

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**202133Orig1s000**

**CHEMISTRY REVIEW(S)**

**Office of New Drug Quality Assessment  
Division of New Drug Quality Assessment I (Branch I)**

**Initial Quality Assessment**

**NDA: 202-133**

<b>OND Division:</b>	Division of Psychiatry Products
<b>Applicant:</b>	Edgemont Pharmaceuticals, LLC.
<b>NDA Filing Category:</b>	505(b)(2)
<b>Letter Date:</b>	09-DEC-10
<b>Stamp Date:</b>	09-DEC-10
<b>PDUFA Date:</b>	09-OCT-11
<b>Proposed Trade Name:</b>	Tradename has not been proposed
<b>Established Name:</b>	Fluoxetine USP
<b>Dosage Form:</b>	Scored Tablet (immediate-release)
<b>Strengths:</b>	60 mg
<b>Route of Administration:</b>	Oral
<b>Indication:</b>	major depressive disorder and obsessive compulsive disorder in adult and pediatric patients, as well as the treatment of bulimia nervosa and panic disorder in adults
<b>Assessor:</b>	Chhagan G. Tele, Ph.D.
<b>ONDQA Fileability:</b>	Yes

**SUMMARY AND CRITICAL ISSUES:**

**Summary**

Fluoxetine hydrochloride is a selective serotonin reuptake inhibitor for oral administration. Fluoxetine HCl Immediate-Release scored tablets (60 mg strength) was developed for the treatment of major depressive disorder and obsessive compulsive disorder in adult and pediatric patients, as well as the treatment of bulimia nervosa and panic disorder in adults under IND 107,525. The applicant had a Pre-IND meeting (05-MAR-2010) with the clinical division to discuss the development of FXT 60 mg (fluoxetine HCl) scored tablets for the same patient populations and indications as the innovator product Prozac. Minutes of this meeting can be found in DARRTS and should be read by the reviewer. This application relies on the Agency's previous findings of safety and effectiveness for the innovator fluoxetine product (Prozac®), as bridged by the bioequivalence to the reference listed drug (RLD) and the characterization of the Fluoxetine 60 mg Scored Tablets and the comparison to the RLD on the basis of CMC aspects. The applicant stated that the bioequivalence is demonstrated between Fluoxetine 60 mg Scored Tablets and Mylan's fluoxetine hydrochloride tablets, EQ 20 mg base, ANDA 075755, as the RLD. Prozac (fluoxetine HCl) was first approved by the FDA in 1987, and Prozac 60 mg capsules was later approved in 1999 (NDA 18-936/S-054). However, the original sponsor, Eli Lilly, discontinued the 60 mg strength Prozac, and today there remains no 60 mg fluoxetine dosage strength available in the U.S. market. The applicant believes there is a clinical need for a 60 mg dosage strength of fluoxetine. The applicant submitted this NDA under section 505(b)(2) seeking approval for FXT 60 mg (fluoxetine HCl) scored tablets for the same patient populations and indications as the innovator product Prozac. For this purpose, Edgemont has acquired a license from Orion Pharma to market their Seronil 60 mg (fluoxetine HCl) scored tablets in the United States. Orion has manufactured and marketed this dosage strength in Finland since 1997. Seronil 60 mg scored tablets was originally approved in Finland on the basis of bioequivalence (BE) to their own Seronil 20 mg capsules (3 x 20 mg caps vs. 1 x 60 mg tab). Seronil 20 mg capsules was approved in Finland (1992) based on demonstrated BE to Eli Lilly's Fontex (fluoxetine HCl) 20 mg capsules (Seronil 2 x 20 mg vs. Fontex 2 x 20 mg). Orion is the sole manufacturer of drug product for Edgemont. Edgemont will (b) (4) tablets bottled by Patheon Inc. at their facility in Puerto Rico. Orion Corporation's Fermion Oy (Fermion) in Hanko, Finland is the fluoxetine HCl drug substance manufacturer to manufacture the drug product. Electronic submission is provided for the CMC information for the review. The applicant provided Quality Overall Summary in the submission.

### **Drug Substance**

The drug substance will be manufactured commercially by Fermion Oy, Espoo, Finland and used (b) (4). Drug substance, Fluoxetine HCl USP, cross-referenced to DMF (b) (4) [Fermion Oy, Espoo, Finland] for information regarding chemistry, manufacture, control, reference standards, stability, and packaging. Fluoxetine HCl supplied by Fermion Oy is a white to off-white crystalline powder. The melting point (b) (4) is approximately 148° C. No polymorphism has been observed by X-ray powder diffraction and differential scanning calorimetry (DSC). Fermion Oy has had an active DMF since January 1995 and has (b) (4). The applicant provided a LoA dated June 14, 2010. The last updated (06-JUN-2008) DMF was found adequate (see latest review by Dr. Lucia Tang, OGD, 24-MAR-2010) (b) (4). DMF (b) (4) will need to be found adequate to support NDA.

### **Drug Product**

Fluoxetine HCl immediate release oral tablets will be available in 60 mg tablet strength containing 67.1 mg of fluoxetine HCl (equivalent to 60 mg fluoxetine base) per tablet. The applicant used Fluoxetine HCl scored tablets throughout submission. The reviewer needs to ask applicant to use only one form (e.g., immediate-release tablets and removing "SCORED" from naming the product, see last bullet in the Critical Issues for Review) and changes needs to be seen in labeling and package insert. The proposed oral immediate release tablets contain 60 mg of fluoxetine as the hydrochloride salt (matches with the labeling). The tablets will be film coated, scored, capsule-shaped, white tablets debossed with "FL 60" on one side ("FL" above the score (b) (4)). They are supplied in bottles of 30 tablets. The Orion manufactured tablets (b) (4) Patheon (manufacturing facility in Manatí, Puerto Rico).

The commercial formulation is comprised of fluoxetine HCl USP/Ph.Eur., mannitol USP/NF/Ph.Eur., maize starch USP/NF/Ph.Eur., povidone (b) (4) USP/NF/Ph.Eur., microcrystalline Cellulose (b) (4) USP/NF/Ph.Eur., (b) (4), magnesium stearate USP/NF/Ph.Eur., (b) (4), hypromellose (b) (4) USP/NF/Ph. Eur., sucrose USP/NF/Ph. Eur., titanium dioxide (b) (4) USP/NF/Ph. Eur., polysorbate (b) (4) USP/NF/Ph. Eur., glycerol (b) (4) Ph. Eur., (b) (4). All excipients are commonly used in the solid dosage forms (no novel excipients). (b) (4)

The applicant provided pharmaceutical and manufacturing process development studies (including (b) (4) and packaging) to achieve required scale up, dissolution profile, and content uniformity. The assigned reviewer will need to review in detail about these studies for the compatibility and robust manufacturability of the drug product.

Fluoxetine tablets are manufactured (b) (4). (b) (4) The commercial drug product will be manufactured at Orion Pharma, Espoo, Finland. The proposed regulatory specifications for Fluoxetine tablets involve straight forward analytical procedures. Validated analytical methods are provided for the determination of ID, assay, content uniformity, related substances, and dissolution. The reviewer needs to look for the adequacy of the validation parameters. Several in-process controls were provided by the applicant (b) (4) tablets: Appearance, Average mass, Uniformity of mass, Crushing strength, Friability, and Disintegration time) from the knowledge of the batches that have been manufactured so far. The reviewer needs to evaluate these parameters in development of robust process.

Upon confirmation of identity by IR and HPLC, the bulk tablets will be packaged into the proposed U.S. container/closure system at Patheon. The proposed U.S. container closure system is a 30 count, 40 mL HDPE bottle with an induction-sealed, (b) (4) child-resistant closure (CRC). The bottle is placed into an outer box with up to 24 bottles per outer shipping box. A label is affixed to the outer box. The boxes are placed on a pallet and wrapped in shrink wrap.

Batch analysis data of three commercial batches (b)(4) and one registration stability/clinical trial material batch (b)(4) is provided.

The existing body of stability data from the Orion Seronil 60 mg tablet (supporting stability data), in conjunction with data from the ongoing stability study conducted at Patheon (primary stability data), are provided. This approach is supported by the fact that the manufacturing of the tablets is the same, and the only differences between the currently marketed Finnish product Seronil 60 mg tablet and the proposed U.S.-marketed Fluoxetine 60mg Scored Tablets are changes in the final commercial packaging site (Patheon versus Orion) and improvement in the container closure system for U.S. packaged product.

For the supporting stability (10 months accelerated and 36 months long-term data), several batches had been manufactured and placed on stability under ICH storage conditions at Orion, Finland. For the primary stability study (6 months accelerated and 6 months long-term data) for one commercial (b)(4) batch of Fluoxetine 60 mg Scored Tablets was manufactured at Orion Pharma, shipped to Patheon for packaging in the proposed U.S. container closure system (b)(4) and placed on stability at Patheon. The balance of the bulk tablets from this batch were used to validate the packaging equipment train at Patheon used for commercial bottle packaging of Fluoxetine 60 mg Scored Tablets.

In order to support the stability of the half tablet, the applicant provided an in-use stability data (stored at 30 °C/65% RH). Daily opening and closing of the containers containing either whole or half tablets (which were split using a splitter device), over a period of 60 days, stored at 30 °C/65% RH was conducted. Samples from the half tablet and the whole tablet containers were analyzed at 0, 2, 4, and 8 weeks. The reviewer need to evaluate the adequacy of the stability of the half tablet.

#### **Critical Issues for Review**

- The NDA applicant references DMF (b)(4) [Fermion Oy, Espoo, Finland] for information on fluoxetine HCl USP. DMF (b)(4) will need to be evaluated and found acceptable to support this NDA.
- The compatibility of the excipients used in the drug product will need to be evaluated.
- The effect of compression force and speed on tablet strength need to be examined closely.
- The applicant has set a dissolution specification:  $Q = (b)(4)$  in 20 minutes. The adequacy of the dissolution method and specification limits will need to be determined in conjunction with the ONDQA biopharm reviewer. The consult for ONDQA biopharm has been sent by the ONDQA PM.
- The applicant has provided four drug product CoAs (lots 1022948, 1053228, 1114423, and 1321498) in NDA 202-133. The dissolution data for all four lots is reported as an average. It is not clear what the range represents. Getting individual tablet data along with the average value at each time point would be useful.
- Limited stability data (i.e., 6 months accelerated and 6 months long-term data) is provided in the NDA submission for the primary batch (#1321498) manufactured at Orion batch packaged in commercial configuration at commercial packaging site Patheon. The reviewer need to request updated stability data by mid cycle before the PDUFA date to confirm the expiry date.
- In order to support the stability of the half tablet, the applicant provided an in-use stability study data. However, the reviewer need to confirm the acceptability of the data in support of the clinical use of the half tablet.
- NDA submission contains no nanoscale materials. However, the reviewer should include Attachment A indicating that no nanoscale materials are present (see MAPP 5015.9 entitled, "Reporting Format for Nanotechnology—Related Information in CMC Review.")
- The reviewer need to confirm consistency in chemical structure, chemical name, molecular formula, and molecular weight of the drug substance with the current USP dictionary and USAN in the Description section of the labeling. Additionally reviewer need to confirm that all the excipients used in the drug product formulation are included.

- The reviewer need to ask the applicant to remove [REDACTED] (b) (4) as it is not included in the CDER Data Standard Manual dated April 14, 1992 version 004 and not included in the approved product though [REDACTED] (b) (4).

**Comments and Recommendation:**

The NDA is fileable from a CMC perspective. The NDA does not appear to incorporate elements of QbD. NDA submission contains no nanoscale materials. The drug substance is manufactured under DMF [REDACTED] (b) (4). DMF should be reviewed to support this NDA. Assignment of the NDA to a single reviewer is recommended. The dissolution should be consulted to the ONDQA biopharm group.

A claim for categorical exclusion under 21 CFR §25.31 (b) is provided in Module 1. In accordance with 21 CFR §25.31, Edgemont Pharmaceuticals claims a categorical exclusion [25.31(a)] from the requirement for an Environmental Assessment or Environmental Impact Statement as approval of the drug product will not increase the use of the active moiety. In addition, the applicant states that to the best of their knowledge, no extraordinary circumstances exist that would preclude this claim for categorical exclusion.

The list of manufacturing, testing, and packaging sites for drug substance and drug product is provided to enter into EES. The PM submitted all testing, packaging, and manufacturing sites into EES. The reviewer will need to confirm that these sites are correct and that there are no additional sites that need to be entered.

## CHEMICAL MANUFACTURING CONTROLS FILING CHECKLIST FOR A NEW NDA

<b>NDA Number:</b> 202-133	<b>Applicant:</b> Edgemont Pharmaceuticals	<b>Stamp Date:</b> 09-DEC-2010
<b>Drug Name:</b> Fluoxetine HCl ER Tablets	<b>NDA Type:</b> Standard	<b>Filing Meeting:</b>

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

	Content Parameter	Yes	No	Comment
1	Is the section legible, organized, indexed, and paginated adequately?	X		
2	Are ALL of the manufacturing and testing sites (including contract sites) identified with full street addresses (and CFNs, if applicable)?	X		
3	Is a statement provided to indicate whether each manufacturing or testing site is ready for inspection or, if not, when it will be ready?	X		
4	Is a statement on the Environmental Impact provided as required in 21 CFR 314.50(d)(1)(iii)?	X		
5	Is information on the Drug Substance provided as required in 21 CFR 314.50(d)(1)(i)?	X		
6	Is information on the Drug Product provided as required in 21 CFR 314.50(d)(1)(ii)?	X		
7	If applicable, has all information requested during the IND phases, and at the pre-NDA meetings been included?	X		
8	Have draft container labels and package insert been provided?	X		
9	Have all DMF References been identified?	X		
10	Is information on the investigational formulations included?	X		
11	Is information on the Methods Validation included?	X		
12	If applicable, is documentation on the sterilization process validation included?	NA		

**IS THE CMC SECTION OF THE APPLICATION FILEABLE? Yes**

If the NDA is not fileable from chemistry, manufacturing, and controls perspective, state the reasons and provide comments to be sent to the Applicant. **NA**

Chhagan G. Tele, Ph.D. 20-DEC-10  
 \_\_\_\_\_  
 CMC Lead, DNDQA I, ONDQA Date

Ramesh Sood, Ph.D. 20-DEC-10  
 \_\_\_\_\_  
 Branch Chief, DNDQA I, ONDQA Date

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/s/  
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CHHAGAN G TELE  
12/20/2010  
Initial Quality Assessment

RAMESH K SOOD  
12/20/2010

**FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
SUMMARY REPORT**

<b>Application:</b>	NDA 202133/000	<b>Sponsor:</b>	EDGEMONT PHARMS
<b>Org. Code:</b>	130		7400 WEST 110TH ST STE 300
<b>Priority:</b>	3		OVERLAND PARK, KS 66210
<b>Stamp Date:</b>	09-DEC-2010	<b>Brand Name:</b>	FLUOXETINE HCL.
<b>PDUFA Date:</b>	09-OCT-2011	<b>Estab. Name:</b>	
<b>Action Goal:</b>		<b>Generic Name:</b>	
<b>District Goal:</b>	10-APR-2011	<b>Product Number; Dosage Form; Ingredient; Strengths</b>	001; TABLET; FLUOXETINE HYDROCHLORIDE; 60MG

<b>FDA Contacts:</b>	T. BOUIE	Project Manager	301-796-1649
	M. SAPRU	Review Chemist	301-796-1718
	C. TELE	Team Leader	301-796-1762

<b>Overall Recommendation:</b>	ACCEPTABLE	on 22-SEP-2011	by M. STOCK	(HFD-320)	301-796-4753
	PENDING	on 22-SEP-2011	by EES_PROD		
	WITHHOLD	on 22-FEB-2011	by EES_PROD		

<b>Establishment:</b>	CFN: 9610101	FEI: 3002607817	
	FERMION OY ORIONINKATU 2 HANKO, FINLAND		
<b>DMF No:</b>	(b) (4)	<b>AADA:</b>	
<b>Responsibilities:</b>	DRUG SUBSTANCE MANUFACTURER		
<b>Profile:</b>	(b) (4)	<b>OAI Status:</b>	NONE
<b>Last Milestone:</b>	OC RECOMMENDATION		
<b>Milestone Date:</b>	20-DEC-2010		
<b>Decision:</b>	ACCEPTABLE		
<b>Reason:</b>	DISTRICT RECOMMENDATION		

<b>Establishment:</b>	CFN: 9610102	FEI: 3003073605	
	ORION CORP ORION PHARMA ORIONINTIE 1 ESPOO, FINLAND		
<b>DMF No:</b>		<b>AADA:</b>	
<b>Responsibilities:</b>	FINISHED DOSAGE MANUFACTURER		
<b>Profile:</b>	TABLETS, PROMPT RELEASE	<b>OAI Status:</b>	NONE
<b>Last Milestone:</b>	OC RECOMMENDATION		
<b>Milestone Date:</b>	22-SEP-2011		
<b>Decision:</b>	ACCEPTABLE		
<b>Reason:</b>	DISTRICT RECOMMENDATION		

**FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
SUMMARY REPORT**

**Establishment:** CFN: 2650213 FEI: 3003113148  
PATHEON PUERTO RICO, INC.  
STATE RD. 670, KM. 2.7  
MANATI, PR 00674

**DMF No:** AADA:

**Responsibilities:** FINISHED DOSAGE PACKAGER

**Profile:** TABLETS, PROMPT RELEASE **OAI Status:** NONE

**Last Milestone:** OC RECOMMENDATION

**Milestone Date:** 08-JUN-2011

**Decision:** ACCEPTABLE

**Reason:** DISTRICT RECOMMENDATION

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/s/

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NIKOO N MANOCHEHRI-KALANTARI  
10/12/2011

**MEMORANDUM****DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH****DATE:** September 27, 2011**TO:** File**THROUGH:** Ramesh K. Sood, Ph.D., Branch Chief, ONDQA**FROM:** Mohan K. Sapru, Ph.D., Regulatory Review Chemist, ONDQA**SUBJECT: Final CMC Approval Recommendation for NDA 202-133 (Fluoxetine 60 mg, USP)**

The applicant, Edgemont, has sought U.S. marketing approval for fluoxetine 60 mg tablets under the provisions of Section 505(b)(2). The applicant has acquired a license from Orion Pharma to market their Seronil 60 mg (fluoxetine HCl, Prozac) scored tablets in the United States. Orion has manufactured and marketed this dosage strength in Finland since 1997. As indicated in the CMC review #1 for NDA 202-133, three major deficiencies were identified. First deficiency concerned the drug product stability data, especially the issue of evaluating the relevance of applicant's supporting stability data for granting expiration dating period for the drug product. Based on primary, secondary and in-use stability data, the applicant has demonstrated robust stability of the drug product. Specifically, drug product stability has been demonstrated for a single primary batch of the drug product stored for 12 months at 25°C/60% RH or up to 6 months at 40°C/75% RH in the to-be-marketed container closure system (40 mL high density polyethylene (HDPE) bottles with child-resistant caps and a tamper-evident induction seal). In addition, the supporting stability studies (involving Orion Seronil 60 mg tablet) have revealed no significant changes in monitored attributes of the drug product following storage in 40 mL HDPE bottles with tamper-evident neck band seal (up to a period of 24 months at 25°C/60% RH) or 75 mL HDPE bottles (up to a period of 38 months at 25°C/60% RH or 8 months under accelerated conditions).

Regarding the relevance of the secondary stability data, the applicant contends that the current proposed U.S. container closure i.e., 40 mL HDPE bottle with tamper-evident induction seal closure is at least the same as, if not superior to, the 40 mL container closure used by Orion for generating supporting stability data for the fluoxetine 60 mg tablets (Seronil). Based on the primary and supporting stability data, the applicant has proposed a (b)(4) expiration period. It is important to note that, previously, stability data requirements have been discussed in-face-to-face pre-NDA meeting between the applicant and the Agency, which was held on March 5, 2010. In the meeting, the applicant "clarified that the NDA submission would contain stability data from the Orion drug product, which has been manufactured and marketed for 12 years in Finland." Furthermore, the applicant stated "that these (stability) data were collected under ICH conditions, and that there were only minor container closure differences between the currently marketed Finnish product Seronil 60 mg and the proposed US product. Three months of long-term and three months of accelerated ICH stability data for one drug product batch manufactured by Orion at the intended commercial scale (b)(4) will be submitted to support the preferred US packaging format. A comparative analysis of these data will be included in the NDA" (for details refer to pre-NDA meeting minutes).

In August 24, 2011 teleconference between the Agency and the applicant, the CMC reviewer asked for additional details concerning supporting data, including a comparison of headspace/tablet ratio for different HDPE bottle configurations used for generating primary and supporting stability data. In response, the applicant provided new information, which indicates that headspace to tablet ratio of (b) (4) for the 20 mL, 40 mL Orion, 40 mL to-be-marketed Edgemont, and 75 mL HDPE bottle configurations, respectively. It is important to note that the headspace to tablet ratio of (b) (4) pertaining to the to-be-marketed HDPE bottle configuration is slightly higher than the headspace to tablet ratio of (b) (4) pertaining to the 40 mL HDPE bottle configuration used to generate supporting stability data. However, the applicant contends that stability data demonstrate that changes in headspace ratio have no effect on the stability of the drug product. In fact, for the entire duration of the primary and secondary stability studies, carried out in different container-closure configurations under long-term and accelerated conditions, the levels of degradation /individual impurities have persistently stayed at (b) (4).

A CMC team meeting, which was attended by division director (Richard Lostritto, Ph.D.), branch chief (Ramesh Sood, Ph.D.), CMC lead (Chhagan, Tele, Ph.D.) and the CMC reviewer (Mohan Sapru, Ph.D.) has held on September 12, 2011 to discuss the unresolved issue concerning the relevance of applicant's supporting stability data for granting expiration dating period for the drug product. In view of the results from primary and secondary stability studies coupled with the facts that : a) Orion has manufactured and marketed Seronil 60 mg fluoxetine HCl drug product in Finland since 1997, b) manufacturing process used for Seronil 60 mg fluoxetine HCl drug product is identical to the manufacturing process for the to-be-marketed 60 mg fluoxetine HCl drug product and c) no (b) (4) degradation product or individual impurity has been observed at or above (b) (4) a consensus decision was taken to grant an expiry period of 24 months for the drug product when stored under approved storage conditions.

Second deficiency related to the post-approval stability protocol and stability commitment. Originally in the NDA submission, the applicant proposed to perform stability studies on the first three commercial lots of fluoxetine 60 mg tablets at 25°C/60% RH but not under accelerated storage conditions. However, the applicant has now satisfactorily addressed this deficiency by accepting the Agency's recommendation to modify post-approval stability protocol and perform stability studies on the first three commercial lots of fluoxetine 60 mg tablets both under accelerated storage conditions (40 ± 2 °C/75 ± 5% RH up to 6 months) as well as long-term storage conditions (25 ± 2 °C/60 ± 5% RH up to 36 months).

Lastly, the third deficiency concerned the "withhold" recommendation from the Office of Compliance (OC) concerning the finished dosage manufacturing facility i.e., Orion Pharma. However, based on updated Establishment Evaluation Request Report dated 22-Sep-2011, OC has revised the assessment of the facility, and has made an overall "acceptable" recommendation for all the listed manufacturing and testing facilities (see Establishment Evaluation Summary at the end of this memo).

In view of the fact that all the identified chemistry, manufacturing and controls (CMC)-related deficiencies have been satisfactorily addressed by the applicant, from the CMC perspective, this new drug application (NDA 202-133) for fluoxetine 60 mg tablet, USP is recommended for approval. Furthermore, it is important to note that the approved expiration dating period for fluoxetine 60 mg tablet, USP is 24 months when stored under approved storage conditions.

**FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
SUMMARY REPORT**

<b>Application:</b>	NDA 202133/000	<b>Sponsor:</b>	EDGEMONT PHARMS
<b>Org. Code:</b>	130		7400 WEST 110TH ST STE 300
<b>Priority:</b>	3		OVERLAND PARK, KS 66210
<b>Stamp Date:</b>	09-DEC-2010	<b>Brand Name:</b>	FLUOXETINE HCL.
<b>PDUFA Date:</b>	09-OCT-2011	<b>Estab. Name:</b>	
<b>Action Goal:</b>		<b>Generic Name:</b>	
<b>District Goal:</b>	10-APR-2011	<b>Product Number; Dosage Form; Ingredient; Strengths</b>	001; TABLET; FLUOXETINE HYDROCHLORIDE; 60MG

<b>FDA Contacts:</b>	T. BOUIE	Project Manager	301-796-1649
	M. SAPRU	Review Chemist	301-796-1718
	C. TELE	Team Leader	301-796-1762

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<b>Overall Recommendation:</b>	ACCEPTABLE	on 22-SEP-2011	by M. STOCK	(HFD-320)	301-796-4753
	PENDING	on 22-SEP-2011	by EES_PROD		
	WITHHOLD	on 22-FEB-2011	by EES_PROD		

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<b>Establishment:</b>	<b>CFN:</b> 9610101	<b>FEI:</b> 3002807817	
	FERMION OY ORIONINKATU 2 HANKO, FINLAND		
<b>DMF No:</b>	(b) (4)	<b>AADA:</b>	
<b>Responsibilities:</b>	DRUG SUBSTANCE MANUFACTURER		
<b>Profile:</b>	(b) (4)	<b>OAI Status:</b>	NONE
<b>Last Milestone:</b>	OC RECOMMENDATION		
<b>Milestone Date:</b>	20-DEC-2010		
<b>Decision:</b>	ACCEPTABLE		
<b>Reason:</b>	DISTRICT RECOMMENDATION		

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<b>Establishment:</b>	<b>CFN:</b> 9610102	<b>FEI:</b> 3003073605	
	ORION CORP ORION PHARMA ORIONINTIE 1 ESPOO, FINLAND		
<b>DMF No:</b>		<b>AADA:</b>	
<b>Responsibilities:</b>	FINISHED DOSAGE MANUFACTURER		
<b>Profile:</b>	TABLETS, PROMPT RELEASE	<b>OAI Status:</b>	NONE
<b>Last Milestone:</b>	OC RECOMMENDATION		
<b>Milestone Date:</b>	22-SEP-2011		
<b>Decision:</b>	ACCEPTABLE		
<b>Reason:</b>	DISTRICT RECOMMENDATION		

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/s/  
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MOHAN K SAPRU  
09/27/2011

RAMESH K SOOD  
09/27/2011

# **NDA 202-133 (Fluoxetine 60 mg, USP)**

**Edgemont Pharmaceuticals, LLC.**

**Quality Review #1**

**Mohan K. Sapru, Ph.D.**

*Office of New Drug Quality Assessment  
Pre-Marketing Assessment Division I/Branch I  
Division of Psychiatry Products, HFD-130.*

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## Chemistry Review Data Sheet

## d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 5
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: The application was submitted under Section 505(b)(2) of the Federal Food Drug and Cosmetic Act and 21 CFR §314.54.

10. PHARMACOL. CATEGORY/INDICATION: A selective serotonin reuptake inhibitor for treatment of major depressive disorder, and obsessive compulsive disorder in adult and pediatric patients, as well as bulimia nervosa and panic disorder in adults.

11. DOSAGE FORM: Immediate-release scored tablets.

12. STRENGTH/POTENCY: 60 mg fluoxetine base (67.1 mg fluoxetine HCl) per scored tablet.

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED:  Rx  OTC

15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#)

SPOTS Product – Form Completed.

Not a SPOTS Product.

## 16. CHEMICAL NAME, MOLECULAR FORMULA, MOLECULAR WEIGHT, STRUCTURAL FORMULA:

Chemical Name: (±)-N-Methyl-3-phenyl-3-[( $\alpha,\alpha,\alpha$ -trifluoro-p-tolyl)oxy]propylamine-, hydrochloride.

Molecular Formula:  $C_{17}H_{18}F_3NO.HCl$

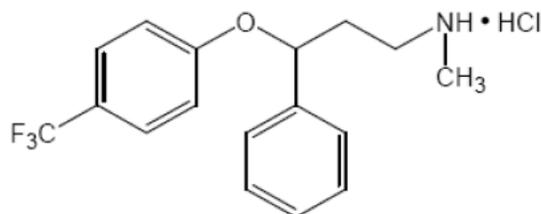
Molecular Weight: 345.79

CAS No.: CAS-59333-67-4 (hydrochloride salt)  
CAS-54910-89-3 (free base)

## Chemistry Review Data Sheet

International Nonproprietary Name (INN): Fluoxetine hydrochloride.

Structure:



## 17. RELATED/SUPPORTING DOCUMENTS:

## A. DMFs

DMF #	TYPE	HOLDER	ITEM REFERENCED	COD E <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED
(b) (4)	II	Fermion Oy, Fin-02200 Espoo, Finland.	Fluoxetine HCl	3	Adequate	24-March-2010
(b) (4)	III	(b) (4)	(b) (4)	3	Adequate	28-Jan-2010
(b) (4)	III	(b) (4)	(b) (4)	3	Adequate	23-June-2006
(b) (4)	III	(b) (4)	(b) (4)	3	Adequate	09-March-2010
(b) (4)	III	(b) (4)	(b) (4)	3	Adequate	22-June-2006

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

## Chemistry Review Data Sheet

6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application; therefore, the DMF did not need to be reviewed).

**B. Other Documents:**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	107,525.	Treatment of bulimia nervosa and panic disorder in adults.

## 18. STATUS:

**ONDQA:**

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Pending	-	
Methods Validation	Not requested. The methods are conventional and don't qualify for internal validation by the FDA laboratories.	22-Aug-2011	Mohan K. Sapru, Ph.D.
Environmental Assessment	Categorical Exclusion	22-Aug-2011	Mohan K. Sapru, Ph.D.
Biopharmaceutics	Approved	02-May-2011	Minerva Hughes, Ph.D.
Microbiology	N/A	N/A	N/A

## Executive Summary Section

**The Executive Summary (NDA 202-133)****I. Recommendations.****A. Recommendation and Conclusion on Approvability.**

From the chemistry, manufacturing and controls (CMC) perspective, this new drug application (NDA 202-133) for fluoxetine 60 mg tablet, USP is not recommended for approval at this stage due to pending issues concerning the relevance of drug product stability data, and the fact that the Office of Compliance has withheld an acceptable recommendation for one of the listed manufacturing and testing facilities (see Establishment Evaluation Summary at the end of this review).

**B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable**

Not applicable at this stage.

**II. Summary of Chemistry Assessments.****A. Description of the Drug Substance (s) and Drug Product (s)**

**Drug Substance:** The drug substance fluoxetine hydrochloride is a white to off-white crystalline powder, and functions as a selective serotonin reuptake inhibitor. It is manufactured as a (b) (4) No polymorphism has been observed by X-ray powder diffraction and differential scanning calorimetry. The applicant has adequately characterized the drug substance using appropriate analytical tools such as mass spectroscopy, ultraviolet (UV) and infrared (IR) spectroscopy, <sup>1</sup>H and <sup>13</sup>C nuclear magnetic resonance (NMR) spectroscopy, and X-ray powder diffraction. For detailed description of the drug substance, including the general properties, characterization/elucidation of structure, manufacturing of the drug substance, control of materials, manufacturing process development, control of critical steps, and process validation, the applicant has referred to Fermion Oy's DMF (b) (4) (b) (4) (b) (4). The last updated (06-June-2008) DMF was been reviewed on 24-March-2010 and found to be adequate (see latest review by Dr. Lucia Tang, OGD for fluoxetine hydrochloride (b) (4) Specification for fluoxetine HCl drug substance, manufactured by Fermion Oy, complies with criteria in USP monographs and European Pharmacopeia (Ph. Eur). The proposed acceptance limits for individual impurities have been set as per the ICH Q3B (R) guidance. Regarding drug substance batch analysis data, in addition to confirming the identity of fluoxetine HCl drug substance by infrared spectroscopy (IR), the applicant has analyzed the profile of individual impurities, which are present at levels of (b) (4) in the tested batches. With regard to inorganic impurities, (b) (4) (b) (4) have been found in tested drug substance batches. (b) (4)

## Executive Summary Section

(b) (4) are controlled by setting an acceptance limit of NMT (b) (4) which is well below the 0.5% limit per USP (b) (4) and ICH (b) (4) guideline. With the exception of the gas chromatographic (GC) method for (b) (4), all analytical procedures used in the testing of the drug substance are compendial (USP or Ph. Eur.). Levels of (b) (4) are determined by GC method using an in-house validated method. Furthermore, the stability data cross-referenced to DMF (b) (4) are adequate to demonstrate physical and chemical stability of the drug substance throughout the period of duration of the stability studies i.e., 60 months at 25°C/60% RH. The drug substance (b) (4) (primary packaging material), which are packed in suitable containers, (b) (4). The stability data cross-referenced to DMF (b) (4) are adequate to demonstrate physical and chemical stability of the drug substance for a period of 60 months at 25°C/60% RH.

**Drug Product:** The proposed drug product, fluoxetine 60 mg tablets, is an immediate-release oral tablet product containing 67.1 mg of fluoxetine HCl (equivalent to 60 mg fluoxetine base) per tablet, compendial excipients, and a rapidly disintegrating film coat. The tablets are capsule-shaped, scored on both sides, and white film-coated. Edgemont Pharmaceuticals, LLC, has sought U.S. marketing approval for fluoxetine 60 mg tablets under the provisions of Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, and in conformance with 21 CFR § 314.54. This application (NDA 202-133) relies on the Agency's previous findings of safety and effectiveness for the innovator fluoxetine product i.e., Prozac®, as bridged by the bioequivalence to the reference listed drug (RLD) and the characterization of the fluoxetine 60 mg tablets and the comparison to the RLD on the basis of CMC aspects. The applicant has demonstrated bioequivalence between fluoxetine 60 mg tablets and Mylan's fluoxetine hydrochloride tablets, EQ 20 mg base, ANDA 075755, as the RLD. For this purpose, Edgemont has acquired a license from Orion Pharma to market their Seronil 60 mg (fluoxetine HCl) scored tablets in the United States. Orion has manufactured and marketed this dosage strength in Finland since 1997. Seronil 60 mg scored tablet formulation was originally approved in Finland on the basis of bioequivalence to their own Seronil 20 mg capsules (3 x 20 mg caps vs. 1 x 60 mg tab). Seronil 20 mg capsule formulation was approved in Finland (1992) based on demonstrated bioequivalence to Eli Lilly's Fontex (fluoxetine HCl) 20 mg capsules (Seronil 2 x 20 mg vs. Fontex 2 x 20 mg). Orion is the sole manufacturer of drug product for Edgemont. Edgemont will import bulk tablets from Orion and then have the tablets bottled by Patheon Inc. at their facility in Puerto Rico.

The formulation excipients, which include mannitol, maize starch, povidone (b) (4), microcrystalline cellulose (b) (4), magnesium stearate, hypromellose (b) (4), sucrose, titanium dioxide, polysorbate (b) (4) and glycerol (b) (4) have been selected to ensure (b) (4) achieve the intended quality of the tablets. (b) (4)

Regarding the proposed drug product, fluoxetine 60 mg tablets, the excipients used are routinely tested to the compendial requirements and are considered safe because each has been previously approved for use in this type of dosage form at or above the concentration in the proposed drug product. Furthermore, the quantity of each excipient used in the proposed drug product is below the maximum approved potency for oral

## Executive Summary Section

tablets listed in the FDA Inactive Ingredient Guide for Approval Drug Products (IIG Database). [REDACTED] In addition, all excipients used in commercial batches, with the exception of [REDACTED] will be tested according to USP/NF and Ph. Eur. [REDACTED] will be tested according to Ph. Eur. The limits for related substances are somewhat tighter than USP monograph requirements and comply with ICH Q3B(R2) guidelines for impurities in drug product with maximum daily dosage less than or equal to 100 mg of drug substance. The drug product also complies with USP [REDACTED]. In addition, the data provided suggest that the halved tablets comply well with the compendial requirements for uniformity of mass for whole tablets, which indicates that fluoxetine 60 mg scored tablets can be consistently divided into dose proportionally halves. Regarding the release rates of fluoxetine HCl from whole and half tablets, the data indicate that the dissolution profiles are similar, suggesting, thereby, that the dissolution profile is not altered if the tablet is divided in halves. Regarding specifications for dissolution method and disintegration, the applicant has satisfactorily addressed the deficiencies by revising dissolution method tolerance limits, and disintegration specification in compliance with the Agency's recommendations. The applicant appropriately contends that because the proposed drug product complies with, or exceeds all requirements of the USP monograph for fluoxetine tablets, this product can be labeled as USP product. The applicant has demonstrated that the proposed drug product specifications are achievable by the production process, and are supported by data from toxicological, clinical and stability evaluations. The non-compendial methods i.e., assay and identification by HPLC, determination of related substances by HPLC, and dissolution assay have been validated by the drug product manufacturer (Orion Pharma). Additionally, the levels of individual impurities or the specified impurity are undetectable in the tested drug product batches. There are no impurities that are unique to the drug product.

The proposed drug product specification contains all of the elements for testing per the USP monograph for fluoxetine tablets. Fluoxetine 60 mg tablets are manufactured by [REDACTED]

[REDACTED]. The proposed U.S. commercial container closure system for the drug product consists of a white 40 mL high density polyethylene (HDPE) bottles with white [REDACTED] child-resistant caps and a tamper-evident induction seal. In essence, the primary container closure system for the U.S. commercial batches is essentially similar to that used in the commercial batches marketed in Finland, with the exception that the proposed closure is child-resistant with an aluminum tamper-evident induction seal; whereas, the Seronil container system only has a tamper-evident neck band. Based on primary, secondary and in-use stability data, the applicant has demonstrated stability of the drug product. However, these stability studies have been carried out following storage of a single primary batch of the drug product in the to-be-marketed container closure system for 12 months at 25°C/60% RH or up to 6 months under accelerated conditions of 40°C/75% RH. In addition, the supporting stability studies have revealed no significant changes in monitored attributes of fluoxetine 60 mg tablets following their storage in 20 mL, 40 mL and 75 mL HDPE bottle configurations up to a period of 38 months at 25°C/60% RH or 8 months under accelerated conditions. Regarding labeling, in compliance with Agency recommendations, the applicant has agreed to remove the word [REDACTED]

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Standard Manual; version 004). From the CMC perspective, there are no outstanding labeling-related issues.

**B. Description of How the Drug Product is Intended to be Used.**

The drug product (fluoxetine 60 mg tablets) is to be used for the treatment of major depressive disorder and obsessive compulsive disorder in adult and pediatric patients, as well as the bulimia nervosa and panic disorder in adults. Specifically, the proposed drug product i.e., fluoxetine 60 mg tablets is intended to be provided as an immediate-release scored oral tablet. Prozac® (fluoxetine HCl) is the innovator fluoxetine product, which has been approved by the FDA in 1987. Subsequently, a specific Prozac 60 mg capsule strength was approved in 1999 (NDA 18-936/S-054). Although approved, Eli Lilly discontinued the 60 mg strength, and today there is no 60 mg fluoxetine dosage strength available in the U.S. market. To meet the clinical need for 60 mg dosage strength of fluoxetine, particularly for achieving effective dose for bulimia nervosa, the applicant, has sought U.S. marketing approval for fluoxetine 60 mg tablets. No proprietary name has been proposed for this product. (b) (4)

**C. Basis for Approvability or Not-Approval Recommendation.**

The major unresolved issue concerns the relevance of the drug product stability data that the applicant has provided to support granting of expiry period for the drug product. Previously, stability data requirements have been discussed in-face-to-face pre-NDA meeting between the applicant and the Agency, which was held on March 5, 2010. As per the minutes of this meeting (refer to pre-NDA meeting minutes), the applicant indicated that the NDA submission would contain stability data from the Orion drug product, which has been manufactured and marketed for 12 years in Finland. In addition, the applicant committed that information to demonstrate that the US container closure is equivalent or superior to the container closure used for the Finnish product along with three months of long-term and three months of accelerated ICH stability data for one drug product batch, manufactured by Orion at the intended commercial scale (b) (4) will be submitted to support the preferred US packaging format. Furthermore, the applicant stated that a comparative analysis of these data will be included in the NDA submission. To demonstrate stability of the drug product and support firm's proposed (b) (4) month expiration period, the applicant has provided stability data from the Orion Seronil 60 mg tablet (supporting stability data), in conjunction with data from the ongoing stability study conducted at Patheon involving a single commercial batch of fluoxetine 60 mg tablets (primary stability data). For the supporting stability, the batches are classified in three categories: pilot-scale packaged in 75 mL HDPE bottle, commercial-scale packaged in 20 mL HDPE bottle, and commercial-scale packaged in 40 mL HDPE bottle. In the pre-NDA meeting held on March 5, 2010 (refer to pre-NDA meeting minutes) as well as in the NDA submission, the applicant has contended that the 40 ml HDPE bottle configuration used for generating the supporting data at Orion is similar to the Edgemont 40 mL HDPE bottle used for generating primary stability data, except that the HDPE bottle used in the primary stability studies has a tamper-evident aluminum induction seal, whereas the bottle used in the supporting stability studies had a tamper-evident

## Executive Summary Section

neck band seal. Regarding the relevance of the secondary stability data, the applicant contends that the current proposed U.S. container closure 40 mL HDPE bottle with tamper-evident induction seal closure is at least the same as, if not superior to, the container closure used by Orion for generating supporting stability data for the fluoxetine 60 mg tablets (Seronil). In the NDA submission, the applicant didn't provide information as per the commitment made in the pre-NDA meeting held on March 5, 2010 (refer to pre-NDA meeting minutes) concerning the head space and headspace to tablet ratios for 75 mL, 20 mL and 40 mL HDPE bottle configurations that have been used for generating the supporting and primary stability studies. However, in response to clarifications sought by CMC reviewer via the teleconference between the applicant and the Agency (held on August 24, 2011), the applicant has provided new information, which indicates that headspace to tablet ratio of (b) (4) for the 20 mL, 40 mL Orion, 40 mL to-be-marketed Edgemont, and 75 mL HDPE bottle configurations, respectively. It is important to note that the headspace to tablet ratio of (b) (4) pertaining to the to-be-marketed HDPE bottle configuration, represents the worst case scenario when compared to headspace to tablet ratio configurations that have been used to generate supporting stability data. This newly revealed information is not consistent with the applicant's original contention that the 40 mL HDPE bottle configuration used for generating the supporting data at Orion is similar to the Edgemont 40 ml HDPE bottle configuration used for generating primary stability data. In view of this, the relevance of supporting stability data to the primary stability data would need to be reviewed before granting an expiry period for the drug product.

In conclusion, at this stage, the new drug application for fluoxetine 60 mg tablet is not recommended for approval due to pending issues concerning a) the relevance of drug product stability data generated in container closure systems of different configurations and headspace to tablet ratios, and b) the fact that the Office of Compliance has withheld an acceptable recommendation for one of the listed manufacturing and testing facilities.

### III. Administrative.

#### A. Reviewer's Signature

*Mohan Sapru*

#### B. Endorsement Block

Review Chemist:	Mohan K. Sapru, Ph.D.
CMC Lead:	Chhagan G. Tele, Ph.D.
Chemistry Team Leader:	Ramesh Sood, Ph.D.

#### B. CC Block

Project Manager:	Hiren Patel
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/s/  
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MOHAN K SAPRU  
09/02/2011

RAMESH K SOOD  
09/02/2011