IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Amitriptyline hydrochloride 10mg/5ml Oral Solution
AMITRIPTYLINE HYDROCHLORIDE
PA22697/002/001

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

This product was initially authorised under procedure number UK/H/5514/2-4/DC with the UK as RMS. The responsibility of RMS was transferred to Ireland on 19/11/2018 under procedure number IE/H/0841/1-3/DC.
Please note the following detail for the product in IE:
Marketing Authorisation Number: PA22697/002/001-003
Marketing Authorisation Holder: SYRI Limited, t/a Thame Laboratories

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

The UK public assessment report published at the time of the initial marketing authorisation is provided herein.

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK and Ireland considered that the applications for Amitriptyline hydrochloride 10mg/5ml, 25mg/5ml and 50mg/5ml Oral Solution (PL 39307/0010-0012; UK/H/5514/002-004/DC) could be approved.
These are prescription-only medicines (POM), which are indicated for the treatment of:

- symptoms of depression (especially where sedation is required);
- nocturnal enuresis where organic pathology is excluded.

These applications were submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS), and Ireland as Concerned Member States (CMS). The applications were submitted under Article 10(3) of Directive 2001/83/EC, as amended, as hybrid applications and cross-refer to the reference products Tryptizol 10mg, 25mg and 50mg film-coated Tablets respectively (PL 0025/0093R-95R; Merck Sharp & Dohme). These licences were subsequently cancelled on 01 April 2008. As the brand leader's products (all strengths and pharmaceutical forms) are no longer available on the EU market, the applications were submitted under Article 10(3), in line with CMDh Questions & Answers Generic Applications guidance (CMDh/272/2012, Rev0).

In the absence of the brand leader's products, for comparison purposes the reference product used for these applications was Amitriptyline hydrochloride 50mg/5ml oral solution which was originally authorised to Verenigde Pharmaceutische Fabrieken BV (VPF BV; c/o R P Drugs House (Leeds) on 28 January 1993. This licence underwent change of ownership to the current Marketing authorisation Holder Rosemont Pharmaceuticals Limited (PL 00427/0116) on 27 March1998.

The active ingredient, amitriptyline, is a tricyclic antidepressant (TCA). Its mode of action in depression is not fully understood. It has anticholinergic and sedative properties.

No paediatric development plan exists for these products.

No new non-clinical or clinical studies were originally submitted with these applications. However, in response to a major objection raised concerning the justification for BCS biowaiver, the Marketing Authorisation Holder submitted one bioequivalence study comparing the test product Amitriptyline Hydrochloride 50mg/5ml Oral Solution (Thame Laboratories) with the reference product Amitriptyline hydrochloride 50mg/5ml oral solution (Rosemont Pharmaceuticals Limited, UK) in healthy subjects under fasting conditions. The applicant has stated that the bioequivalence study was conducted in accordance with ethical principles outlined in the Declaration of Helsinki, and Good Clinical Practices (GCPs).

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 the products being hybrid medicinal products of originator products that has been in clinical use for over 10 years.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place at all sites responsible for the manufacture, assembly and batch release of these products.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturing authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

The RMS and CMS considered that the applications could be approved at the end of procedure on 22 March 2015. After a subsequent national phase, licences were granted in the UK on 21 April 2015.

II. QUALITY ASPECTS

II QUALITY ASPECTS

II.1 Introduction

The submitted documentation concerning the proposed products is of sufficient quality and meets the current EU regulatory requirements.

The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

The products are clear colourless to yellow coloured solutions.

Each 5 mlof Amitriptyline hydrochloride 10mg/5ml Oral Solution contains 10 mg of amitriptyline hydrochloride.

Each 5 ml of Amitriptyline hydrochloride 25mg/5ml Oral Solution contains 25 mg of amitriptyline hydrochloride.

Each 5 ml of Amitriptyline hydrochloride 50mg/5ml Oral Solution contains 50 mg of amitriptyline hydrochloride.

The products also contain ascorbic acid (E300), disodium edetate, saccharin sodium (E954), methyl hydroxybenzoate (E218), propyl hydroxybenzoate (E216) and purified water. Appropriate justification for the inclusion of each excipient has been provided.

The finished products are supplied in Type III glass amber bottles, with tamper evident, child resistant polypropylene plastic screw caps. The products are packaged with double-ended polypropylene plastics spoons with 2.5ml and 5 ml measuring ends.

Amitriptyline hydrochloride 10mg/5ml, 25mg/5ml and 50mg/5ml Oral Solution are available in pack sizes of 150ml, 200ml, 300ml and 500ml.

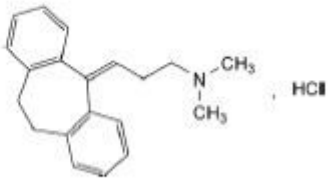
Satisfactory specifications and Certificates of Analysis for the primary packaging materials have been provided. All primary packaging complies with current European regulations concerning materials in contact with foodstuff.

II.2 DRUG SUBSTANCE

Amitriptyline hydrochloride

INN:	Amitriptyline hydrochloride
Chemical Name:	3-(10,11-Dihydro-5*H*-dibenzo[*a*,*d*][7]annulen-5-ylidene)-N,N-dimethylpropan-1-amine hydrochloride

Structure



Molecular Formula:	$C_{20}H_{23}N.HCl$
M_r:	313.9
Appearance:	White or almost white powder or colourless crystals
Solubility	Freely soluble in water, in ethanol (96%) and in methylene chloride.

Amitriptyline hydrochloride is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, amitriptyline hydrochloride, are covered by a European Directorate for the Quality of Medicine (EDQM) Certificate of Suitability.

II.3 MEDICINAL PRODUCT

Pharmaceutical Development

The objective of the development programme was to formulate safe, efficacious, stable, oral solutions, containing 10mg/5/ml, 25mg/5ml and 50mg/5ml of amitriptyline hydrochloride, that were comparable in performance to the reference products Tryptizol 10mg, 25mg and 50mg film-coated Tablets, (PL 0025/0093R-95R; Merck Sharp & Dohme). Suitable pharmaceutical development data have been provided for these applications.

The different strengths and forms (tablets, capsules, syrup, and injection) of the reference products (Tryptizol) are no longer available in Member States, as they are no longer marketed. In the absence of marketed originator references products, for comparison purposes a bioequivalence study and physico-chemical comparisons have been provided for the test product and surrogate reference product, Rosemont Pharmaceutical Limited's Amitriptyline hydrochloride 50mg/5ml Oral Solution. The results were satisfactory.

All the excipients comply with their respective European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for all excipients.

None of the excipients contain materials of animal or human origin.

No genetically modified organisms (GMO) have been used in the preparation of these excipients.

Manufacturing Process

Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate description of the manufacturing process. Based on pilot-scale batches, the manufacturing process has been validated and has shown satisfactory results. The Marketing Authorisation Holder has committed to performing process validation studies on future full-scale production batches.

Control of Finished Product

The finished product specifications are acceptable. Test methods have been described and have been validated adequately. 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 Product

Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. Based on the results, a shelf-life of 12 months for the 10mg/5ml and 25 mg/5ml strength unopened products and 9 months for the 50mg/5ml strength unopened product has been accepted. Once opened, the products should be discarded 30 days after first opening. The special storage conditions for the products are 'Do not store above 25°C.'

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

Bioequivalence/Bioavailability

Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence study. The bioequivalence study is discussed in Section IV, Clinical Aspects.

II.4 Discussion on chemical, pharmaceutical and biological aspects

It is recommended that Marketing Authorisations are granted for Amitriptyline hydrochloride 10mg/5ml, 25mg/5ml and 50mg/5ml Oral Solution.

II.5 Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels

The SmPCs, PILs and labelling are satisfactory and, where appropriate, in line with current guidance.

III. NON-CLINICAL ASPECTS

III NON-CLINICAL ASPECTS

III.1 Introduction

The pharmacodynamic, pharmacokinetic and toxicological properties of amitriptyline hydrochloride are well known. No new non-clinical data have been submitted for these applications and none are required.

The applicant has provided an overview based on published literature. The non-clinical overview 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, see Section III.1 Introduction, above.

III.3 Pharmacokinetics

Not applicable, see Section III.1 Introduction, above.

III.4 Toxicology

Not applicable, see Section III.1 Introduction, above.

III.5 Ecotoxicity/Environmental Risk Assessment (ERA)

Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the products are intended for substitution with products that are already marketed, no increase in environmental exposure to amitriptyline hydrochloride is anticipated. Thus, the justification for non-submission of an Environmental Risk Assessment is accepted.

III.6 Discussion of the non-clinical aspects

It is recommended that Marketing Authorisations are granted for Amitriptyline hydrochloride 10mg/5ml, 25mg/5ml and 50mg/5ml Oral Solution, from a non-clinical point of view.

IV. CLINICAL ASPECTS

IV. CLINICAL ASPECTS

IV.1 Introduction.

The clinical pharmacology of amitriptyline hydrochloride is well-known.

Initially, no new clinical studies were submitted to support these applications; a BCS biowaiver was sought. However, in response to a major objection raised concerning the justification for BCS biowaiver, the Marketing Authorisation Holder submitted one bioequivalence study comparing the test product Amitriptyline Hydrochloride 50mg/5ml Oral Solution (Thame Laboratories) with the reference product Amitriptyline Hydrochloride 50mg/5ml Oral Solution (Rosemont Pharmaceuticals Limited, UK) in healthy subjects under fasting conditions.

IV.2 Pharmacokinetics

The clinical pharmacokinetic properties of amitriptyline hydrochloride are well known. With the exception of data from the bioequivalence study detailed below, no new pharmacokinetic data are provided or required for these applications.

In support of the applications, the Marketing Authorisation Holder submitted the following bioequivalence study:

A randomised, open label, two-sequence, two-treatment, two-period, truncated, crossover, single dose bioequivalence study comparing the rate ad extent of absorption of the test product Amitriptyline Hydrochloride 50mg/5ml Oral Solution (Thame Laboratories) with reference product Amitriptyline Hydrochloride 50mg/5ml Oral Solution (Rosemont Pharmaceuticals Limited, UK), in healthy adult male and female human subjects under fasting conditions.

The subjects were administered a single 50 mg dose (5ml of 50mg/5ml oral solution) of either the test product or the reference product with 240 ml of water after at least a 10-hour overnight fast. Blood

samples were collected pre-dose and up to 72 hours after each administration. The washout period between the treatment arms was 14 days. The results of the study are summarised in the table below:

Pharmacokinetic parameters (geometric Mean, ratios and confidence intervals for amitriptyline

Parameters	*Geometric mean		% Ratio	90 % Confidence Interval for	
	Test (A)	Reference(B)	A/B	Lower Limit	Upper Limit
AUC_{0-72}	963.96	938.84	102.6760	98.7374	106.7718
C_{max}	43.50	43.36	100.3075	94.3594	106.6305

**Geometric mean was taken as the antilog (exponential) of the Least square mean of the log-transformed data.*

AUC_{0-72} area under the plasma concentration-time curve from time zero to72 hours
C_{max} maximum plasma concentration
Ratios and 90% confidence intervals calculated from log-transformed data

Conclusion of the bioequivalence study

The confidence intervals of the test/reference ratio for AUC_{0-72} and C_{max} values lie within the acceptable limits of 80.00 % to 125.00%, in line with Guidance on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/ Corr**). Hence the test product has been shown to be bioequivalent to the reference Amitriptyline 50mg/5ml oral solution (Rosemont Pharmaceuticals Limited, UK) under fasting conditions.

The justification for biowaiver for the 10mg/5ml and 25mg/5ml strengths of the product can be accepted as the applicant's 10mg/5ml, 25mg/5ml and 50mg/5ml strength oral solutions meet the biowaiver criteria specified in the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**).

IV.3 Pharmacodynamics

The clinical pharmacodynamics properties of amitriptyline hydrochloride are well-known. No new pharmacodynamic data were submitted and none are required for applications of this type.

IV.4 Clinical Efficacy

The clinical efficacy of c amitriptyline hydrochloride is well-known. No new efficacy data are presented or are required for applications of this type.

IV.5 Clinical Safety

The safety profile of amitriptyline hydrochloride is well-known. With the exception of the safety data generated during the bioequivalence study no new safety data were submitted and none are required for applications of this type. No new or unexpected safety issues were raised during the bioequivalence study.

IV.6 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 Amitriptyline hydrochloride 10mg/5ml, 25mg/5mland 50mg/5ml Oral Solution.

A summary of safety concerns is listed in the table below table:

Table: Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Hypersensitivity • Concomitant use of monoamine oxidase inhibitors (MAOIs) • Use in patients previously sensitised to amitriptyline • Use in patients with cardiovascular disorders • Mania • Use in patients with liver disease • Use in patients with porphyria • Use in lactation • Use in children less than 6 years of age • Use in patients with glaucoma • Use in patients with a history of urinary retention problem • Use in patients with history of epilepsy • Suicide/suicidal thoughts or worsening of the disease • Bone marrow depression • Testicular swelling, gynaecomastia, galactorrhoea, interference with sexual function and syndrome of inappropriate antidiuretic hormone (ADH) secretion • Confusional states, disturbed concentration, delusions, hallucinations, nightmares, peripheral neuropathy, coma and extrapyramidal symptoms including abnormal involuntary movements, tardive dyskinesia and dysarthria • Parotid swelling, stomatitis and black tongue Overdose • Worsening of psychotic symptoms in schizophrenia
Important potential risks	• Use in elderly patients • Concomitant use of electroconvulsive therapy • Use in patients undergoing surgery • Use in patients with hyperthyroidism • Hyponatraemia • Increased risk of bone fractures in patients receiving selective serotonin reuptake

Summary of safety concerns	
	inhibitors (SSRIs) and tricyclic antidepressants (TCAs)
Missing information	• Use in pregnancy

Routine Pharmacovigilance and routine risk minimisation are proposed for all safety concerns. No additional risk minimisation activities were required beyond those included in the product information.

IV.7 Discussion of the clinical aspects

It is recommended that Marketing Authorisations are granted for Amitriptyline hydrochloride 10mg/5ml, 25mg/5mland 50mg/5ml Oral Solution.

V. USER CONSULTATION

A 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 pack leaflet was English.

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.

V. OVERALL CONCLUSIONS

VI. OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

QUALITY

The important quality characteristics of Amitriptyline hydrochloride 10mg/5ml, 25mg/5ml and 50mg/5ml Oral Solution are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL

No new non-clinical data were submitted and none are required for applications of this type. As the pharmacokinetics, pharmacodynamics and toxicology of amitriptyline hydrochloride are well-known, no additional data were required.

EFFICACY

With the exception of the bioequivalence study, no new data were submitted and none are required for applications of this type.

Bioequivalence has been demonstrated between the applicant's test product Amitriptyline hydrochloride 50mg/5ml Oral Solution and the reference Amitriptyline 50mg/5ml Oral Solution (Rosemont Pharmaceutical Limited, UK) under fasting conditions.

The justification for biowaiver for the 10mg/5ml and 25mg/5ml strengths of the product can be accepted as the applicant's 10mg/5ml, 25mg/5ml and 50mg/5ml strength oral solutions meet the biowaiver criteria specified in the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**).

SAFETY

The safety profile of amitriptyline hydrochloride is well-known. With the exception of the safety data generated during the bioequivalence no new safety data were submitted and none are required for applications of this type. No new or unexpected safety issues were raised during the bioequivalence study.

PRODUCT LITERATURE

The SmPCs, PILs and labelling are satisfactory and, where appropriate, in line with current guidance.

BENEFIT/RISK ASSESSMENT

The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with amitriptyline hydrochloride is considered to have demonstrated the therapeutic value of the compound. The benefit/risk assessment is therefore considered to be positive.

RECOMMENDATION

The grant of Marketing Authorisations is recommended.

VI. REVISION DATE

25/02/2022

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
RMS transfer	From UK/H/5514/2-4/ DC to IE/H/0841/1-3/DC			