person for Pharmacovigilance (EU-QPPV) and the means for notification of adverse reaction reports in the EU or from a Third Country.

Risk Management Plan (usual pharmacovigilance requirements +/- additional requirements)
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 Astilin 10 mg and 25 mg film-coated tablets.

Safety specification

Summary of safety concerns	
Important identified risks	• Cardiovascular disorders • Exacerbated psychotic disorders • Suicidal behaviour • Drug-drug interactions with monoamine oxidase inhibitors (MAOI) • Use in children and adolescents • Overdose
Important potential risks	• Reproductive toxicity • Use in elderly patients • Use in patients with hepatic impairment
Missing information	• None

Pharmacovigilance Plan

Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures

Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP

The submitted Risk Management Plan, version 1.1 signed 27-11-2017 is considered acceptable.

With regard to PSUR submission, the MAH should take the following into account:
-PSURs shall be submitted 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. Marketing authorisation holders shall continuously check the European medicines webportal for the DLP and frequency of submission of the next PSUR.
-For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.
-For medicinal products that do not fall within the categories waived of the obligation to submit routine PSURs by the revised pharmacovigilance legislation, the MAH should follow the DLP according to the EURD list.

IV.6 Discussion on the clinical aspects

Amitriptyline hydrochloride is a well-known active substance with established efficacy and tolerability. This application is based on well-established use and therefore the clinical dossier is based upon published literature. The wording of the product information is harmonised with the agreed wording for amitriptyline products following the recent Referral under Article 30 of Directive 2001/83/EC.
The content of amitriptyline hydrochloride in this medicinal product is marginally higher compared to other amitriptyline hydrochloride medicinal products authorised in Ireland. The difference is not considered to be clinically relevant however both healthcare professionals and patients should be aware of this if changing between amitriptyline hydrochloride medicinal products. A Product Information Update was prepared to inform healthcare professionals. In addition the SmPCs and PL are amended with the following text to inform both healthcare professionals and patients:
Astilin 10 mg film-coated tablets: Each film-coated tablet contains 10 mg amitriptyline equivalent to 11.32mg amitriptyline hydrochloride.
Astilin 25 mg film-coated tablets: Each film-coated tablet contains 25 mg amitriptyline equivalent to 28.3mg amitriptyline hydrochloride.
The content of amitriptyline hydrochloride in these medicinal products is marginally higher compared to other brands of amitriptyline hydrochloride medicinal products authorised in Ireland. Please be aware of this if changing between amitriptyline hydrochloride medicinal products.

V. OVERALL CONCLUSIONS

Bioequivalence has been shown to be in compliance with the CHMP guidance documents. The SmPC is consistent with that of the reference product.

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

VI. REVISION DATE

February 2021

VII. UPDATES

This section reflects the significant changes following finalisation of the initial procedure.

SCOPE	PROCEDURE NUMBER	PRODUCT INFORMATION AFFECTED	DATE OF START OF PROCEDURE	DATE OF END OF PROCEDURE
MAH transfer	CRN00C3PK	SmPC section 7, 8, 10 Package Leaflet New MA Holder: Ascot Laboratories Ireland Limited New PA number:	N/A	05/02/2021

		PA23163/001/001		