IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Escitalopram Pinewood 5 mg Film-coated tablets
Escitalopram oxalate
PA0281/262/001

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

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Escitalopram Pinewood 5 mg, 10 mg, 15 mg & 20 mg Film-coated tablet, from Pinewood Laboratories Ltd on 23rd June 2023 for the following indications in adults,

- Treatment of major depressive episodes.
- Treatment of panic disorder with or without agoraphobia.
- Treatment of social anxiety disorder (social phobia).
- Treatment of generalised anxiety disorder.
- Treatment of obsessive-compulsive disorder.

This application for a marketing authorisation was submitted in accordance with Article 10(1) of Directive 2001/83/EC as amended and via the decentralised procedure with Ireland (IE) as the Reference Member State and Malta as sole Concerned member State.

The European reference product is Lexapro 5mg, 10mg, 50mg and 20 mg Film-Coated Tablets by H. Lundbeck A/S, registered in IE since Oct 11th 2002.

The applicant's product Escitalopram Pinewood 5 mg, 10 mg, 15 mg & 20 mg Film-coated tablet are of the same indication, strength and route of administration as that of the reference medicinal product Lexapro 5mg, 10mg, 50mg and 20 mg Film-Coated Tablets.

No scientific advice was applied for by the applicant prior to submission of this applicant.

Escitalopram Pinewood 5 mg, 10 mg, 15 mg & 20 mg Film-coated tablet are subject to medical prescription, which may not be renewed.

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	Escitalopram Pinewood 5 mg Film-coated tablet
Name(s) of the active substance(s) (INN)	Escitalopram oxalate
Pharmacotherapeutic classification (ATC code)	N06AB10
Pharmaceutical form and strength(s)	5 mg Film-coated tablet
Marketing Authorisation Number(s) in Ireland (PA)	PA0281/262/001
Marketing Authorisation Holder	Pinewood Laboratories Ltd
MRP/DCP No.	IE/H/1212/001/DC
Reference Member State	IE
Concerned Member State	MT

II. QUALITY ASPECTS

II.1. Introduction

This application is for Escitalopram Pinewood 5 mg, 10 mg, 15 mg & 20 mg Film-coated tablet.

II.2 Drug substance

The active substance is escitalopram oxalate, 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

The finished drug products are film-coated tablets containing escitalopram oxalate equivalent to 5 mg, 10 mg, 15 mg and 20 mg of escitalopram.

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/*Ancillary Substances*)

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 the dosage form, 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/or 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 Escitalopram Pinewood 5 mg, 10 mg, 15 mg & 20 mg Film-coated tablet.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This active substance is a generic formulation of Lexapro 5, 10, 15, and 20 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 Escitalopram Pinewood 5, 10, 15, and 20 mg film-coated tablets are generic products, they will not lead to an increased exposure to the environment. Additional studies on environmental risk assessment are therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of escitalopram oxalate are well known. As escitalopram oxalate is a widely used, well-known active substance, the applicant has not provided 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.

IV. CLINICAL ASPECTS

IV.1 Introduction

Escitalopram Oxalate 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 European reference product Lexapro 5mg, 10mg, 15mg and 20 mg film-coated tablets marketed by H. Lundbeck A/S Ottiliavej 9 DK-2500 Copenhagen-Valby Denmark, registered in IE since Oct 11th 2002.

For this generic application, the applicant has submitted one bioequivalence study in which the pharmacokinetic profile of the test product Escitalopram Oxalate 20mg Tablets by Torrent Pharmaceuticals Ltd. is compared with the pharmacokinetic profile of the reference product Cipralex 20mg film coated tablets. Lundbeck GmbH, Kamapp 25, 21079 Hamburg.

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out. Escitalopram Oxalate 20mg Tablets by Torrent Pharmaceuticals Ltd., was compared to the reference product to Cipralex 20mg film coated tablets, Lundbeck GmbH.

Bioequivalence has been shown in accordance with the Bioequivalence Guideline CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **. The 90% confidence interval for the ratio of the test and reference products are contained within the acceptance interval of ≥80.00% and ≤125.00% for the parameters (≥0.80 and ≤1.25): C_{max} 1.02 (0.98 - 1.06) and AUC_{0-t} 1.02 (0.98 - 1.05).

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range)

Treatment	AUC_{0-t} (hr*ng/mL) (%CV)	C_{max} ng/ml (%CV)	t_{max} h
Test	826.217 ± 329.777 (39.91%)	19.665 ± 4.210 (21.41%)	4.881 (2.5-7.5)
Reference	812.797 ± 314.344 (38.67%)	19.225 ± 3.577 (18.61%)	4.857 (2.0-7.0)

***Ratio (90% CI)**	1.02 (0.98-1.05)	1.02 (0.98-1.06)	-
AUC_{0-t} The area under the plasma concentration versus time curve, from time 0 to the last measurable concentration, where t = time of last measurable concentration **C_{max}** Maximum plasma concentration **t_{max}** Time until Cmax is reached			

**ln-transformed values*

Based on the pharmacokinetic parameters of active substance Escitalopram Oxalate, the reference tablet Cipralex 20mg film coated tablets marketed by Lundbeck GmbH and test tablet Escitalopram Oxalate 20mg Tablet are bioequivalent with extent to the rate and extent of absorption and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

The Escitalopram Oxalate tablets 15 mg, 10 mg and 5 mg are dose proportional with the Escitalopram Oxalate tablet 20 mg strength. The pharmacokinetics of the active substance Escitalopram Oxalate are linear in the range 5 to 20 mg. The results of the bioequivalence study performed with the 20mg tablet therefore apply to the other strengths. A biowaiver for the Escitalopram Oxalate tablets 15 mg, 10 mg and 5 mg is granted.

The content of the SmPC approved during the decentralised procedure is in accordance with that accepted for the reference product Lexapro 5mg, 10mg, 15mg and 20 mg film-coated tablets marketed by H. Lundbeck A/S.

The HPRA has been assured that GCP standards were followed in an appropriate manner in the studies conducted.

IV.2 Pharmacokinetics

No additional studies investigating the pharmacokinetic effects of Escitalopram Pinewood 20mg, 15mg, 10mg and 5 mg Film-Coated Tablets were conducted which is acceptable for this generic application.

Absorption
Absorption is almost complete and independent of food intake. (Mean time to maximum concentration (mean Tmax) is 4 hours after multiple dosing). As with racemic citalopram, the absolute bio-availability of escitalopram is expected to be about 80%.

Distribution
The apparent volume of distribution (Vd,β/F) after oral administration is about 12 to 26 L/kg. The plasma protein binding is below 80% for escitalopram and its main metabolites.

Biotransformation and Elimination
Escitalopram is metabolised in the liver to the demethylated and didemethylated metabolites. Both of these are pharmacologically active. Alternatively, the nitrogen may be oxidised to form the N-oxide metabolite. Both parent substance and metabolites are partly excreted as glucuronides. After multiple dosing, the mean concentrations of the demethyl and didemethyl metabolites are usually 28-31% and <5%, respectively, of the escitalopram concentration. Biotransformation of escitalopram to the demethylated metabolite is mediated primarily by CYP2C19. Some contribution by the enzymes CYP3A4 and CYP2D6 is possible.

Elimination
The elimination half-life ($t_{½\ \beta}$) after multiple dosing is about 30 hours and the oral plasma clearance (Cl_{oral}) is about 0.6 L/min. The major metabolites have a significantly longer half-life. Escitalopram and major metabolites are assumed to be eliminated by both the hepatic (metabolic) and the renal routes, with the major part of the dose excreted as metabolites in the urine.

Linearity
There is linear pharmacokinetics. Steady-state plasma levels are achieved in about 1 week. Average steady-state concentrations of 50 nmol/L (range 20 to 125 nmol/L) are achieved at a daily dose of 10 mg.

IV.3 Pharmacodynamics

No additional studies investigating the pharmacodynamic effects of Escitalopram Pinewood 20mg, 15mg, 10mg and 5 mg Film-Coated Tablets were conducted which is acceptable for this generic application.

For further information see the SmPCs Section 5.1.

IV.4 Clinical Efficacy

The efficacy of escitalopram in the proposed indications is established in clinical use. No new clinical efficacy studies are provided and none are required.

IV.5 Clinical Safety

No new Applicant-generated efficacy studies or bibliographical data were submitted in this application and none are required.

The reference product for this application, Lexapro 20 mg film-coated tablets has been on the market in IE since 2002. Therefore, escitalopram oxalate has an established clinical safety profile. The safety information in the SmPC and Package Leaflet are in line with those of the reference product.

During the pivotal bioequivalence study, both the test and reference products were well tolerated by the subjects. Three AEs reported during the course of the study, were mild in intensity and resolved completely without sequelae. There were no deaths, serious AEs or other significant AEs noted in the bioequivalence study.

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 Escitalopram Pinewood 5 mg, 10 mg, 15 mg, 20 mg Film-Coated Tablets.

Important identified risks None
Important potential risks None
Missing information None

Routine pharmacovigilance activities and routine risk minimisation measures are considered sufficient.

Periodic Safety Update Reports (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 web-portal for the DLP and frequency of submission of the next PSUR.

IV.6 Discussion on the clinical aspects

This decentralised marketing authorisation application was submitted in accordance with Article 10.1 of Directive 2001/83/EC as amended (generic application).

One bioequivalence study was submitted, in which the pharmacokinetic profile of the test product Escitalopram Oxalate 20mg tablet of Torrent Pharmaceuticals Ltd. was compared with the pharmacokinetic profile of the reference product Cipralex 20mg film coated tablets of Lundbeck GmbH,

The 90% confidence intervals for C_{max} and AUC_{0-t} were 0.98 - 1.06 and 0.98 - 1.05 respectively, all of which are within the accepted ranges and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

With respect to the grant of a biowaiver for the Escitalopram Oxalate tablets 15 mg, 10 mg and 5 mg, the bioequivalence guideline requirements were found to have been met.

Escitalopram Oxalate is a well-known active substance with established efficacy and tolerability. The European reference product for this application, Lexapro 20 mg film-coated tablets by H. Lundbeck A/S has been on the market in Ireland since

2002. The safety results reported in the bioequivalence study were found to be consistent with the known safety profile of Escitalopram Oxalate and no other safety studies were submitted in support of this application which is acceptable.

V. OVERALL CONCLUSIONS

Escitalopram Pinewood 5 mg, 10 mg, 15 mg and 20 mg film-coated tablets are a generic form of Lexapro 5mg, 10mg, 15mg and 20 mg film-coated tablets. Lexapro 5mg, 10mg, 15mg and 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 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.

The HPRA, on the basis of the data submitted considered that Escitalopram Pinewood 5 mg, 10 mg, 15 mg and 20 mg film-coated tablets demonstrated bioequivalence with the reference product as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

VI. REVISION DATE

09.05.2028