

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202133Orig1s000

MEDICAL REVIEW(S)

**Review and Evaluation of Clinical Data
NDA #202133**

Sponsor:	Edgemont Pharmaceuticals, LLC
Drug:	Fluoxetine 60mg Tablets
Indications:	Major Depressive Disorder Obsessive Compulsive Disorder Bulemia Nervosa Panic Disorder
Material Submitted:	505(b)(2) New Drug Application
Correspondence Date:	12/9/2010
Date Received:	12/9/2010
PDUFA Goal Date:	10/9/2011

I. Regulatory Background

Fluoxetine is a selective serotonin reuptake inhibitor initially manufactured by Eli Lilly and Company. It was first approved on 12/29/1987 for the treatment of Major Depressive Disorder (MDD) under the trade name Prozac (NDA 18,936). Fluoxetine is currently approved for acute and maintenance treatment of MDD in adults and children age 8 and older, acute and maintenance treatment of Obsessive Compulsive Disorder (OCD) in adults and children age 7 and older, acute and maintenance treatment of Bulemia Nervosa in adults, and acute treatment of Panic Disorder with or without agoraphobia in adults. Edgemont Pharmaceuticals has filed a 505(b)(2) application for a new 60mg tablet form which will have these indications.

Fluoxetine is also approved for Premenstrual Dysphoric Disorder (PMDD) under the trade name Sarafem®, and as a combination product with olanzapine (Symbyax ®) for Treatment Resistant Depression and Depressive Episodes Associated with Bipolar I Disorder. These additional indications are covered under patents held by Eli Lilly and Company; Edgemont is not seeking these indications for their product.

Edgemont has acquired a license from Orion Pharma (Orion) to market their Seronil® 60 mg fluoxetine scored tablets in the United States. Orion has manufactured and marketed this dosage strength in Finland since 1997. Seronil 60 mg scored tablets originally were approved by the Finnish National Agency for Medicines on the basis of bioequivalence to Orion's own Seronil 20 mg capsules (3 × 20 mg capsules versus 1 × 60 mg tablet; Study 451005). These Seronil 20 mg fluoxetine capsules had been approved in Finland (1992) based on demonstrated bioequivalence to Eli Lilly's Fontex® fluoxetine 20 mg capsules (Seronil 2 × 20 mg versus Fontex 2 × 20 mg; Study 45101).

During development, bioequivalence to the innovator product was evaluated in the following studies:

- Study 101 (Edgemont): Comparative bioequivalence study of 1 x 60mg fluoxetine scored tablet (Edgemont, manufactured by Orion Pharma) vs. 3 x 20mg fluoxetine

tablets (labeled Par Pharmaceutical Companies, Inc. [ANDA holder: Mylan; only RLD in tablet form]) under fasted conditions. The study was an open-label, single-dose, 2-period, 2-treatment, 2-sequence crossover study. The primary measure of bioequivalence was based on fluoxetine (parent drug) PK. Secondary objectives of this study included obtaining PK data on norfluoxetine (major metabolite) and to confirm the safety of single doses of 60mg fluoxetine in healthy subjects.

- Study 451005 (Orion Pharma): Comparative bioequivalence study of 2 formulations of fluoxetine manufactured by Orion Pharma, a 60mg tablet and a 20mg capsule (Seronil®), under fasted conditions. The study was an open-label, single-dose, 2-period, 2-treatment, 2-sequence crossover study. The sponsor identified this study as the bridge to the innovator product.
- Study 45101 (Orion Pharma): Comparative bioequivalence study of fluoxetine 20mg capsule (Seronil®) manufactured by Orion Pharma and fluoxetine 20mg capsule (Fontex®) manufactured by Eli Lilly, after a single oral dose of 40mg in healthy subjects under fasted conditions. The study was an open-label, single-dose, 2-period, 2-treatment, 2-sequence crossover study.

Bioequivalence data from the above three studies will be reviewed in detail by the OCP review team and will not further discussed in this review, which will focus on important clinical safety data from these trials and labeling for the tablet formulation.

II. Materials Reviewed

Submission Date	Materials
12/9/2010	451005 Legacy study report 45101 Legacy study report 101 Study report JMP Datasets Case Report Forms Debarment Certification Financial Disclosure Certification Patent Certification Request for waiver of pediatric studies
3/31/2011	Updated patent certification Draft labeling
6/3/2011	Draft carton labeling

III. Financial Disclosures

On 7/7/2010, Douglas A Saltel, President and Chief Executive Officer of Edgemont Pharmaceuticals, LLC, certified that Edgemont had not entered into any financial arrangement with the principal or sub-investigators from studies 101, 45101, or 451005 whereby the value of the compensation could have been affected by the outcome of the study. Also, he certified that each investigator required to disclose a proprietary interest in the product or significant equity interest in the sponsor did not disclose any such interests. He further certified that none of these investigators was the recipient of significant payments of other sorts.

IV. Review of Clinical Safety Data

Given the extensive safety experience to date with Prozac® and marketed generic fluoxetine products, the relatively brief duration of the bioequivalence studies, and the subject samples for these studies (healthy volunteers), the conducted studies are not capable of producing meaningful new safety data that could be extrapolated to the clinical use of fluoxetine products. Therefore, this safety review will focus only on the more serious adverse experiences from the three bioequivalence studies, that is, any deaths and other events classified as serious and any adverse experiences that led to premature discontinuation from the study, based on my review of the individual study reports.

A. Deaths

There were no deaths in any of the studies.

B. Non-Fatal Serious Adverse Events

There were no non-fatal serious adverse events in any of the studies.

C. Adverse Events Resulting in Dropout

Study 101: No subjects discontinued prematurely as a result of an adverse event while taking the study drug. Two subjects discontinued prematurely as a result of an adverse event while taking the reference drug. One subject experienced mild increase in white blood cell count and mild elevated blood pressure. A second subject experienced mild increase in white blood cell count. Both subject recovered.

Study 451005: No subjects discontinued prematurely as a result of an adverse event.

Study 45101: No subjects discontinued prematurely as a result of an adverse event.

V. Pediatric Plan

The sponsor has requested a full waiver of the requirement for pediatric studies for fluoxetine 60mg scored tablets.

In conformance with 21 CFR § 314.54, Edgemont is seeking approval of this NDA for fluoxetine 60mg scored tablets under the provisions of Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, relying upon the Agency's previous findings of safety and effectiveness in pediatric patients for the innovator fluoxetine product (Prozac®), as bridged by the bioequivalence to the reference listed drug (RLD), fluoxetine hydrochloride tablets, EQ 20 mg base (Mylan), for oral administration, ANDA 075755, Product Number 002.

Those previous findings allow for dosing of fluoxetine 60mg tablets in pediatric patients.

VI. DSI Inspection

The Division of Scientific Investigations (DSI), GLP Bioequivalence Branch was consulted on 1/24/11 for inspection of Study 101: Clinical Site, Craig Sprenger, MD, Cetero Research, Fargo, ND; and Analytical Site, (b)(4),

(b)(4) The results of this inspection are pending.

VII. Labeling Review

The sponsor's proposed labeling is based on the Prozac® label. However, this product is only available in a 60mg dosage form. Because of this, additional language should be added to the Dosage and Administration section of the label regarding the need for titration with an alternate formulation prior to use of this product.

The Study Endpoint and Label Development (SEALD) Team was consulted during the review of this application to ensure that the prescribing information (PI) for this product meets the requirements under 21 CFR 201.56 and 201.57 in addition to all related labeling regulations with attention to all labeling-related FDA guidances and policies. The SEALD reviewer attended the 6/7/2011 labeling planning meeting. The labeling comments below reflect the results of the SEALD review and the discussion at the labeling planning meeting.

- Product name: The use of the term “scored” is not an approved standard terminology for drug product nomenclature. The product name should be “FLUOXETINE TABLETS USP, 60mg” in all labeling.
- General: A number of minor changes in labeling are recommended to improve clarity and readability, and to reduce redundancy.
- Highlights/Contraindications: The list of contraindications in the highlights (HL) section does not need to include the adverse reaction associated with the contraindication.
- HL/Warnings and Precautions: These should be listed in the same order in which they appear in the Full Prescribing Information (FPI). Only the most clinically significant warnings should be listed in the HL section. An additional comment should then be added to refer the reader to the FPI.
- HL/Adverse Reactions: The toll free number for reporting adverse reactions needs to be inserted into the adverse reaction reporting statement, both here and in the FPI.
- HL/Drug Interactions: Items already listed in the Contraindications section may be deleted from this section. A concise summary of the outcome of interactions should be included. Only the most clinically significant interactions should be listed in the HL section. An additional comment should then be added to refer the reader to the FPI.
- HL/Specific Populations: The information regarding (b) (4)
- FPI/Contraindications: For each contraindication listed, a brief description of the anticipated consequences of the contraindicated use should be included here.
- FPI/Warnings and Precautions: Additional text related to cautious use in patients with acute narrow-angle glaucoma was added for consistency with most recent Prozac® label.
- FPI/Adverse Reactions: Additional text related to occasional persistence of sexual dysfunction following discontinuation or fluoxetine treatment (6.1) and memory impairment (6.2) was added for consistency with most recent Prozac® label.
- FPI/Adverse Reactions: Section 6.2 is reserved for Postmarketing Experience. “Other Reactions” should be considered a subcategory under Section 6.1 and relabeled “Other Adverse Reactions Observed During the Premarketing Evaluation of Fluoxetine” for clarity.

- FPI/Clinical Pharmacology: All PK information should be presented under section 12.3 and not under a separate subheading. (b) (4)

VIII. Conclusions and Recommendations

From a clinical perspective, this application may be approved following agreement on the above labeling issues.

[See appended electronic signature]

Tiffany R Farchione, MD
Medical Officer, DPP

cc: NDA #202133
HFD-130 (Div. File)
HFD-130/Farchione
/Khin
/Laughren
/Patel

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

TIFFANY R FARCHIONE
07/21/2011

NI A KHIN
07/21/2011

From a clinical perspective, I agree with Dr. Farchione's recommendation that this NDA be approved.