IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Fluoxetine 40 milligram(s) hard capsule
FLUOXETINE HYDROCHLORIDE
PA1567/007/004

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 Fluoxetine 40 milligram(s) hard capsule, from Activase Pharmaceuticals Limited, on 23rd January 2026 for indication:

Adults:

- Major depressive episodes.
- Obsessive-compulsive disorder.
- Bulimia nervosa: Fluoxetine is indicated as a complement of psychotherapy for the reduction of binge-eating and purging activity.

Children and adolescents aged 8 years and above:

Moderate to severe major depressive episode, if depression is unresponsive to psychological therapy after 4–6 sessions. Antidepressant medication should be offered to a child or young person with moderate to severe depression only in combination with a concurrent psychological therapy.

This application for a marketing authorisation was submitted in accordance with Article 10(1) Generic application (for Fluoxetine 20 milligram(s)) and Article 10(3) Hybrid application (for Fluoxetine 10 milligram(s) hard capsule, Fluoxetine 30 milligram(s) hard capsule, Fluoxetine 40 milligram(s) hard capsule, Fluoxetine 60 milligram(s) hard capsule). Article 10(3) is a hybrid application, as the 10 mg, 30 mg and 40 mg strengths of the product are cross-referred to the 20 mg strength of the reference product Prozac 20 mg hard capsules by Eli Lilly Nederland B.V., registered in Ireland since 09/02/1989. The HPRA was the reference member state (RMS) and Malta was the only concerned member state (CMS).

The products are subject to 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	Fluoxetine 40 milligram(s) hard capsule,
Name(s) of the active substance(s) (INN)	FLUOXETINE HYDROCHLORIDE
Pharmacotherapeutic classification (ATC Code)	N06AB03
Pharmaceutical form and strength(s)	40 milligram(s) hard capsule
Marketing Authorisation Number(s) in Ireland (PA)	PA1567/007/004
Marketing Authorisation Holder	Activase Pharmaceuticals Limited Boumpoulinas 11 Nicosia 1060 Cyprus
MRP/DCP No.	IE/H/1287/004/DC
Reference Member State	IE
Concerned Member State(s)	MT

II. QUALITY ASPECTS

II.1. Introduction

This application is for Fluoxetine 40 milligram(s) hard capsule

II.2 Drug substance

The active substance is Fluoxetine 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

Each hard capsule contains fluoxetine hydrochloride equivalent to 40 mg fluoxetine

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 Capsules 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./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 Fluoxetine 40 milligram(s) hard capsule

III. NON-CLINICAL ASPECTS

III.1 Introduction

This active substance is a generic formulation of fluoxetine 10, 20, 30, 40 and 60 milligram(s) hard capsules on the European market. No new preclinical data have been submitted. This is acceptable for this type of application.

The pharmacodynamic, pharmacokinetic and toxicological properties of fluoxetine hydrochloride are well known.

III.2 Pharmacology

N/A.

III.3 Pharmacokinetics

N/A

III.4 Toxicology

N/A

III.5 Ecotoxicity/environmental risk assessment

Since fluoxetine 10, 20, 30, 40 and 60 milligram(s) hard capsules are intended for generic substitution, this 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

The pharmacodynamic, pharmacokinetic and toxicological properties of fluoxetine hydrochloride are well known. As fluoxetine hydrochloride is a widely used, well-known active substance, the applicant has not provided additional studies, and further studies are not required. A nonclinical overview based on literature review was provided and is acceptable. Non-clinical findings are adequately represented in the appropriate sections of the SmPC.

IV. CLINICAL ASPECTS

IV.1 Introduction

Fluoxetine hydrochloride 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 Prozac 20 mg hard capsules marketed by Eli Lilly Nederland B.V.

For this generic application, the applicant has submitted one bioequivalence study in which the pharmacokinetic profile of the test product Fluoxetine 60 mg strength is compared with the pharmacokinetic profile of the reference product Prozac 20 mg (3x20 mg). For the lower strengths, 10 mg, 20 mg, 30 mg and 40 mg a biowaiver is requested.

An open label, randomised, single-dose, two-treatment, two-sequence, two-period, crossover oral bioequivalence study of the test Fluoxetine Capsules 60 mg and reference Prozac 20 mg hard capsules (20 mg x 3 capsules). It was conducted in healthy, adult, human subjects under fasting conditions. Results are shown below.

Based on the pharmacokinetic parameters of fluoxetine, the 60 mg test and 3 x 20 mg reference product formulations are considered bioequivalent with respect to the extent and rate of absorption under fasting conditions. A biowaiver, based on the criteria outlined in the Guideline on the investigation of bioequivalence, CPMP/EWP/QWP/1401/98 Rev. 1/Corr, has been proposed for the 10 mg, 20 mg, 30 mg, and 40 mg test strengths. This is considered acceptable.

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

IV.2 Pharmacokinetics

Absorption: Fluoxetine is well absorbed from the gastrointestinal tract after oral administration. Following an oral dose of fluoxetine maximal plasma concentrations occur at approximately 6 to 8 hours. The pharmacokinetics of fluoxetine is not affected by food, and therefore there are no restrictions with respect to food in the SmPC of the originator.

Linearity and biotransformation: Fluoxetine has a non-linear pharmacokinetic profile with first pass liver effect. Fluoxetine is extensively metabolised by the polymorphic enzyme CYP2D6. Fluoxetine is primarily metabolised by the liver to the active metabolite norfluoxetine (desmethylfluoxetine), by desmethylation.

Elimination: The elimination half-life of fluoxetine is 4 to 6 days and for norfluoxetine 4 to 16 days. These long half-lives are responsible for persistence of the drug for 5-6 weeks after discontinuation.

IV.3 Pharmacodynamics

No new pharmacodynamic data were submitted and none are required for an application of this type.

IV.4 Clinical Efficacy

No new efficacy data were submitted and none are required for an application of this type.

IV.5 Clinical Safety

No new safety data were submitted and none are required for an application of this type.

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 Fluoxetine 10mg, 20mg, 30mg, 40mg and 60mg hard capsule.

Safety specification

Important identified risks	Withdrawal symptoms Suicide-related behaviours (suicide attempt and suicidal thoughts) Hostility (predominantly aggression, oppositional behaviour and anger) Mania/hypomania Rash and allergic reactions Seizures Concomitant use with Tamoxifen Cardiovascular Effects (including QT interval prolongation, ventricular arrhythmia and torsade de pointes) Weight loss Akathisia/psychomotor restlessness Haemorrhage Mydriasis Concomitant use with St John's Wort (Hypericum perforatum) Concomitant use with Monoamine oxidase inhibitors Concomitant use with oral anticoagulants Use during lactation Effect on sperm quality Risk of bone fractures Use in patients with diabetes Concomitant use with other serotonergic (among others L-tryptophan) Concomitant use with neuroleptic drugs Serotonin syndrome/ neuroleptic malignant syndrome Use in patients with Hepatic/Renal impairment

Important potential risks	Long-term effect on safety in children and adolescents(including effects on growth, sexual maturation and cognitive, emotional and behavioural developments) Risk of persistent pulmonary hypertension in the newborn (PPHN) Risk of cardiovascular birth defects
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 0.1 signed 13 September 2023 is acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

Periodic Safety Update Report (PSUR)
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 web-portal 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.

In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification

IV.6 Discussion on the clinical aspects

This application concerns a generic medicinal product Fluoxetine 10 mg, 20 mg, 30 mg, 40 mg and 60 mg hard capsules referencing Prozac 20 mg hard capsules by Eli Lilly Nederland B.V., registered in Ireland since 09/02/1989. Bioequivalence with the reference medicinal product has been demonstrated. No clinically relevant differences in efficacy or safety are anticipated in the proposed indication. The benefit–risk balance is favourable.

V. OVERALL CONCLUSIONS

Fluoxetine 40 milligram(s) hard capsule is a generic form of Prozac 20 mg hard capsules marketed by Eli Lilly Nederland B.V. Prozac 20 mg hard capsules 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.