

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**202133Orig1s000**

**SUMMARY REVIEW**

<i>Cross-Discipline Team Leader Review</i>	
<b>NDA Number:</b>	202133
<b>Submission Type; Code:</b>	Original NDA, 505 b(2)
<b>Applicant Name:</b>	Edgemont
<b>Submission Dates:</b>	12/19/2010, 3/31/2011
<b>Brand Name:</b>	
<b>Generic Name</b>	Fluoxetine
<b>Dosage Form/Strengths:</b>	60 mg
<b>Proposed Indication:</b>	Major Depressive Disorder, Obsessive Compulsive Disorder, Bulimia Nervosa, Panic Disorder
<b>Advisory Committee Meeting</b>	No
<b>CDTL</b>	Joga Gobburu

## 1 INTRODUCTION TO REVIEW

This application was filed as a 505(b)(2) NDA. The sponsor is seeking indications approved for prozac capsules (refer to indications below). The application relies on the Agency's previous findings of safety and efficacy for fluoxetine (Prozac) capsules by Eli Lilly for these indications. Prozac immediate release capsules are currently available in 10mg, 20 mg and 40 mg strengths. Fluoxetine 60 mg strength is not currently available in the US. The sponsor intends to introduce Fluoxetine 60 mg tablets with this application because 60 mg/day is the recommended dose for bulimia nervosa in adults and is within the dosing range for other indications such as MDD, OCD and panic disorder (PD). And the 60 mg strength should improve compliance. Prozac tablets were approved in 1999 but were discontinued and are not currently marketed in the US. The discontinuation of Prozac tablets was not due to safety and efficacy reasons. Therefore, in the pivotal bridging bioequivalence studies, the reference listed drug (RLD) for the tablet, fluoxetine hydrochloride tablets (Mylan, ANDA 75755) was used as the reference drug. The RLD was demonstrated to be bioequivalent to Prozac (Eli Lilly) tablets.

## 2 BACKGROUND/REGULATORY HISTORY/PREVIOUS ACTIONS/FOREIGN REGULATORY ACTIONS/STATUS

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 Bulimia 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). Table 1 lists the studies submitted to support the approval of fluoxetine 60 mg.

**Table 1. List of studies submitted under NDA 202133.**

<b>Studies Submitted</b>
<p><b>Study 101 – BE Study</b>                      Study 101 (Edgemont): Comparative bioequivalence study of 1 x 60mg fluoxetine scored tablet (Edgemont, manufactured by Orion Pharma) vs. 3 x 20mg fluoxetine tablets under fasted conditions. The study was an open-label, singledose, 2-period, 2-treatment, 2-sequence crossover study.</p>
<p><b>Study 451005- Bioavailability Study</b>                      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.</p>
<p><b>Study 45101 - Bioavailability Study</b>                      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.</p>

### 3 RECOMMENDATIONS

#### 3.1 Summary of Recommendations

Table 2 shows the various recommendations by the inter-disciplinary team. The Division of Scientific Investigations found that the conduct of Study 101 (pivotal BE study) was acceptable. DDMAC, DRISK and DMEPA provided various specific labeling recommendations that have been incorporated in the draft label and is under negotiations with the sponsor. These specific labeling recommendations are not discussed in this memo.

**Table 2. Summary of recommendations by the review team.**

<i>Key Decision</i>	<i>Clinical</i>	<i>Clin Pharm</i>	<i>Chemistry/Biopharm</i>	<i>Compliance</i>
Primary Basis for Approval	-	Acceptable	Acceptable	Acceptable

al (BE)				
<b>Labeling</b>	Specific	Specific	-	-
<b>g</b>	language	language		
	recommended	recommended		
	d	d		

### 3.2 Primary Basis for Approval

The pivotal BE study 101 reviewed by Dr. Kofi Kumi provides the primary basis for approval. Following a single dose administration of 1 x Fluoxetine 60 mg tablet and 3 x Fluoxetine 20 mg tablets (Mylan, RLD), Fluoxetine 60 mg (Edgemont) was demonstrated to be bioequivalent to 3 x Fluoxetine 20 mg tablets (Mylan), the reference listed drug. As shown in the following figure, the 90% confidence interval around the ratio of means for C<sub>max</sub> and AUC after administration of Fluoxetine 60 mg (Edgemont) and 3 x Fluoxetine 20 mg (Mylan) was contained within the 80% to 125% regulatory requirement for bioequivalence. The key results are shown in Figure 1. There are no additional efficacy or safety related issues identified in the clinical review.

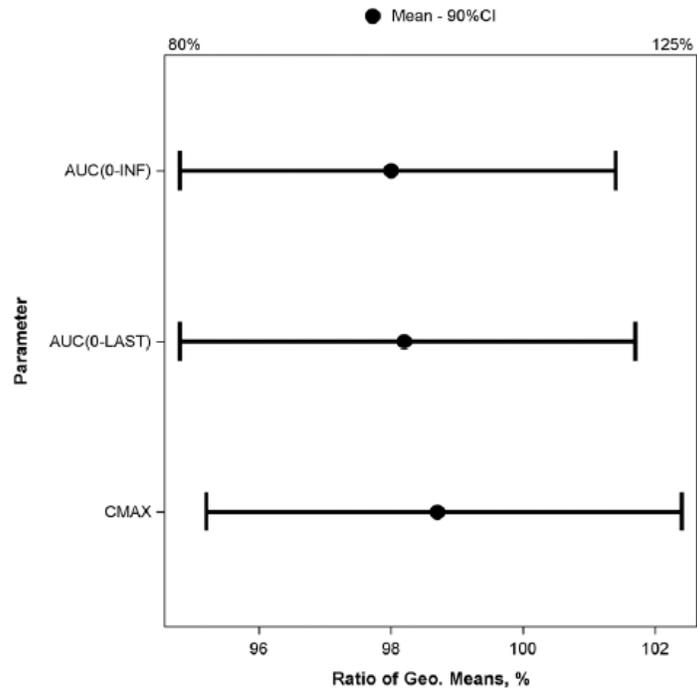
### 3.3 Labeling

The major focus of the labeling has been to clarify and highlight the limitation of Edgemont's fluoxetine 60 mg tablets. For example, the current product cannot be used during titration period as doses as low as 20 mg are recommended for some indications.

### 3.4 Major Issues

All Chemistry, Biopharmaceutics and Compliance issues identified during the review were addressed by the sponsor to FDA's satisfaction. I recommend approval of this NDA provided satisfactory agreement is reached with regards to labeling.

Figure 1. Ratio of the mean PK parameters for the Mylan 3x20 mg (reference) and Edgemont 60 mg formulations meet the BE criteria.



### 3.5 Final Recommendation

I recommend approval of this NDA, provided satisfactory agreement on labeling is reached.

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JOGARAO V GOBBURU  
10/03/2011  
CDTL Memo