

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-860**

**PHARMACOLOGY REVIEW(S)**

Memorandum

Date: April 26, 2006

From: Leslie McKinney, PhD  
Pharm/Tox reviewer, DRUP

To: Lesley Furlong, MD  
Medical Officer, DRUP

Lisa Soule, MD  
Medical Team Leader, DRUP

Subject: Major amendment for NDA 21-860

The major amendment to NDA 21-860, submitted 3-23-2006, does not contain any new pharm/tox data. I have reviewed the label, and find it acceptable. Therefore, no additional pharm/tox review is needed for this NDA. Reference can be made to the original review filed in DFS on 10-20-2005.

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/s/

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Leslie McKinney  
5/2/2006 11:23:54 AM  
PHARMACOLOGIST

Lynnda Reid  
5/2/2006 02:30:39 PM  
PHARMACOLOGIST



DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

## PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	<b>21-860</b>
SERIAL NUMBER:	<b>000</b>
DATE RECEIVED BY CENTER:	<b>May 20, 2005</b>
PRODUCT:	<b>Sarafem (fluoxetine hydrochloride)</b>
INTENDED CLINICAL POPULATION:	<b>Pre-menstrual dysphoric disorder (PMDD)</b>
SPONSOR:	<b>Warner Chilcott</b>
DOCUMENTS REVIEWED:	<b>Vol. 1</b>
REVIEW DIVISION:	<b>Division of Urologic and Reproductive Products</b>
PHARM/TOX REVIEWER:	<b>Leslie McKinney, Ph.D.</b>
PHARM/TOX SUPERVISOR:	<b>Lynnda Reid, Ph.D.</b>
DIVISION DIRECTOR:	<b>Daniel Shames, M.D.</b>
PROJECT MANAGER:	<b>Karen Kirchberg, N.P.</b>

Date of review submission to Division File System (DFS): 10-20-2005

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## ***EXECUTIVE SUMMARY***

### **I. Recommendations**

#### A. Recommendation on approvability

NDA 21-860 (fluoxetine hydrochloride) has been submitted by the Warner Chilcott Co. for the treatment of pre-menstrual dysphoric disorder (PMDD) at a dose of 15 mg. Fluoxetine was originally approved on 12-29-1987 under the trade name Prozac® (NDA 18-936) for the treatment of depression. It was approved on 7-6-2000 under the trade name Sarafem® (NDA 18-936) for the treatment of PMDD at 10 and 20 mg dosages, using continuous and intermediate dosing regimens. The proposed new dose is intermediate to those already marketed, and will be prescribed using the same regimens. There are no new non-clinical issues for the proposed intermediate dosage. Based on previously submitted Pharm/Tox data to support the safety of the 10 and 20 mg dosages, we recommend approval of the 15 mg dose.

#### B. Recommendation for nonclinical studies

The nonclinical pharmacology and toxicology of fluoxetine HCl has been documented in NDA 18-936. DRUP has previously indicated to the sponsor that no new pharm/tox studies were needed for this submission.

#### C. Recommendations on labeling

There are no pharm/tox recommendations for changes in the current labeling.

### **II. Summary of nonclinical findings**

#### A. Brief overview of nonclinical findings

There were no nonclinical studies submitted in support of this application.

#### B. Pharmacologic activity

Pharmacologic activity at the intermediate dosage is not expected to be different from the approved dosages.

#### C. Nonclinical safety issues relevant to clinical use

There are no new nonclinical safety issues relevant to clinical use.

## 2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

### 2.6.1 INTRODUCTION AND DRUG HISTORY

**NDA number:** 21-860

**Review number:** 1

**Sequence number/date/type of submission:** N000 May 20, 2005

**Information to sponsor:** Yes ( ) No (X)

**Sponsor and/or agent:** Warner Chilcott Co.

**Manufacturer for drug substance:** \_\_\_\_\_

\_\_\_\_\_ For the drug product:  
Pharmaceutics International, Inc (PII), Hunt Valley, MD 21031

**Reviewer name:** Leslie McKinney

**Division name:** Division of Urologic and Reproductive Products

**Review completion date:** 10-20-2005

**Drug:**

Trade name: Sarafem

Generic name: fluoxetine hydrochloride

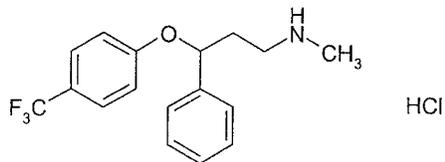
Code name: WC2059

Chemical name: (±)-N-methyl-3-phenyl-3-[(α,α,α,-trifluoro-p-tolyl)oxy]  
propylamine hydrochloride

CAS registry number:

Molecular formula/molecular weight: C<sub>17</sub>H<sub>18</sub>F<sub>3</sub>NO · HCl / 345.79

Structure:



**Relevant INDs/NDAs/DMFs:** IND 68,098 (Warner Chilcott)  
NDA 18-936 S-058 and S-067 (Eli Lilly)

**Drug class:** selective serotonin reuptake inhibitor (SSRI)

**Intended clinical population:** women with pre-menstrual dysphoric disorder (PMDD)

**Clinical formulation:**

sponsor's table

Item No.	Components	Quality Standard Reference	Function	Amount per Tablet (mg)		
				10 mg	15 mg	20 mg
1	Fluoxetine Hydrochloride	USP	Drug			
2	Microcrystalline Cellulose	NF				
3	Croscarmellose Sodium	NF				
4		Non-compendial*				
5	Colloidal Silicon Dioxide	NF				
6	Magnesium Stearate	NF				
	Total					

1 Equivalent to 10.0 mg of Fluoxetine base

2 Equivalent to 15.0 mg of Fluoxetine base

3 Equivalent to 20.0 mg of Fluoxetine base

\* composed of FD&C Yellow No. 6 and D&C Yellow No. 10, both of which can be safely used as colorants

**Route of administration:** oral

**Studies reviewed within this submission:** There were no new Pharm/Tox studies submitted for this NDA.

**OVERALL CONCLUSIONS AND RECOMMENDATIONS**

From a Pharm/Tox perspective, there are no new safety concerns for approval of an intermediate dosage of 15 mg of fluoxetine. Contraindications for and complications following use of fluoxetine are detailed in the labeling for Sarafem® and should be applied to use of the intermediate dosage.

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Leslie McKinney  
10/20/2005 03:34:58 PM  
PHARMACOLOGIST

Lynnda Reid  
10/24/2005 10:49:46 AM  
PHARMACOLOGIST

**45 Day NDA Meeting Checklist  
Pharmacology/Toxicology**

**NDA Number: 21-860**

**Drug Name: Sarafem (fluoxetine hydrochloride tablets)**

**Sponsor: Warner Chilcott (US), Inc.**

**Date: 29-Jun-05**

**Reviewer: Leslie McKinney Leonard**

**Date CDER Received: 20-May-05**

**Filing Date: 06-Jul-05**

**User Fee Date: 30-Mar-06**

**Expected Date of Draft Review: 25-Jan-06**

**On initial overview of the Pharm/Tox portion of the NDA application**

1)	On its face, is the Pharm/Tox section of the NDA organized in a manner to allow substantive review to begin?	See NDA 18,936	The nonclinical pharmacology and toxicology of fluoxetine HCl has been documented in NDA 18,936. DRUDP has previously agreed that no new pharm/tox information is necessary for this NDA submission.
2)	Is the Pharm/Tox section of the NDA indexed and paginated in a manner to allow substantive review to begin?	See NDA 18,936	
3)	On its face, is the Pharm/Tox section of the NDA legible so that substantive review can begin? Has the data been presented in an appropriate manner?	See NDA 18,936	
4)	Are all necessary and appropriate studies for this agent, including special studies/data requested by the Division during pre-submission communications/discussions, completed and submitted in this NDA?	See NDA 18,936	
5)	If the formulation to be marketed is not identical to the formulation used in the toxicology studies (including the impurity profiles), has the Sponsor clearly defined the differences and submitted reviewable supportive data?	See NDA 18,936	Formulation includes one new intermediate dose (15 mg). All dosages will be formulated in tablets instead of pulvules. At the pre-NDA meeting, DRUDP agreed that slight changes in the quantities of approved excipients did not raise any pharm/tox safety issues.

6)	Does the route of administration used in animal studies appear to be the same as the intended human exposure? If not, has the sponsor submitted supportive data and/or an adequate scientific rationale to justify the alternative route?	See NDA 18,936	
7)	Has the sponsor submitted a statement(s) that all the pivotal Pharm/Tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?	See NDA 18,936	
8)	Has the sponsor submitted a statement(s) that the Pharm/Tox studies have been performed using acceptable, state-of-the-art protocols which also reflect agency animal welfare concerns?	See NDA 18,936	
9)	Has the proposed draft labeling been submitted?  Are the appropriate sections for the product included and generally in accordance with 21 CFR 201.57?  Is information available to express human dose multiples in either mg/m <sup>2</sup> or comparative serum/plasma AUC levels?	yes  yes  yes	
10)	From a Pharm/Tox perspective, is this NDA fileable? If not, please state in item #11 below why it is not.	yes	
11)	Reasons for refusal to file:		

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/s/

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