IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Fluoxetine 20 mg/ 5 ml Oral Solution
FLUOXETINE HYDROCHLORIDE
PA22697/010/001

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/6145/1/DC with the UK as RMS. The responsibility of RMS was transferred to Ireland on 12/09/2018 under procedure number IE/H/0767/1/DC.
Please note the following detail for the product in IE:
Marketing Authorisation Number: PA22697/010/001
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, Reference Member State (RMS) and Concerned Member State (CMS) considered that the application for Fluoxetine 20mg/5ml Oral Solution (PL 39307/0057; UK/H/6145/001/DC) is approvable.

This product is a prescription-only medicine (legal status POM) indicated for:

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 was submitted using the Decentralised Procedure (DCP), with the UK as RMS and The Republic of Ireland as a CMS.

This application was submitted according to Article 10(1) of Directive 2001/83/EC, as amended, as a generic application. The applicant has cross referred to Prozac 20mg/5ml oral solution (PL 00006/0272), authorised in the UK to Eli Lilly & Company Limited on 25 November 1988.

Fluoxetine is a selective inhibitor of serotonin reuptake, and this probably accounts for the mechanism of action. Fluoxetine has practically no affinity to other receptors such as α_1-, α_2-, and β-adrenergic; serotonergic; dopaminergic; histaminergic$_1$; muscarinic; and GABA receptors.

No new non-clinical or clinical studies were conducted, which is acceptable given that this is a generic application, which is cross-referring to an oral solution. The product is an oral solution containing the same active substance in the same concentration as the currently authorised reference product. Thus, in accordance with the *Note for Guidance on the Investigation of Bioequivalence* (CPMP/EWP/QWP/1401/98 Rev 1**), the applicant was not required to submit bioequivalence studies for this application.

Since Fluoxetine 20mg/5ml Oral Solution is intended for generic substitution, its use will not lead to an increased exposure to the environment. An Environmental Risk Assessment (ERA) is, therefore, not deemed necessary.

A detailed Risk Management Plan has been submitted for this product and it is satisfactory.

The RMS has been assured that acceptable standards of GMP are in place for this product type at all sites responsible for the manufacture and assembly of this product.
For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer 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 application could be approved at the end of procedure (Day 209) on 03 May 2016. After a subsequent National phase, the UK granted a Marketing Authorisation (PL 39307/0057) for this product on 27 May 2016.

II. QUALITY ASPECTS

II Quality aspects

II.1 Introduction

This product is an oral solution. Each 5 ml of oral solution contains 20 mg of the active substance fluoxetine (as fluoxetine hydrochloride).

Other ingredients consist of pharmaceutical excipients, benzoic acid (E210), sucrose, glycerol (E422), garden mint flavor (contains propylene glycol (E1520)) and purified water.

All of the excipients used in the manufacture of Fluoxetine 20mg/5ml Oral Solution, with the exception of the garden mint flavor meet the requirements of the current European Pharmacopoeia. The garden mint flavor is controlled by a satisfactory in-house specification. Satisfactory Certificates of Analysis have been provided for these excipients.

None of the excipients are sourced from animal or human origin.

No genetically modified organisms (GMO) have been used in the preparation of this product.

The finished product is supplied in amber (Type III) glass bottles containing 60 ml, 70 ml and 140 ml of the oral solution with a tamper evident, child resistant white plastic cap consisting of a polypropylene inner, polyethylene outer and an expanded polyethylene (EPE) liner.

A 10 ml oral syringe with 0.5ml graduations and a syringe adaptor is also provided.

Specifications and Certificates of Analysis for the primary packaging material have been provided. These are satisfactory. All primary packaging are controlled to satisfactory standards and comply with relevant European Pharmacopoeia monograph and/or EU regulation requirements on plastic materials and articles intended to come in contact with food.

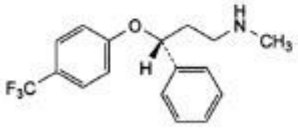
II.2 Drug Substance

Fluoxetine hydrochloride

INN: Fluoxetine hydrochloride

Chemical Names: (3*RS*)-*N*-Methyl-3-phenyl-3-[4-(trifluoromethyl)phenoxy]propan-1-amine hydrochloride

Structure:



and enantiomer , HCl

Molecular formula: $C_{17}H_{19}ClF_3NO$
Molecular weight: 345.8 g/mol
Physical form: White or almost white, crystalline powder.
Solubility: Fluoxetine hydrochloride is freely soluble in methanol; sparingly soluble in water and in dichloromethane.

Fluoxetine hydrochloride is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, fluoxetine hydrochloride, are covered by European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificates of Suitability.

II.3 Medicinal Product

Pharmaceutical development

The objective of the pharmaceutical development programme was to obtain a stable oral solution containing fluoxetine hydrochloride that could be considered a generic medicinal product of Prozac 20mg/5ml oral solution (Eli Lilly & Company Limited).

Suitable pharmaceutical development data have been provided for this application.

Comparative impurity profiles have been provided for the proposed and originator products.

Manufacture of the product

A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated using suitable sized batches and has shown satisfactory results. The process validation scheme to be followed for a minimum of 3 consecutive full-scale production batches has also been submitted and is satisfactory.

Product Specification

The finished product specification is satisfactory. The test methods have been described and adequately validated. 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

Stability studies were performed in accordance with current guidelines on batches of the finished product, packed in the packaging proposed for marketing. The data from these studies support a shelf-life for the unopened bottle of 24 months, with no special storage conditions. Once the bottle is opened, the product should be used within 60 days.

Suitable post approval stability commitments have been provided.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The grant of a Marketing Authorisation is recommended for this application.

III. NON-CLINICAL ASPECTS

III Non-clinical aspects

III.1 Introduction

The pharmacodynamic, pharmacokinetic and toxicological properties of fluoxetine hydrochloride are well-known. As this is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. An overview based on literature review is, thus, appropriate.

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 for this product type. Refer to section 'III.1; Introduction' detailed above.

III.3 Pharmacokinetics
Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.4 Toxicology
Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.5 Ecotoxicity/environmental risk assessment (ERA)
Since this product is intended for substitution of an originator product, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects
There are no objections to the approval of this application from a non-clinical point of view.

IV. CLINICAL ASPECTS

IV Clinical aspects

IV.1 Introduction
No new clinical data have been submitted and none are required for an application of this type. The applicant's clinical overview has been written by an appropriately qualified person and is considered acceptable.

IV.2 Pharmacokinetics
No bioequivalence study to compare the test and the reference product has been provided. The applicant has adequately justified the absence of a bioequivalence study in accordance with the CHMP *Guideline on the investigation of bioequivalence* (CPMP/EWP/QWP/1401/98 Rev.1/Corr**).

IV.3 Pharmacodynamics
No new pharmacodynamics data are required for this application and none have been submitted.

IV.4 Clinical efficacy
No new clinical efficacy data are required for this application and none have been submitted.

IV.5 Clinical safety
No new clinical safety data are required for this application and none have been submitted.

IV.6 Risk Management Plan (RMP)
The Marketing Authorisation holder has submitted an RMP, 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 20mg/5ml Oral Solution.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, is listed below:

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Important Identified Risks		
Hypersensitivity to active substance or to any of the excipients	The risk of hypersensitivity to active substance or to any of the excipients of the drug product is described in the SPC Sections 4.3, 4.4, 4.8 and PIL Sections 2, 4 and appropriate advice is provided to the prescriber to minimise this risk.	None
Concomitant use with MAOIs	The risk associated with concomitant use of the drug product with MAOIs is described in the SPC Sections 4.3, 4.4, 4.5 and PIL Section 2, and appropriate advice is provided to the prescriber to minimise this risk.	None
Use in patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency	The risks associated with use of the drug product in patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency are described in the SPC Section 4.4 and PIL Section 2 and appropriate advice is provided to the prescriber to minimise these risks.	None
Important Potential Risks		
Seizures and use in patients with epilepsy	The risk (1) of seizures associated with use of the drug product (2) associated with use of the drug product in patients with epilepsy (3) associated with use of the drug product when used in combination with phenytoin and drugs lowering the epileptogenic threshold is described in the SPC Sections 4.4, 4.5, 4.8 and PIL Sections 2, 4 and appropriate advice is	None

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
	provided to the prescriber to minimise this risk.	
Activation of mania	The risk of activation of mania associated with use of the drug product is described in the SPC Sections 4.4, 4.8 and PIL Sections 2, 4 and appropriate advice is provided to the prescriber to minimise this risk.	None
Suicide/suicidal thoughts or clinical worsening of the disease	The risk of suicide/suicidal thoughts or clinical worsening of the disease associated with use of the drug product is described in the SPC Sections 4.4, 4.8 and PIL Sections 2, 4 and appropriate advice is provided to the prescriber to minimise this risk.	None
Withdrawal symptoms	The risk of withdrawal symptoms associated with discontinuation of the drug product is described in the SPC Sections 4.2, 4.4, 4.8 and PIL Sections 3, and appropriate advice is provided to the prescriber to minimise this risk.	None
Serotonin syndrome/neuroleptic malignant syndrome	The risk of serotonin syndrome/neuroleptic malignant syndrome associated with use of the drug product is described in the SPC Sections 4.4, 4.5, 4.8 and PIL Sections 2, 4 and appropriate advice is provided to the prescriber to minimise this risk.	None
Use in children and adolescents under the age of 18 years	The risks associated with use of the drug product in children and adolescents under the age of 18 years are described in the SPC Sections 4.4, 4.8, 5.1 and PIL Sections 2, 4 and appropriate advice is provided to the prescriber to minimise these risks.	None

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Use in patients suffering from renal or hepatic impairment	The risks associated with use of the drug product in patients suffering from renal or hepatic impairment are described in the SPC Sections 4.2, 4.4, 5.2 and PIL Section 2 and appropriate advice is provided to the prescriber to minimise these risks.	None
Concomitant use with drugs metabolised by CYP2D6 isoenzyme including tamoxifen	The risk associated with concomitant use of the drug product with drugs metabolised by CYP2D6 isoenzyme including tamoxifen is described in the SPC Sections 4.4, 4.5 and PIL Section 2 and appropriate advice is provided to the prescriber to minimise this risk.	None
Concomitant use of St John's Wort	The risks associated with concomitant use of the drug product with St John's Wort are described in the SPC Section 4.5 and PIL Section 2, and appropriate advice is provided to the prescriber to minimise these risks.	None
Cardiovascular disorders (especially QT prolongation, arrhythmia including torsades de pointes)	The risks of cardiovascular disorders (especially QT prolongation, arrhythmia including torsades de pointes) (i) associated with use of the drug product and (ii) associated with concomitant use with metoprolol are described in the SPC Sections 4.3, 4.4, 4.5, 4.8, 4.9 and PIL Sections 2, 3, 4 and appropriate advice is provided to the prescriber to minimise these risks.	None
Weight loss	The risk of weight loss associated with use of the drug product is described in the SPC Sections 4.4, 4.8 and PIL Section 4 and appropriate advice is provided to the prescriber to	None

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
	minimise this risk.	
Alteration in glycaemic control in patients with diabetes	The risk of alteration in glycaemic control associated with use of the drug product in patients with diabetes is described in the SPC Section 4.4 and PIL Section 2 and appropriate advice is provided to the prescriber to minimise this risk.	None
Akathisia/psychomotor restlessness	The risk of akathisia/ psychomotor restlessness associated with use of the drug product is described in the SPC Sections 4.4, 4.8 and PIL Sections 2, 4 and appropriate advice is provided to the prescriber to minimise this risk.	None
Haemorrhage	The risk (1) of haemorrhage associated with use of the drug product (2) associated with concomitant use of the drug product with oral anti-coagulants, atypical antipsychotics or other drugs that may increase risk of bleeding is described in the SPC Sections 4.4, 4.5, 4.8 and PIL Sections 2, 4 and appropriate advice is provided to the prescriber to minimise this risk.	None
Mydriasis	The risk of mydriasis associated with use of the drug product is described in the SPC Sections 4.4, 4.8 and PIL Sections 2, 4 and appropriate advice is provided to the prescriber to minimise this risk.	None
Use in patients receiving ECT	The risk associated with use of the drug product in patients receiving ECT is described in the SPC Section 4.4 and PIL Section 2 and appropriate advice is provided to the prescriber to minimise this risk.	None

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Co-administration with alcohol	The risk associated with co-administration of the drug product with alcohol is described in the SPC Section 4.5 and PIL Section 2 and appropriate advice is provided to the prescriber to minimise this risk.	None
Use in pregnancy and lactation	The risk associated with use of the drug product in pregnancy and lactation is described in the SPC Section 4.6 and PIL Section 2 and appropriate advice is provided to the prescriber to minimise this risk.	None
Increased risk of bone fractures in patients receiving SSRIs and TCAs	The increased risk of bone fractures associated with use of the drug product in patients receiving SSRIs and TCAs is described in the SPC Section 4.8 and PIL Section 4 and appropriate advice is provided to the prescriber to minimise this risk.	None
Effect on fertility	The risk associated with use of the drug product and effect on fertility is described in the SPC Sections 4.6, 5.3 and PIL Section 2 and appropriate advice is provided to the prescriber to minimise this risk.	None
Reduced antidepressant activity of fluoxetine on concomitant use with cyproheptadine	The risk of reduced antidepressant activity of fluoxetine associated with concomitant use of the drug product with cyproheptadine is described in the SPC Section 4.5 and PIL Section 2 and appropriate advice is provided to the prescriber to minimise this risk.	None
Hyponatremia	The risk of hyponatremia (i) associated with use of the drug product and (ii) associated with concomitant use of the drug	None

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
	product with drugs inducing hyponatremia is described in the SPC Sections 4.5, 4.8 and PIL Sections 2, 4 and appropriate advice is provided to the prescriber to minimise this risk.	
Missing Information		
None		

IV.7 Discussion on the clinical aspects

The grant of a Marketing Authorisation is recommended for this application.

V User consultation

The 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 patient information leaflet (PIL) was English.

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, benefit/risk assessment and recommendation

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

VI. REVISION DATE

24/02/2022

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/6145/1/DC to IE/H/0767/1/DC			