IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Tranylcypromine Eignapharma 20 mg Film-coated Tablet
Tranylcypromine sulfate
PA23229/012/001

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.

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I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Tranylcypromine Eignapharma 20 mg & 40 mg Film-coated Tablet, from Neuraxpharm Ireland Limited, on 10th February 2023 for the treatment of episodes of major depression in adults as a reserve antidepressant.

This is a generic product and the legal basis for this application is article 10 (1) of Directive 2001/83/EC as amended.

HPRA was RMS in this decentralised procedure and Luxembourg was a CMS. Luxembourg was subsequently withdrawn as CMS during the procedure.

This medicinal product is subject to prescription, which may not be renewed.

The Summary of Product Characteristics for (SmPC) and Patient Information Leaflet for this medicinal product is available on the HPRA's website.

Name of the product	Tranylcypromine Eignapharma 20 mg Film-coated Tablet
Name(s) of the active substance(s) (INN)	Tranylcypromine Sulfate
Pharmacotherapeutic classification (ATC code)	N06AF04
Pharmaceutical form and strength(s)	20 mg Film-coated Tablet
Marketing Authorisation Number(s) in Ireland (PA)	PA23229/012/001
Marketing Authorisation Holder	Neuraxpharm Ireland Limited
MRP/DCP No.	IE/H/1197/001/DC
Reference Member State	IE
Concerned Member State	None

II. QUALITY ASPECTS

II.1. Introduction

This application is for Tranylcypromine Eignapharma 20 mg & 40 mg Film-coated Tablet

II.2 Drug substance

The active substance is Tranylcypromine Sulfate, an established active substance and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP)

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

II.3 Medicinal product

P.1 Composition

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/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 film-coated 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 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./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 Tranylcypromine Eignapharma 20 mg & 40 mg Film-coated Tablet.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This active substance is a generic formulation of Jatrosom 20 mg and 40 mg film-coated tablets on the European market. No new preclinical data have been submitted. This is acceptable for this type of application.

III.2 Pharmacology

N/A

III.3 Pharmacokinetics

N/A

III.4 Toxicology

N/A

III.5 Ecotoxicity/environmental risk assessment

Since Tranylcypromine Eignapharma 20 mg and 40 mg film-coated tablets are generic products, they will not lead to an increased exposure to the environment. Additional studies on environmental risk are therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of tranylcypromine sulfate are well known. As tranylcypromine sulfate is a widely used, well-known active substance, the applicant has not provided any additional nonclinical studies and further studies are not required. A nonclinical overview based on literature review was provided and is acceptable for this type of generic application. Nonclinical findings are adequately represented in the appropriate sections of the SmPC.

IV. CLINICAL ASPECTS

IV.1 Introduction

The active substance, tranylcypromine sulfate is a well known active substance with established efficacy and tolerability.

The content of the SmPC approved during the decentralised procedure is in accordance with that accepted for the reference product Jatrosom 20 mg film-coated tablets marketed by Aristo Pharma GmbH.

For this generic application, the applicant requested a bio-waiver in accordance with Appendix III of guideline on the investigation of bioequivalence (Doc.Ref.:CPMP/EWP/QWP/1401/98 Rev.1/Corr **). The active tranylcypromine sulfate is highly soluble, with a low permeability and without a narrow therapeutic index. Tranylcypromine can be classified as a BCS Class 3 active substance. The Test product (Tranylcypromin Eignapharma 20 mg and 40 mg film coated tablets) is comparable to the Reference product (Jatrosom 20 mg and 40 mg film-coated tablets); both are immediate-release oral dosage forms with systemic action and very rapidly dissolved formulations (yielding > 85% in less than 15 minutes). The drug product is the same dosage from and strength as the Reference product. The excipient content is appears essentially similar in qualitative composition. The comparative dissolution profiles between the Test and Reference products show similarity in dissolution across the physiological pH range. All the requirements for a BCS-based class 3 biowaiver are met. The justification for a biowaiver is acceptable.

IV.2 Pharmacokinetics

Absorption

Tranylcypromine is rapidly absorbed after oral administration. Maximum plasma levels are expected 0.5 to 3.5 hours after oral administration. The plasma concentration of the (-)-isomer is always higher than that of the (+)-isomer.

Distribution

A distribution volume of 1.1 to 5.7 l/kg body weight can be assumed. It is known that tranylcypromine is excreted in breast milk.

Biotransformation

The primary products of hepatic biotransformation are p-hydroxytranylcypromine and N-acetyl-tranylcypromine. Only about 4% of the tranylcypromine dose is excreted in urine in an unchanged form. Even after the administration of high doses no amphetamine in the form of a metabolite was found in human urine or plasma.

Elimination

In a study with depressive patients a half-life of about 2.5 hours was determined after a single dose of 20 mg tranycypromine. A large amount of the substance is excreted in the form of metabolites (hippuric acid and benzoic acid) by the bile and in particular the kidneys. Renal excretion of tranylcypromine depends strongly on the pH, a low pH facilitates excretion.

IV.3 Pharmacodynamics

Tranylcypromine belongs to the group of irreversible and non-selective monoamine oxidase (MAO) inhibitors without a hydrazine structure. The mechanism of the antidepressant effect is not yet fully understood.

Within two hours of administration, the non-selective inhibition of MAO-A and MOA -B prevents the intracellular and intraneural inactivation of biogenic amines such as serotonin, noradrenaline and dopamine. This means that a larger amount of

transmitters is available in the CNS. Although tranylcypromine and its metabolites are completely eliminated within 24 hours after the last dose taken, due to irreversible MAO inhibition, full enzyme activity of monoamine oxidase is restored after 3 to 5 days only.

In the longer term use the density of β-adrenoceptors and serotonin 5-HT2-receptors is reduced.

Tranylcypromine is a racemic mixture of (-)- and (+)-isomers: the (+)-isomer has a stronger inhibitory effect on the monoamine oxidase, the (-)-isomer can additionally inhibit noradrenaline reuptake.

IV.4 Clinical Efficacy

No clinical efficacy data are provided as this is a generic application.

IV.5 Clinical Safety

As this is a generic application, no other clinical safety data are required.

Risk Management Plan
A risk management plan was submitted, 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 Tranylcypromine Eignapharma 20 mg / 40 mg film coated tablets.

Safety specification

Important identified risks	• Hypertensive crisis or severe hypertension due to concomitant use of certain drugs or ingestion of tyramine-rich foods • Serotonin syndrome and other serotoninergic reactions when used concomitantly with other serotoninergic drug • Suicide/suicidal ideation, clinical deterioration
Important potential risks	• Use in pregnancy and lactation • Decrease of seizure threshold • Influence on blood glucose concentration and increase of the effect of antidiabetic treatment
Missing information	• None

Routine pharmacovigilance activities and routine risk minimisation measures are proposed by the applicant, which is endorsed.

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.

IV.6 Discussion on the clinical aspects

As this approval concerns a generic application, there are no new efficacy or safety studies required, as the applicant can refer to the data of the reference medical products.

V. OVERALL CONCLUSIONS

Tranylcypromine Eignapharma 20 mg & 40 mg Film-coated Tablet is a generic form of Jatrosom 20 mg film-coated tablets. Jatrosom 20 mg film-coated tablets is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

Bioequivalence was waived 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.

The HPRA, on the basis of the data submitted considered that Tranylcypromine Eignapharma 20 mg & 40 mg Film-coated Tablet a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

VI. REVISION DATE

01.07.2027