IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Amitriptyline Hydrochloride 25 mg/ 5 ml Oral Solution
AMITRIPTYLINE HYDROCHLORIDE
PA0281/233/001

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/2624/1-2/DC with the UK as RMS. The responsibility of RMS was transferred to Ireland on 18/12/2018 under procedure number IE./H/0891/1-2/DC
Please note the following detail for the product in IE:
Marketing Authorisation Number: PA0281/233/001
Marketing Authorisation Holder: Pinewood Laboratories Ltd

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.

Based on the review of the data on quality, safety and efficacy, the Reference Member State (RMS) and Concerned Member States (CMSs) consider that the applications for Amitriptyline Hydrochloride 25mg/5ml and 50mg/5ml Oral Solution, in the treatment of
symptoms of depression (especially where sedation is required) and Nocturnal enuresis
where organic pathology is excluded, could be approved.

These applications were submitted under Article 10(1), claiming to be generic medicinal products of Tryptizol 25mg and 50mg Tablets (PL 00025/0094R and 0095R), which were licensed in the UK to Merck Sharp & Dohme Limited on 13th July 1983.

With UK as the RMS in these Decentralised Procedures (UK/H/2624/001-2/DC), Wockhardt UK Limited is applying for the Marketing Authorisations for Amitriptyline 25mg/5ml and 50mg/5ml Oral Solution in Cyprus, Ireland, Malta and Poland.

Amitriptyline, a dibenzocycloheptadiene, is a tricyclic antidepressant that was developed from phenothiazine compounds related to chlorpromazine and possess a 3-ring molecular structure. Amitriptyline inhibits the neuronal reuptake of noradrenaline and serotonin in the CNS. Its specific mechanism of action is not fully understood, however, prevention of the reuptake of these monoamine neurotransmitters, which potentiates their action in the brain, appears to be associated with antidepressant activity. Tricyclic antidepressants, such as amitriptyline, also possess affinity for muscarinic and histamine H1 receptors to varying degrees. Amitriptyline is one of the more sedating tricyclics.

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

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

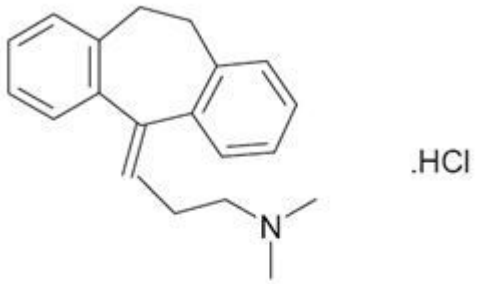
The RMS considers that the Pharmacovigilance System as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country. A suitable justification has been provided for non-submission of a Risk Management Plan.

All member states agreed to grant respective licences for the above products at the end of procedure (Day 210 – 14th July 2010). After a subsequent national phase, the UK granted licences for these products on 27th August 2010 (PL 29831/0356 and 0439).

II. QUALITY ASPECTS

INN: Amitriptyline hydrochloride
Chemical Names: 3-(10,11-dihydro-5H-dibenzo[[a,d]]cycloheptene-5-ylidene)-N,N-dimethyl-1-propanamine

Structure:



.HCl

Molecular formula: $C_{20}H_{23}NHCL$
Molecular weight: 313.9
Physical form: White to almost white crystalline powder or small crystal. Freely soluble in water, in Alcohol, and in Methylene Chloride, in Methanol and in Chloroform; insoluble in Ether.

Synthesis of the drug substance from the designated starting material 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 analysis data are provided and 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 generated, supporting a suitable retest period for active amitriptyline hydrochloride when stored in the proposed packaging.

DRUG PRODUCT

Other Ingredients

Other ingredients consist of the pharmaceutical excipients methyl hydroxybenzoate (E218), propyl hydroxybenzoate (E216), propylene glycol, ascorbic acid, quinoline yellow (E104), orange flavour 10950-56 (contains ethanol), orange/tangerine flavour 10888-56 (contains ethanol), sucralose powder, liquid maltitol, and purified water.

All excipients comply with the European Pharmacopoeia monograph with the exception of quinoline yellow (E104), orange/tangerine flavour 10888-56 (contains ethanol) and orange

flavour 10950-56 which comply with in house specification and sucralose complies with National Formulae. Satisfactory Certificates of Analysis have been provided for these excipients.

The above excipients do not contain materials of animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of these products.

Pharmaceutical Development

The products have been developed as generic versions of the reference products Tryptizol 25mg and 50mg Tablets (PL 00025/0094R and 0095R). The licences for Tryptizol 25mg and 50mg Tablets (PL 00025/0094R and 0095R) were cancelled in the UK on 01/04/2008. As the reference products have been cancelled and are no longer available on the EU market, physiochemical comparisons have been made to the licensed generic medicinal products, Amitriptyline 25mg/5ml and 50mg/5ml Oral Solution (PL 00427/0115-6, Rosemont Pharmaceuticals Limited) during development and presented as supportive data.

Suitable pharmaceutical development data have been provided for these applications.

Manufacture

A description and flow-chart of the manufacturing method have been provided. In-process controls are satisfactory based on process validation data and controls on the finished products. Process validation has been carried out on batches of each product. The results are satisfactory.

Finished Product Specifications

The finished product specifications are satisfactory. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Container Closure System

The finished products are supplied in amber soda glass (type III) bottle fitted with white child resistant tamper evident cap, with expanded polyethylene (EPE) liner, and outer cardboard carton. Pack size is 150ml.

Specifications and Certificates of Analysis for the primary packaging material have been provided. These are satisfactory. All primary packaging is controlled to European Pharmacopoeia standards and complies with guidelines.

Stability

Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.

Based on the results, a shelf-life of 2 years has been set when the product is unopened and after first opening 1 month, with the storage conditions "Do not store above 25°C" and "Store in the original bottle and outer carton in order to protect from light".

Bioequivalence

No bioequivalence studies are presented to support the applications and absence has been suitably justified in accordance with the "Note for guidance on the investigation of bioavailability and bioequivalence" (CPMP/EWP/QWP/1401/98).

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling

The SPC, PIL and labelling are pharmaceutically satisfactory.

A package leaflet has been submitted to the MHRA together with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

Marketing Authorisation Application (MAA) Forms

The MAA forms are pharmaceutically satisfactory.

Expert Report

A pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Conclusion

There are no objections to the approval of these products from a pharmaceutical point of view.

III.2 PRE-CLINICAL ASPECTS

PHARMACODYNAMICS, PHARMACOKINETICS, TOXICOLOGY

The pharmacological, pharmacokinetic and toxicological properties of Amitriptyline Hydrochloride are well-known.

No new preclinical data have been supplied with these applications and none are required for applications of this type. The pre-clinical expert report has been written by an appropriately qualified person and is a suitable summary of the pre-clinical aspects of the dossier.

A suitable justification has been provided for non-submission of the environmental risk assessment.

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

III. NON-CLINICAL ASPECTS

PHARMACODYNAMICS,PHARMACOKINETICS,TOXICOLOGY

The pharmacological, pharmacokinetic and toxicological properties of Amitriptyline Hydrochloride are well-known.

No new preclinical data have been supplied with these applications and none are required for applications of this type. The pre-clinical expert report has been written by an appropriately qualified person and is a suitable summary of the pre-clinical aspects of the dossier.

A suitable justification has been provided for non-submission of the environmental risk assessment.

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

IV. CLINICAL ASPECTS

Pharmacokinetics

No new data have been submitted and none are required for applications of this type.

These applications are for generic medicinal products of Tryptizol 25mg and 50mg Tablets (PL 00025/0094R and 0095R), which were licensed in the UK to Merck Sharp & Dohme Limited on 13th July 1983. The use of the reference products is well-established in the UK.

The absence of a bioequivalence study has been suitabley justified in accordance with the Committee for Proprietary Medicinal Products Notes for Guideline on "Note for guidance on the investigation of bioavailability and bioequivalence" (CPMP/EWP/QWP/1401/98).

Pharmacodynamics
No new data have been submitted and none are required for applications of this type.

Clinicalefficacy
No new data have been submitted and none are required for applications of this type.

Clinicalsafety
Amitriptyline hydrochloride has an acceptable adverse events profile. No new safety data are supplied or required for these generic applications. Amitriptyline hydrochloride has a
well-established side-effect profile and is generally well-tolerated.

SummaryofProductCharacteristics(SmPC),PatientInformationLeaflet(PIL)and labelling
The SmPC, PIL and labelling are medically satisfactory and consistent with those for the reference products.

ClinicalExpertReport
The clinical expert report is written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

MarketingAuthorisationApplication(MAA)Forms
The MAA forms are medically satisfactory.

ClinicalConclusion
There are no objections to the approval of these products from a clinical point of view.

V. OVERALL CONCLUSIONS

QUALITY
The important quality characteristics of Amitriptyline Hydrochloride 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.

PRE-CLINICAL
The pre-clinical data submitted have not revealed any evidence of potential risks to human health from treatment with Amitriptyline Hydrochloride 25mg/5ml and 50mg/5ml Oral Solution beyond those already described.

EFFICACY
These applications are for generic medicinal products of Tryptizol 25mg and 50mg Tablets (PL 00025/0094R and 0095R), which were licensed in the UK to Merck Sharp & Dohme Limited on 13th July 1983. The use of the reference products is well-established in the UK.

The proposed products were considered to contain the same quantitative and qualitative composition of the active substance as their respective reference products and the absence of a bioequivalence study has been suitably justified in accordance with the Committee for
Proprietary Medicinal Products "Note for guidance on the investigation of bioavailability and bioequivalence" (CPMP/EWP/QWP/1401/98).

No new safety data are supplied or required for these generic applications. Amitriptyline hydrochloride has a well-established side-effect profile and is generally well-tolerated.

The SPC, PIL and labelling are satisfactory.

BENEFIT-RISKASSESSMENT

The quality of the product is acceptable, and no new preclinical or clinical safety concerns have been identified. The data supplied supports the claim that the applicant's products and
the innovator products are interchangeable. Extensive clinical experience with amitriptyline hydrochloride is considered to have demonstrated the therapeutic value of the compound.
The benefit-risk is, therefore, considered to be positive.

VI. REVISION DATE

18th February 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/2624/1-2/ DC to IE/H/0891/1-2/DC			