

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-860

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

From: Sandhya Apparaju, HFD 870

To: DOCUMENT ROOM (LOG-IN and LOG-OUT)
Please log-in this consult and review action for the specified
IND/NDA submission

DATE: 05/01/2006

IND No.:
Serial No.:

NDA No.
21-860

DATE OF DOCUMENT
03/22/2006

NAME OF DRUG
**Fluoxetine HCl (Sarafem
Tablets)**

PRIORITY CONSIDERATION

Date of informal/Formal
Consult:

NAME OF THE SPONSOR: Warner Chilcott

TYPE OF SUBMISSION

CLINICAL PHARMACOLOGY/BIPHARMACEUTICS RELATED ISSUE

- | | | |
|--|--|---|
| <input type="checkbox"/> PRE-IND | <input type="checkbox"/> DISSOLUTION/IN-VITRO RELEASE | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> ANIMAL to HUMAN SCALING | <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> IN-VITRO METABOLISM | <input type="checkbox"/> IN-VIVO WAIVER REQUEST | <input type="checkbox"/> CORRESPONDENCE |
| <input type="checkbox"/> PROTOCOL | <input type="checkbox"/> SUPAC RELATED | <input type="checkbox"/> DRUG ADVERTISING |
| <input type="checkbox"/> PHASE II PROTOCOL | <input type="checkbox"/> CMC RELATED | <input type="checkbox"/> ADVERSE REACTION REPORT |
| <input type="checkbox"/> PHASE III PROTOCOL | <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> ANNUAL REPORTS |
| <input type="checkbox"/> DOSING REGIMEN CONSULT | <input type="checkbox"/> SCIENTIFIC INVESTIGATIONS | <input type="checkbox"/> FAX SUBMISSION |
| <input type="checkbox"/> PK/PD- POPPK ISSUES | <input type="checkbox"/> MEETING PACKAGE (EOP2/Pre-
NDA/CMC/Pharmacometrics/Others) | <input checked="" type="checkbox"/> OTHER (<i>SPECIFY BELOW</i>): |
| <input type="checkbox"/> PHASE IV RELATED | | [Resubmission of NDA] |

REVIEW ACTION

- | | | |
|---|---|---|
| <input checked="" type="checkbox"/> NAI (No action indicated) | <input type="checkbox"/> Oral communication with
Name: [] | <input type="checkbox"/> Formal Review/Memo (attached) |
| <input type="checkbox"/> E-mail comments to: | <input type="checkbox"/> Comments communicated in
meeting/Telecon. see meeting minutes
dated: [] | <input type="checkbox"/> See comments below |
| <input type="checkbox"/> Medical <input type="checkbox"/> Chemist <input type="checkbox"/> Pharm-Tox | | <input type="checkbox"/> See submission cover letter |
| <input type="checkbox"/> Micro <input type="checkbox"/> Pharmacometrics <input type="checkbox"/> Others
(Check as appropriate and attach e-mail) | | <input type="checkbox"/> OTHER (<i>SPECIFY BELOW</i>):
[] |

REVIEW COMMENT(S)

- NEED TO BE COMMUNICATED TO THE SPONSOR HAVE BEEN COMMUNICATED TO THE SPONSOR

Warner Chilcott's original NDA for Sarafem Tablets was submitted on 05/19/2005. The clinical pharmacology section of this NDA contained a pivotal bioequivalence study comparing 20 mg Sarafem tablets (proposed) against the marketed Sarafem pulvules; In addition, the clinical pharmacology submission also contained requests for biowaivers for lower tablet strengths and food effect waivers. The original NDA 21-860 was found acceptable from a clinical pharmacology perspective.

Due to a pending CMC issue, the NDA had received an approvable (AE) action during the first cycle and hence was resubmitted on March 22nd, 2006 with the necessary CMC information. The updated and resubmitted package insert (label) was reviewed from a clinical pharmacology perspective and was found to be acceptable.

Conclusions: The resubmitted label has been reviewed and found acceptable from a clinical pharmacology perspective.

SIGNATURE OF REVIEWER: _____

Date _____

SIGNATURE OF TEAM LEADER: _____

Date _____

CC.: HFD-870; TL: Parekh; DD: Malinowski

Project Manager: _____ Date _____

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

/s/

Sandhya Apparaju
5/1/2006 12:14:14 PM
BIOPHARMACEUTICS

Ameeta Parekh
5/3/2006 09:28:52 AM
BIOPHARMACEUTICS

**OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
REVIEW**

NDA: 21-860	Submission Date(s): 05/19/2005, 08/30/2005, 09/15/2005
Brand Name	Sarafem™
Generic Name	Fluoxetine Hydrochloride
Reviewer	Sandhya Apparaju, Ph.D.
Team Leader	Ameeta Parekh, Ph.D.
OCP Division	Division of Clinical Pharmacology 3 (DCP 3)
OND division	Division of Reproductive and Urology Products (DRUP)
Sponsor	Warner-Chilcott
Relevant IND(s)	68,098
Submission Type; Code	505b(1); Original NDA; New dosage form
Formulation; Strength(s)	Tablets; 10, 15 and 20 mg
Indication	Premenstrual Dysphoric Disorder (PMDD)

An optional intra-divisional CPB briefing for Sarafem Tablets (NDA 21-860) was held on 01/24/2006, in conf room 3560 of WO Building 21 from 12 to 1 PM. Briefing attendees included John Hunt, Ameeta Parekh, Lesley Furlong, Julie Bullock, Doanh Tran and Amjad Iqbal (Fellow) and Sandhya Apparaju.

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1 Executive Summary

Warner-Chilcott (WC) seeks the approval of Sarafem (Fluoxetine Hydrochloride) Tablets (NDA 21-860) for the treatment of premenstrual dysphoric disorder (PMDD). Sarafem is currently marketed as pulvules (capsules) for the same indication. This NDA (21-860) consists of results from a pivotal bioequivalence study conducted in order to establish BE between the currently marketed pulvule formulation (20 mg) and the newly proposed tablet formulation of Sarafem (20 mg). In addition, requests for waiver of *in vivo* BE studies (Biowaivers) have also been submitted for the lower 10 mg and 15 mg strengths of tablets based on the results of this pivotal BE study, formulation similarity and proportional compositions of the various tablet strengths and comparable dissolution profiles of all strengths. In addition, food-effect study waiver for the 20 mg strength is also justified using dissolution profile comparisons in three different pH media and the food-effect information derived from the approved pulvule formulation.

Because this was a pivotal BE study, DSI inspection of the clinical and bioanalytical sites was requested by DRUP. The results of this inspection and subsequent conclusions can be found in 3.1.7.

1.1 Recommendation

NDA 21-860 is acceptable from a clinical pharmacology and Biopharmaceutics perspective.

1.2 Phase IV Commitments

None.

**Appears This Way
On Original**

2 Summary of CPB Findings

- Sponsor is seeking the approval of a new Tablet dosage form of Sarafem (fluoxetine HCl) in three strengths (10, 15 and 20 mg) for the treatment of PMDD. The clinical pharmacology section of NDA 21-860 consists of 1) results of a pivotal bioequivalence study comparing the highest (20 mg) strength of the proposed tablet vs. the marketed pulvule formulation, 2) biowaiver requests for the lower strength 10 mg and 15 mg tablets and 3) food-effect study waiver request for the 20 mg Sarafem tablets.
- Pivotal BE study: Sponsor has conducted a 2-sequence, 2-period, 2-treatment, randomized 2-way crossover study in healthy adult female volunteers aged 18-45 years. Study established bioequivalence between the two formulations as seen from the ratio of the log-transformed systemic exposure parameters and the 90 % CI surrounding these estimates that are completely within the 80-125 % bounds:

	Test (T)	Reference (R)		90 % CI	
	Tablets	Pulvules	Ratio(T/R)	Lower	Upper
C _{max}	12.85	13.06	98.08	95.22	101.02
AUC _{0-t}	454.23	480.99	94.74	91.47	98.14
AUC _{inf}	524.4	553.56	94.92	90.98	99.02

- In addition, the study also demonstrated bioequivalence between the two formulations (test and reference) with respect to the active metabolite, norfluoxetine.
- Requests of biowaivers for the lower 10 mg and 15 mg tablet strengths are justified based on 1) documentation of BE for the highest proposed tablet strength (20 mg) with that of the reference 20 mg pulvule formulation, 2) proportionally similar composition of the new strengths in relation to the 20 mg tablet whose BA is documented and 3) comparable dissolution profiles of the lower tablet strengths with that of the 20 mg tablet using the approved USP dissolution test for Fluoxetine tablets and in pH 4.5 and pH 6.8 buffers.
- Food-effect waiver for the 20 mg tablet formulation is justified based on 1) establishment of bioequivalence to that of reference pulvule formulation under fasted conditions, 2) dissolution profile comparability for the tablets in three different pH media (pH 1.2, 4.5 and 6.8) and 3) lack of a significant food-effect for the currently marketed pulvule formulation and the resultant labeling language in the approved Sarafem PI.

3 QBR

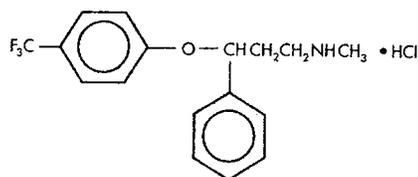
3.1 General Attributes

Regulatory history: Sarafem (Fluoxetine hydrochloride pulvules) is a selective serotonin reuptake inhibitor (SSRI) indicated in the treatment of premenstrual

dysphoric disorder (PMDD). The drug was originally approved for this indication by US FDA in July 2000 (NDA 018-936, S-058) for use as a continuous regimen. Subsequently in June 2002, an intermittent dosage regimen (S-067) was approved for Sarafem use in PMDD. Fluoxetine hydrochloride was initially developed and marketed in US under the trade name of Prozac for the treatment of psychiatric disorders including major depressive disorder and obsessive-compulsive disorder. The originally approved NDA for Sarafem pulvules in the treatment of PMDD was submitted by Eli Lilly and company. Warner-Chilcott (WC) subsequently obtained the market rights for Sarafem including the use of the currently approved trade name. Eli Lilly still holds the rights to the original NDA and all its supplements, but has authorized the FDA to cross-reference supplements 058 & 067 of the original NDA 18-936 in the review of Warner-Chilcott's NDA 21-860. In this new NDA, WC seeks the approval of a new tablet formulation of Sarafem. A new intermediate strength of 15 mg has also been developed by WC, in addition to the currently marketed 10 and 20 mg strengths.

3.1.1 Physico-chemical properties

The active ingredient of Sarafem tablets is Fluoxetine hydrochloride, designated (\pm)-N-methyl-3-phenyl-3-[(a,a,a-trifluoro-p-tolyl)oxy]propylamine hydrochloride and has the empirical formula of $C_{17}H_{18}F_3NO \cdot HCl$. Its molecular weight is 345.79. The structural formula is:



Fluoxetine hydrochloride is a white to off-white crystalline solid. Solubility data suggests that fluoxetine is slightly soluble in water and with sonication at pH 1.2, 4.5 and 7.0 (1-2 mg/mL), with a maximum solubility of 14 mg/mL in water. Each SARAFEM tablet contains fluoxetine hydrochloride equivalent to 10 mg (32.3 μ mol), 15 mg (48.5 μ mol) or 20 mg (64.7 μ mol) of fluoxetine. Each tablet also contains microcrystalline cellulose, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate, FD&C Yellow No. 6 aluminum lake (10 mg and 20 mg tablets) and D&C Yellow No. 10 aluminum lake (10 mg and 20 mg tablets).

Table 2. Unit Dose Composition of Sarafem Tablets

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					

¹Equivalent to 10.0 mg of Fluoxetine base.

²Equivalent to 15.0 mg of Fluoxetine base.

³Equivalent to 20.0 mg of Fluoxetine base.

3.1.2 Proposed mechanism of action

The mechanism of action of fluoxetine in premenstrual dysphoric disorder (PMDD) is unknown, but is presumed to be linked to its inhibition of CNS neuronal uptake of serotonin. Studies at clinically relevant doses in humans have demonstrated that fluoxetine blocks the uptake of serotonin into human platelets. Studies in animals also suggest that fluoxetine is a much more potent uptake inhibitor of serotonin than of norepinephrine.

3.1.3 Therapeutic indication

SARAFEM is currently approved as pulvules for the treatment of premenstrual dysphoric disorder (PMDD).

The essential features of PMDD include markedly depressed mood, anxiety or tension, affective lability, and persistent anger or irritability. Other features include decreased interest in usual activities, difficulty concentrating, lack of energy, change in appetite or sleep, and feeling out of control.

Physical symptoms associated with PMDD include breast tenderness, headache, joint and muscle pain, bloating, and weight gain. These symptoms occur regularly during the luteal phase and remit within a few days following onset of menses; the disturbance markedly interferes with work or school or with usual social activities and relationships with others.

3.1.4 Proposed dosage(s) and route of administration

Initial Treatment

The recommended dose of SARAFEM for the treatment of PMDD is 20 mg/day given continuously (every day of the menstrual cycle) or intermittently (defined as starting a daily dose 14 days prior to the anticipated onset of menstruation through the first full day of menses and repeating with each new cycle). The maximum fluoxetine dose should not exceed 80 mg/day.

Maintenance/Continuation Treatment

Systematic evaluation of SARAFEM has shown that its efficacy in PMDD is maintained for periods of up to 6 months at a dose of 20 mg/day given continuously and up to 3 months at a dose of 20 mg/day given intermittently. Patients should be periodically reassessed to determine the need for continued treatment.

3.1.5 What are the primary components of NDA 21-860?

NDA 21-860 consists of the following components to support approval of the new Sarafem tablet formulation:

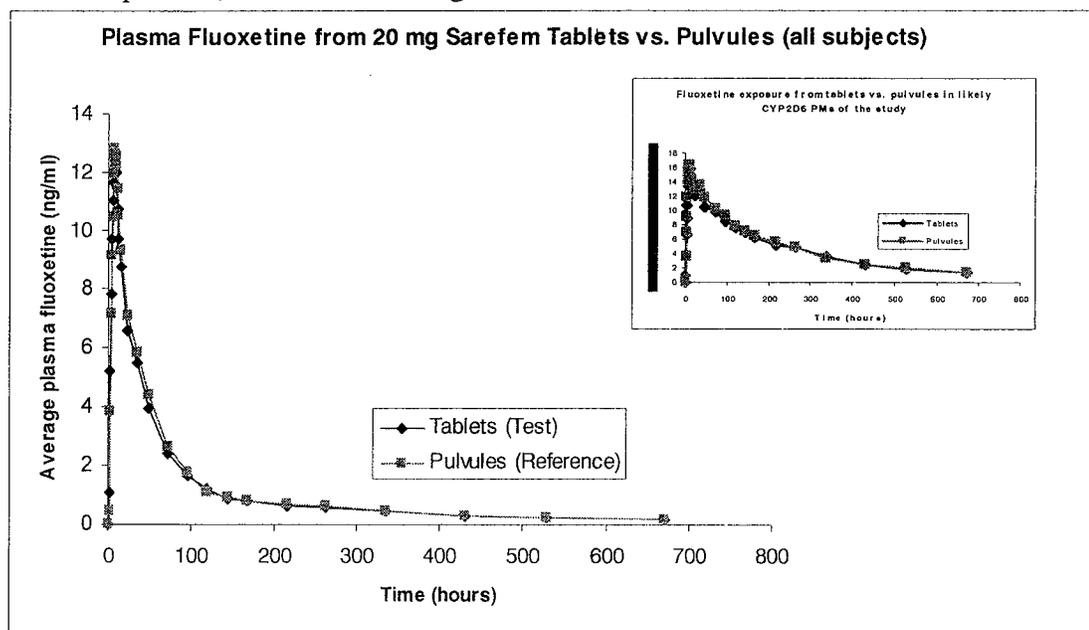
- Completed clinical study report for the relative bioavailability study PR-10603.1 to compare fluoxetine bioavailability following Sarafem tablets (test), 20 mg relative to that of Sarafem pulvules (reference), 20 mg.
- Biowaiver requests for the lower (10 and 15 mg) tablet strengths.
- Food-effect study waiver request

3.1.6 Pivotal BE study

- Study Design: A single center, non-blinded, single-dose, 2-sequence, randomized, 2-treatment, 2-period crossover study.
- Subject Demographics: Twenty-six (26) healthy, non-smoking, non-pregnant female volunteers aged 18-45 years; median (range) age of 27 (20-45) years; 24 Caucasian, 1 black and 1 Asian. 24/26 subjects completed the study;
- Treatments: All subjects received a single dose of either the Sarafem 20 mg tablet (test) or Sarafem 20 mg pulvule (reference) treatment in each of the two treatment periods. Each treatment period was effectively separated by 56 days from the time of the dosing. Treatment was administered with 240 mL of water. Subjects were fasted for 10 hours (overnight) before dosing and for 4 hours post-dosing.
- Blood samples were collected from all subjects for the analysis of plasma fluoxetine and norfluoxetine concentrations at pre-dose and up to 28 days post-dose. The time points for blood sampling were as follows: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 16, 24, 48, 72, 96, 120, 144, 168, 216, 264, 336, 432, 528, and 672 hours (28 days) post-treatment.
- Analytical methodology: Plasma fluoxetine and norfluoxetine concentrations were determined by using a validated LC-MS/MS technique, with upper and lower limits of quantification of 1.00-500 ng/ml.
- Pharmacokinetic and Statistical analysis: Fluoxetine and norfluoxetine noncompartmental pharmacokinetic parameters were calculated for the test and reference treatments using non-compartmental pharmacokinetic analysis. Descriptive statistics were obtained for all the pharmacokinetic parameters.
- Analysis of variance (ANOVA) was performed on the log-transformed PK parameters C_{max} , AUC_{0-12h} and AUC_{0-inf} . The ANOVA model included sequence, formulation and period as fixed effects and subject nested within sequence as the error term. A 10 % level of significance was used to test

the sequence effect. Statistical analyses were conducted using the appropriate SAS procedure.

- Bioavailability measures of the test and reference treatment were compared using the average bioequivalence approach. The treatments were defined as bioequivalent if the 90 % CI for the exponential of the difference between treatment LSM for the parameters C_{max} and $AUC_{0-t_{lde}}$ were between 80.00 and 125.00 %.
- **Results:** The plasma concentration vs. time profiles of fluoxetine from the test and reference formulations were compared for each patient. The average plasma concentration profiles are shown in the figure below:
- Three subjects (17, 23 and 24) who had distinctly higher systemic exposures of fluoxetine, longer elimination $T_{1/2}$ values (ranging from 100-300 h vs. ~25 h in the remaining subjects) and lower norfluoxetine (active metabolite) concentrations were assumed to be CYP2D6 poor metabolizers (subjects were not genotyped in this study). The test and reference formulations however, demonstrated comparable rate and extent of fluoxetine (& norfluoxetine) systemic exposure in each of these three patients, as shown in the figure inset below:



- The ratio of the log-transformed fluoxetine rate and extent of systemic exposure and their surrounding 90 % confidence intervals (expressed as % relative to the LSM of the reference formulation) are presented in the table below:

Arithmetic mean (% CV); median value reported for T_{max}		
Parameter	Tablets (Test)	Pulvules (Reference)
C_{max}	13.14	13.38

	(21.6)	(22.1%)			
Tmax	8	8			
AUC0-t	710.5 (138 %)	747.46 (138.2%)			
AUCinf	829.2 (142 %)	861.96 (141.8%)			
Geometric means & estimated BE criterion and its 90 % CI					
	Test (T)	Reference (R)		90 % CI	
	Tablets	Pulvules	Ratio(T/R)	Lower	Upper
Cmax	12.85	13.06	98.08	95.22	101.02
AUC0-t	454.23	480.99	94.74	91.47	98.14
AUCinf	524.4	553.56	94.92	90.98	99.02
% CV was high for overall exposure due to the inclusion of data from three individuals who were presumed to be poor metabolizers for CYP2D6 (subjects had T1/2 values of ~100 h vs. 25 h in all others)					

- As shown in the data above, the 90 % confidence intervals for the log-transformed ratio of bioavailability measures (Cmax and AUC) for fluoxetine were well within the 80.00-125.00 % limits suggesting that the new 20 mg tablet formulation is bioequivalent to the currently approved 20 mg pulvule formulation of Sarafem (*BE Data was verified by reviewer using WinNonlin BE wizard, version 5.0.1*).
- **Conclusion:** The new Sarafem 20 mg tablets are bioequivalent to the existing 20 mg Sarafem pulvules, based on the observed relative systemic exposures of the parent drug fluoxetine from these two formulations.

Metabolite Pharmacokinetics: Supportive information

- Fluoxetine undergoes hepatic metabolism into its active metabolite, norfluoxetine. In this pivotal BE study, the sponsor also derived the plasma PK parameters of norfluoxetine that are then subjected to average bioequivalence analysis. The information gained from the sponsor's analysis of the norfluoxetine data is shown below. While BE has been already demonstrated for the two formulations using the parent fluoxetine concentrations, comparable systemic exposures of the active metabolite, (although not necessary for the demonstration of BE for this drug: see explanation below) act as supportive information for bioequivalence of the two products.

- Based on the guidance recommendation, measurement of parent drug and establishment of BE based on the parent exposure in Sarafem test vs. reference formulations is adequate for this pivotal BE study. It is not mandatory to show metabolite BE, as fluoxetine is not a pro-drug, is found in measurable quantities in the systemic circulation and the active metabolite is not formed pre-systemically.
- The metabolite data submitted by the sponsor may therefore be included only as supportive evidence.

3.1.7 What was the outcome from the DSI inspection of the clinical and analytical sites?

At the request of DRUP, the clinical and analytical portions of the bioequivalence study, performed at _____ and _____ respectively, were audited by DSI.

A portion of the DSI inspection report is shown below along with the final recommendation pertaining to the acceptability of the data submitted to the NDA (the complete DSI report can be found by accessing DFS entry by Amalia Himaya signed off on 02/28/2006):

DSI report author: Michael F. Skelly, Ph.D., Division of Scientific Investigations

Following the inspection at _____ there were no objectionable observations and no Form 483 was issued. Following the inspection at _____, Form 483 was issued. The objectionable observations and our evaluation are as follows:

1. Failure to maintain sample integrity during analysis to prevent sample mix-up between subjects. Specifically, samples — #632-643 (Subject 12, Period 1 samples) were switched with samples — #644-655 (Subject 12, Period 2 samples) during the _____ of samples preparation for _____

The suggestion that the listed samples were accidentally exchanged was based on a perceived lack-of-fit of the original results to the expected pharmacokinetic profile. The sponsor requested that the listed samples be reassayed. The singlet reassay results generally supported the hypothesis of accidental exchange. Following the inspection, _____ responded that an amended bioanalytical report will list the Subject 12 samples as NR, Not Reportable. DSI agrees with this resolution.

DSI Conclusion:

DSI recommends that the clinical and analytical data from study PR-10603 are acceptable for review, after excluding the data from Subject #12.

Clinical pharmacology response: Formulation bioequivalence was re-assessed using fluoxetine plasma PK parameters from study PR-10603 1) after removing PK data from Subject # 12 and 2) after reversing the test and reference formulation PK data for Subject 12 so as to match the accidental switching of samples that supposedly occurred during the extraction process. In both cases, the test and reference formulations demonstrated bioequivalence as demonstrated by the 90 % Confidence intervals surrounding the BE criterion that were contained entirely within the 80-125% bounds.

OCPB Conclusion: The office of clinical pharmacology finds the data submitted to NDA 21-860 acceptable.

- 3.1.8 What is the basis of the biowaiver requests made for the two lower strength tablet formulations and can biowaivers be allowed based on the submitted evidence?

According to the agency' guidance for industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products-General Considerations, Waiver of in vivo studies for different strengths of a drug product can be granted under § 320.22(d)(2) when (1) the drug product is in the same dosage form, but in a different strength; (2) this different strength is proportionally similar in its active and inactive ingredients to the strength of the product for which the same manufacturer has conducted an appropriate in vivo study; and (3) the new strength meets an appropriate in vitro dissolution test. This guidance defines proportionally similar in the following ways:

1. All active and inactive ingredients are in exactly the same proportion between different strengths (e.g., a tablet of 50-mg strength has all the inactive ingredients, exactly half that of a tablet of 100-mg strength, and twice that of a tablet of 25-mg strength).
2. Active and inactive ingredients are not in exactly the same proportion between different strengths as stated above, but the ratios of inactive ingredients to total weight of the dosage form are within the limits defined by the SUPAC-IR and SUPAC-MR guidances up to and including Level II.
3. For high potency drug substances, where the amount of the active drug substance in the dosage form is relatively low, the total weight of the dosage form remains nearly the same for all strengths (within + 10 % of the total weight of the strength on which a biostudy was performed), the same inactive ingredients are used for all strengths, and the change in any strength is obtained by altering the amount of the active ingredients and one or more of the inactive ingredients. The changes in the inactive ingredients are within the limits defined by the SUPAC-IR and SUPAC-MR guidances up to and including Level II.

Waiver request for Sarafem 10 mg and 15 mg tablets: Sponsor is requesting waiver for the bioavailability/bioequivalence study requirement for Sarafem 10 mg and 15 mg tablet strengths under 21 CFR 320.22(d)(2). In vitro release comparisons as well as information on formulation proportionality/similarity have been provided in support of this request.

- Bioequivalence of the new tablet formulation has been demonstrated with respect to the reference pulvule formulation using the highest (20 mg) strength of the formulations.
- The composition for the lower strength tablets (10 mg and 15 mg) is proportionally similar to that of the highest strength 20 mg tablets, as shown below:

Table 2. Unit Dose Composition of Sarafem Tablets

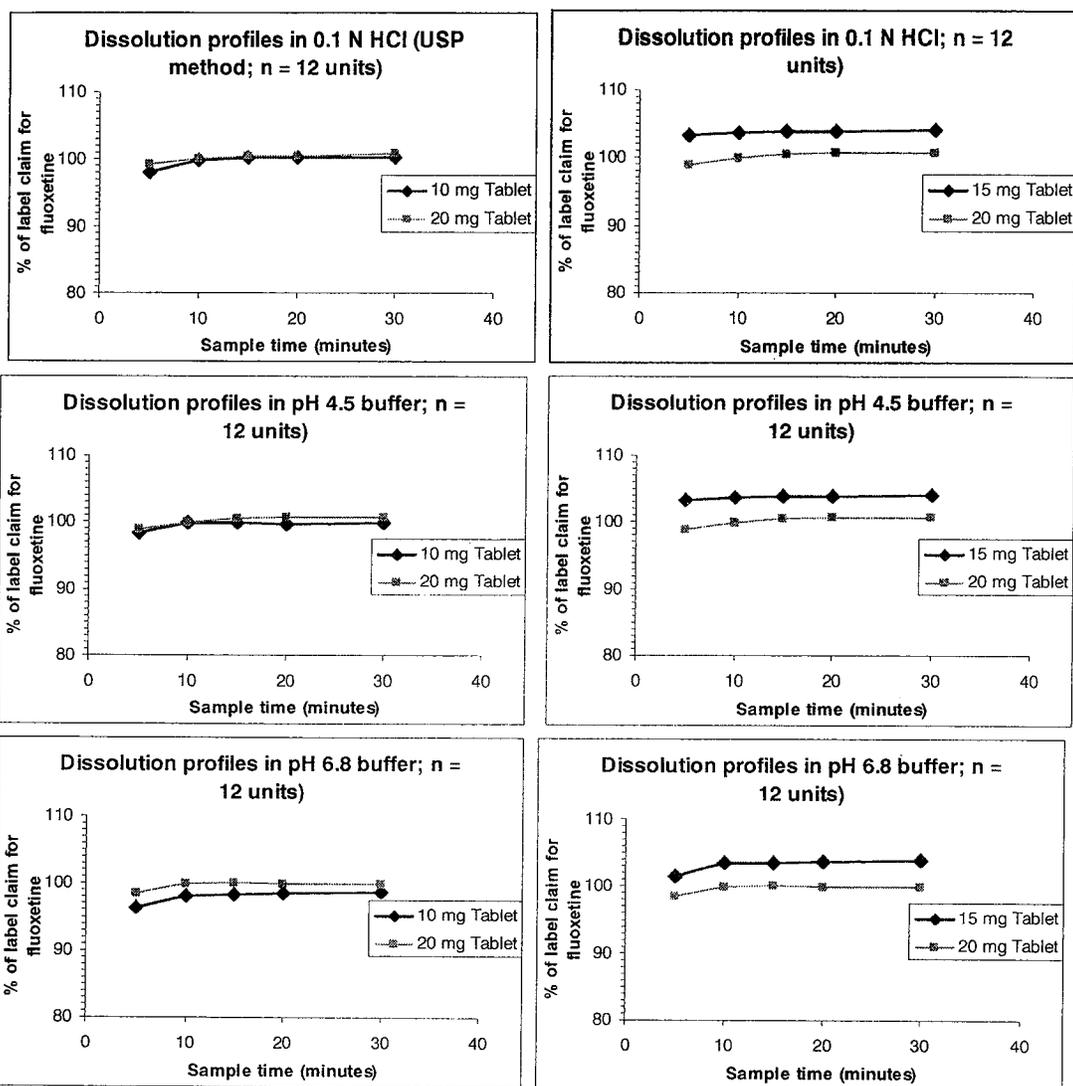
Item No.	Components	Quality Standard Reference	Function	Amount per Tablet (mg)		
				10 mg	15 mg	20 mg
1	Fluoxetine Hydrochloride	USP	Drug	↘		
2	Microcrystalline Cellulose	NF				
3	Croscarmellose Sodium	NF				
4		Non-compendial				
5	Colloidal Silicon Dioxide	NF				
6	Magnesium Stearate	NF				
	Total					

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.

- The new strengths meet an appropriate in vitro dissolution test: In vitro dissolution profile comparisons have been generated for the various tablet strengths as a function of strength and pH of the dissolution media. The following settings for dissolution testing were employed in these studies:
 - Equipment: USP Dissolution Apparatus 1 (Basket)
 - Apparatus speed: 100 rpm
 - Medium volume: 1000 mL
 - Medium Temperature: 37° C ± 0.5° C
 - Sampling times: 5, 10, 15, 20 and 30 minutes
- Dissolution profiles for the 10 mg and 15 mg strengths are identical to the 20 mg Sarafem tablets using an established USP dissolution method for fluoxetine tablets: Not less than — (Q) of the labeled amount of C₁₇H₁₈F₃NO is dissolved in 15 minutes; As all the tablet strengths exhibited rapid dissolution in vitro, with > 90 % of the drug released within the first 5 minutes under all pH conditions, an f2 comparison of the profiles is not necessary. Nevertheless for the USP method, the f2 “similarity” factors for dissolution profile comparisons to the 20 mg tablet were > 50 (96.4 and 94.9, for the 10 mg and 15 mg strengths, respectively) suggesting sufficient similarity between the profiles.



- **Conclusion:** Biowaivers can be allowed for the 10 mg, and 15 mg tablet strengths, based on 1) Establishment of bioequivalence between the highest strength (20 mg) tablet with the reference formulation, 2) proportionally similar composition of all tablet strengths, 2) comparable in vitro dissolution profiles of the tablets employing the USP method and in various pH conditions.

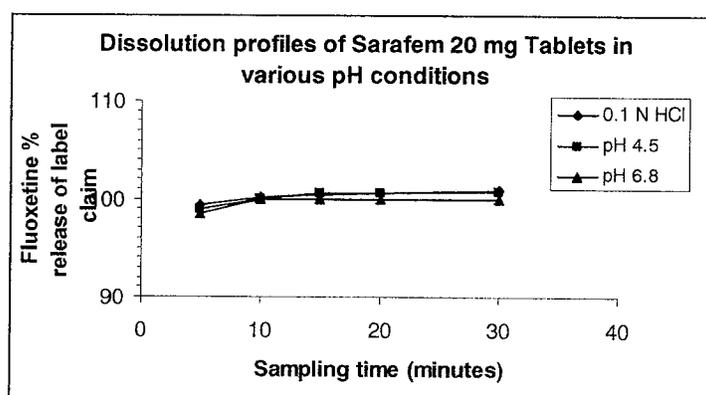
3.1.9 What is the basis for the food-effect study waiver request for the new tablet formulation and can a food-effect waiver be granted based on the submitted evidence?

- Warner-Chilcott is requesting a waiver of the food-effect study requirement for Sarafem tablets, 20 mg. The justifications primarily supporting this waiver request include: 1) comparative dissolution profiles in various pH conditions, 2)

the establishment of in vivo bioequivalence under fasted conditions 3) the outcome of the food-effect study conducted on Sarafem pulvules and the food-effect related labeling language in the currently approved PI.

- Dissolution profiles in various pH media were similar for Sarafem tablets, as shown below:

Average values for amount dissolved (% label claim) by sample time (minutes); mean data from n = 12 tablets.					
Media: 0.1 N HCl (USP method)	5	10	15	20	30
10 mg Tablet	98.1	99.8	100.2	100.3	100.2
15 mg Tablet	100.9	101.6	101.7	101.4	101.5
20 mg Tablet	99.3	100.1	100.4	100.5	100.8
Media: pH 4.5 buffer					
10 mg Tablet	98.2	99.8	99.8	99.7	99.8
15 mg Tablet	103.2	103.6	103.8	103.9	104.1
20 mg Tablet	98.8	99.9	100.5	100.6	100.7
Media: pH 6.8 buffer					
10 mg Tablet	96.3	98	98.3	98.4	98.6
15 mg Tablet	101.4	103.4	103.5	103.6	103.9
20 mg Tablet	98.4	99.9	100	99.9	99.9



- A food-effect study with the pulvule formulation demonstrated that while the rate of absorption of fluoxetine and the time to reach peak plasma concentrations are delayed by food (3.5 h delay in T_{max} on average; Table 2 on page 37, volume 6 of NDA 21-860), there was no difference in the AUCs in the fed and fasted states.
- Current label for Sarafem (fluoxetine) pulvules states the following regarding food-effect: “Food does not appear to affect the systemic bioavailability of fluoxetine, although it may delay its absorption inconsequentially. Thus fluoxetine may be administered with or without food”.
- Although the sponsor claims a BCS class I classification for fluoxetine, the available solubility, permeability and in vivo absorption data that was submitted in support of this claim was not conclusive and therefore cannot be used to definitively conclude the BCS classification of this drug.

- Based on the dissolution comparability in various pH media, the establishment of BE between the proposed tablet and the approved pulvule formulation and the absence of significant food effect with fluoxetine pulvules, food-effect study waiver for the 20 mg tablet strength can be allowed.

3.1.10 Are the clinical vs. to-be-marketed formulations identical?

- The clinical-scale batch formula differs from the commercial-scale batch formula in scale and in one of the color components. For commercial batches the _____ was changed from _____ contains FD&C Yellow No 6 and No 10, not _____. The similarity (f2) factors of dissolution profile comparisons between Sarafem Tablets, 20 mg and 10 mg for clinical and to-be-marketed batches suggest that the dissolution profiles following this change in colorant are comparable as shown below:

Table 2. Dissolution Profile Data for Stability, Clinical, and To-Be-Marketed Formulations of Sarafem Tablets, 20 mg, 15 mg, and 10 mg

Strength	20 mg		15 mg	10 mg	
Batch Number	2517.002 ¹	F-1008-003 ²	2521.001 ³	2516.001 ⁴	F-1008-001 ⁵
Formulation Purpose	Clinical / Stability	Stability / To-Be-Marketed	Stability	Stability	Stability / To-Be-Marketed
Intervals	Mean (n=12) Amount Dissolved (%Label Claim) by Sample Time				
5 min	98.1	100.1	100.9	98.9	102.9
10 min	98.6	100.3	101.6	100.8	104.9
15 min	98.9	100.7	101.7	101.3	104.5
20 min	99.0	100.9	101.4	101.4	103.3
30 min	99.5	100.9	101.5	101.4	103.3
Similarity Factor (f2)	84.57		N/A	73.91	

The dissolution test method is the USP dissolution method for fluoxetine hydrochloride tablets.

Data references: [Redacted]

3.2 Analytical

- A _____ method for fluoxetine and norfluoxetine has been validated for the concentration range of 1.00 to 500 ng/ml in human plasma.
- Method summary: 2.0 mL of 0.1 M potassium phosphate buffer (pH 6.0) and 50 µl of a 2.00 µg/mL internal standard solution are added to 1.0 mL of human plasma. The samples are then loaded _____

A 40 µL aliquot was analyzed by _____ The method has been demonstrated to be precise, accurate and sufficiently robust for analysis of clinical samples:

- Specificity: No significant interfering peaks due to endogenous compounds or reagents were observed.
- Intra-Day Precision and Accuracy: Precision (% RSD) of 1.83 to 8.3 % and accuracy (% RE) between -9.25 to -2.72 % were obtained for Fluoxetine. Precision of 2.53 to 8.49 % and accuracy (% RE) between -6.5 and 5.9 % were obtained for Norfluoxetine.
- Inter-Day Precision and Accuracy: Precision (% RSD) of 4.38-5.75 % and accuracy (% RE) between -6.64 and -5.23 % were obtained for Fluoxetine. Precision of 4.91 to 7.68 % and accuracy (% RE) between -0.31 and 3.17 % were obtained for Norfluoxetine.
- Limits of quantitation: The lower and upper limits of quantitation for both Fluoxetine and Norfluoxetine were 1.00 and 500 ng/ml, respectively.
- Extraction efficiency: Ratios of the peak area of processed samples to the mean peak area of five unprocessed analytical solutions provided an overall recovery ranging from 80.25 to 114.58 % for fluoxetine and 71.7 to 102.82 % for Norfluoxetine.
- Freeze/Thaw: The samples were found to be stable for three cycles of freeze/thaw at -20°C and room temperature, respectively. The accuracy of the freeze/thaw samples for these cycles ranged from -7.4 to -1.3 % for fluoxetine and -8.8 to 6.89 % for norfluoxetine.

4 Labeling

The labeling of the currently approved pulvule formulation has been modified only with the following PK information generated from the pivotal BE study;

Recommended Labeling changes to the clinical pharmacology section are shown as:

- 1) Strikethroughs for ~~deletions~~
- 2) Highlighted and underlined for additions.
- 3) Italicized and strikethrough for content that has been *~~moved to~~* another portion of the label.
- 4) Italicized and underlined for content that has been *moved from* another portion of the label.
- 5) Bold, italicized and underlined for ***Note to the sponsors***.

CLINICAL PHARMACOLOGY

Pharmacodynamics

The mechanism of action of fluoxetine in premenstrual dysphoric disorder (PMDD) is unknown, but is presumed to be linked to its inhibition of CNS neuronal uptake of serotonin. Studies at clinically relevant doses in humans have demonstrated that fluoxetine blocks the uptake of serotonin into human platelets. Studies in animals also suggest that fluoxetine is a much more potent uptake inhibitor of serotonin than of norepinephrine.

3 Page(s) Withheld

 Trade Secret / Confidential

✓ Draft Labeling

 Deliberative Process

Withheld Track Number: Clin Pharm/Bio- 1

Renal disease — In depressed patients on dialysis (N=12), fluoxetine administered as 20 mg once daily for 2 months produced steady-state fluoxetine and norfluoxetine plasma concentrations comparable with those seen in patients with normal renal function. While the possibility exists that renally excreted metabolites of fluoxetine may accumulate to higher levels in patients with severe renal dysfunction, use of a lower or less frequent dose is not routinely necessary in renally impaired patients (*see Use in Patients with Concomitant Illness under PRECAUTIONS and DOSAGE AND ADMINISTRATION*).

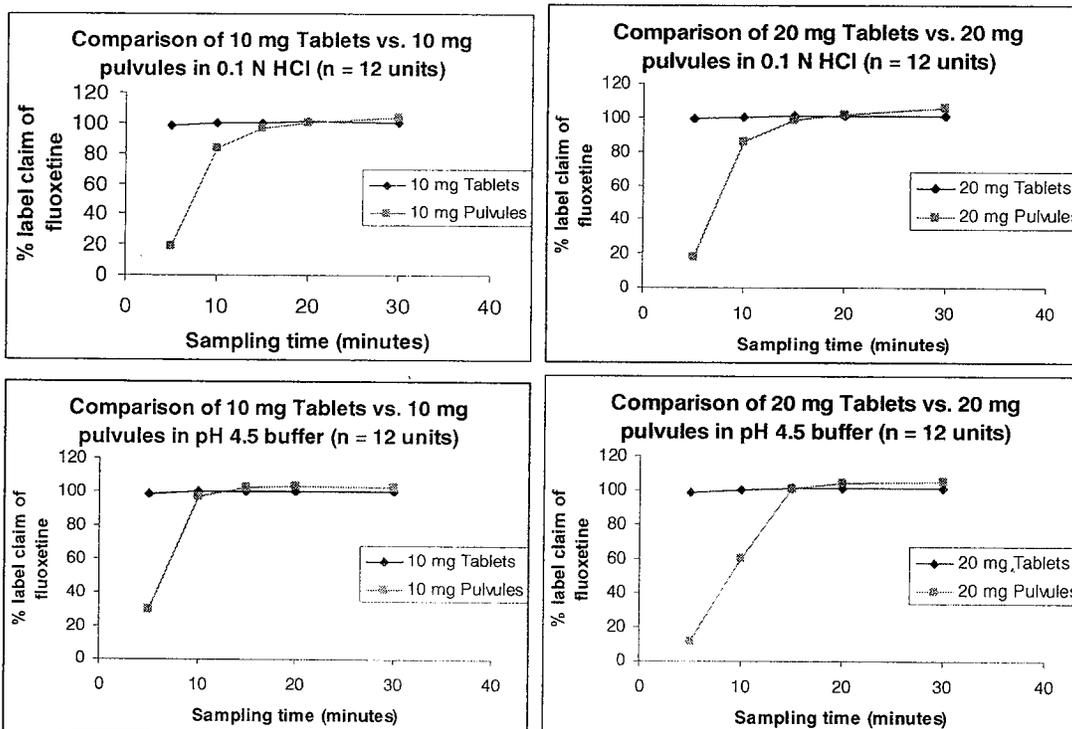
Pediatrics: *Safety and effectiveness in the pediatric population have not been established (see BOX WARNING and WARNINGS, Clinical Worsening and Suicide Risk, Pediatric use).*

Geriatrics: *The diagnosis of PMDD is not applicable to postmenopausal women.*

5 Appendix

Dissolution profile comparisons as a function of dosage form:

- The dissolution behavior as a function of dosage form was also investigated, by comparing in vitro drug release from fluoxetine HCl tablets, 10 mg and 20 mg vs. Sarafem (fluoxetine HCl) pulvules:



- In vitro, the release of drug was complete within the first 5 minutes for the tablets vs. within 10-20 minutes for the reference (pulvule) formulation. These differences in the initial release rates resulted in f_2 values < 50 , when all time points were included. The release however, was identical for both dosage forms at all strengths and pH conditions with f_2 values greater than 75, when the first one or two time points were removed from the comparison. [The sponsor has submitted a table containing the calculated f_2 values (page 57 of volume 6) and has apparently excluded the 5 and/or 10 minute time points thereby resulting in f_2 values greater than 50].

- These differences in the initial release rate between the proposed tablets and reference capsules should not have a meaningful consequence based on the fact that the in vivo study demonstrated bioequivalence (with respect to both rate and extent of systemic bioavailability) between the test and reference formulations.

Non-compartmental plasma fluoxetine pharmacokinetic parameters and descriptive statistics for the reference treatment (Sarafem Pulvules) are shown for all patients who completed the study:

Subjects	Lambda_z	HL_Lambda_z	Tmax	Cmax	AUClast	AUCall	AUCINF_obs
1	0.0377	18.4084	7	11.4	245.77	268.21	295.433
2	0.0314	22.0412	9	7.25	181.04	202.76	238.5958
3	0.0374	18.5521	4	13.5	275.135	299.615	329.7358
4	0.0362	19.1583	6	13.1	370.96	384.76	402.7456
5	0.0277	25.0011	7	16.4	523.21	538.21	568.2963
6	0.0195	35.5545	9	11.9	488.78	502.1	545.7167
7	0.0286	24.2191	6	14.5	466.82	479.06	502.4596
8	0.0265	26.2053	10	14.1	507.18	522.66	555.9501
9	0.0429	16.1616	8	8.18	185.185	203.305	220.3925
10	0.0187	37.0545	8	19.9	826.81	840.25	886.6833
11	0.0363	19.0738	6	14.1	380.61	395.49	414.732
12	0.0273	25.3698	9	12.7	366.545	388.745	434.2565
13	0.0248	27.9979	6	13.6	425.355	437.955	467.7671
14	0.0289	24.0228	8	11.6	340.65	360.33	397.4884
15	0.0218	31.8612	7	12.9	455.92	471.04	513.8371
16	0.0261	26.5581	8	12.7	463.56	477.48	508.0058
17	0.0026	268.2499	11	18.4	4168.72	4168.72	5082.047
18	0.0231	29.9789	7	17.4	607.26	628.86	685.1107
19	0.0278	24.9034	8	10.7	318.445	336.445	372.337
21	0.039	17.7727	9	12.5	270.75	312.87	360.7487
22	0.0203	34.0889	8	12.8	417.58	433.18	481.5138
23	0.0066	104.2828	11	13.8	1688.71	1756.39	1900.842
24	0.0031	225.9107	10	17.3	3736.82	3736.82	4245.256
26	0.0357	19.4205	3	10.6	227.295	248.655	277.1668
Arithmetic Mean	0.02625	46.74365	7.708333	13.38875	747.4629	766.4129	861.9632
Geometric Mean	0.0222	31.23705	7.420555	13.0629	480.9924	505.4019	553.9698
Harmonic Mean	0.014872	26.4083	7.06362	12.71776	387.2819	413.091	452.9956
Median	0.0275	25.18	8	13	421.46	435.56	474.64
Standard dev	0.010795	64.34	1.966	2.96	1033.47	1030.14	1222.42
% CV	41.125	137.65*	25.51	22.1	138.22*	134.41*	141.81*

* indicates parameters showing high % CV due to the inclusion of 3 individuals demonstrating higher exposure and longer T1/2 due to CYP2D6 PM phenotype.

Non-compartmental plasma fluoxetine pharmacokinetic parameters and the descriptive statistics for the test treatment (Sarafem Tablets) are shown below for all patients who completed the study:

Subjects	Lambda_z	HL_Lambda_z	Tmax	Cmax	AUClast	AUCall	AUCINF_obs
1	0.036	19.2368	8	11.9	263.485	290.845	326.7613
2	0.056	12.3769	6	8.79	147.845	158.765	180.3431

3	0.0416	16.6602	6	11.7	279.54	301.5	323.5251
4	0.0331	20.948	7	15.3	355.355	369.755	391.621
5	0.0261	26.5581	6	15.9	471.35	484.31	512.7305
6	0.022	31.4445	9	10.8	414.89	430.61	474.3178
7	0.035	19.7834	8	14	374.37	388.77	408.6196
8	0.0253	27.3522	8	13.2	424.845	437.325	465.8843
9	0.0423	16.3796	8	8.66	177.59	193.55	209.0189
10	0.0197	35.2545	9	18.5	807.76	829.24	898.8022
11	0.0382	18.1676	4	14.8	315.38	344.06	378.0225
12	0.0225	30.8709	8	12.2	416.925	430.485	467.2522
13	0.0233	29.7484	4	14.5	420.83	432.83	463.7479
14	0.0233	29.7267	8	10.5	386.84	400.28	434.873
15	0.0187	37.0389	9	12.8	500.935	513.895	558.6457
16	0.0182	38.1408	9	12	444.905	482.705	618.2356
17	0.0022	310.0366	8	18.9	3992.89	3992.89	4985.87
18	0.0247	28.1148	7	17.7	602.54	621.14	665.4096
19	0.0305	22.715	7	10.2	305.29	320.65	347.2367
21	0.0444	15.6085	5	11	227.72	247.88	265.5506
22	0.0264	26.2817	9	10.7	336.61	358.33	405.2388
23	0.0059	117.5157	9	13.7	1699.37	1773.29	1960.461
24	0.0033	209.288	10	15.8	3466.74	3466.74	3913.609
26	0.0457	15.1526	2	11.9	217.95	233.43	246.1502
Arithmetic mean	0.027683	48.10002	7.25	13.14375	710.4981	729.3031	829.2469
Geometric mean	0.022623	30.6156	6.892441	12.85648	454.2395	476.6374	524.403
Harmonic mean	0.01434	25.03533	6.365646	12.57759	362.7366	384.7847	420.3684
Median	0.0257	26.95	8	12.5	400.86	415.38	449.31
Standard deviation	0.0134	69.82	1.96	2.84	981.26	979.06	1178.61
% CV	48.53	145.16*	27.05	21.6	138.11	134.24	142.13

* indicates parameters showing high % CV due to the inclusion of 3 individuals demonstrating higher exposure and longer T1/2 due to CYP2D6 PM phenotype.

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Table 8. Plasma Norfluoxetine Pharmacokinetic Values Following Administration of Sarafem Tablets, 20 mg to Healthy Female Volunteers; PR-10603.1

Subject	C _{max} (ng/mL)	T _{max} (h)	AUC(0-t _{lde}) (ng/mL·h)	AUCinf (ng/mL·h)	k _{el} (1/h)	t _{1/2} (h)
01	11.8	36.0	1684.6	1886.0	0.0104	66.79
02	8.1	48.0	1284.0	1445.0	0.0096	72.43
03	14.7	36.0	2425.6	2546.9	0.0086	80.82
04	12.5	72.0	2934.0	3155.8	0.0072	96.06
05	7.6	36.0	1172.8	1289.9	0.0103	67.08
06	9.1	72.0	2747.4	3178.8	0.0042	164.29
07	15.5	36.0	3220.3	3871.0	0.0043	162.25
08	8.6	48.0	1852.8	1991.6	0.0074	93.37
09	12.3	11.0	1677.8	1825.0	0.0103	67.59
10	9.8	48.0	1931.8	2179.4	0.0073	94.81
11	12.6	36.0	2790.4	3038.9	0.0062	111.09
12	10.7	36.0	3658.0	4110.6	0.0036	193.66
13	10.9	36.1	2461.9	2732.7	0.0063	109.75
14	7.0	36.0	1678.3	2023.1	0.0044	157.23
15	10.3	36.1	3708.3	4756.9	0.0023	307.98
16	10.8	120.0	2830.8	3139.8	0.0048	144.74
17	2.3	144.0	963.8	-- ^a	-- ^a	-- ^a
18	9.4	72.1	2400.8	2644.7	0.0062	111.18
19	10.2	48.0	2881.6	3342.4	0.0040	172.64
21	13.2	36.0	3004.7	3217.9	0.0054	127.39
22	9.8	48.0	2214.7	2399.4	0.0064	107.60
23	2.4	120.0	571.4	823.0	0.0041	169.32
24	2.0	96.0	522.1	823.8	0.0034	203.03
26	11.3	36.1	1669.7	1850.1	0.0100	69.08
N	24	24	24	23	23	23
Mean	9.7	56.0	2178.7	2533.6	0.0064	128.27
Standard	3.54	32.99	895.95	1011.03	0.00251	58.071
%CV	36.47	58.95	41.12	39.91	39.32	45.27
Median	10.3	42.0	2307.8	2546.9	0.0062	111.09
Minimum	2.0	11.0	522.1	823.0	0.0023	66.79
Maximum	15.5	144.0	3708.3	4756.9	0.0104	307.98
Geometric Mean	8.7	--	1952.2	2315.3	--	--
Harmonic Mean	--	--	--	--	--	108.59

^a Parameter not determined as concentration versus time curve did not exhibit a terminal log-linear phase
Source data: CR-11804.0; Archived at Warner Chilcott

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Table 9. Plasma Norfluoxetine Pharmacokinetic Values Following Administration of Sarafem Pulvules, 20 mg to Healthy Female Volunteers; PR-10603.1

Subject	Cmax (ng/mL)	Tmax (h)	AUC(0-t _{lde}) (ng/mL·h)	AUCinf (ng/mL·h)	kel (1/h)	t _{1/2} (h)
01	11.6	36.0	1708.5	2015.3	0.0073	94.51
02	8.7	36.0	1343.3	1596.8	0.0075	92.51
03	14.5	36.0	2371.1	2706.5	0.0068	102.39
04	14.4	36.0	2925.2	3128.8	0.0072	95.99
05	7.5	36.0	1120.4	1237.4	0.0102	67.63
06	9.1	120.0	3004.4	3340.3	0.0034	202.50
07	13.9	36.0	3498.1	3776.0	0.0053	131.97
08	9.4	36.0	2053.0	2265.9	0.0061	114.43
09	12.6	36.0	1660.6	1804.1	0.0109	63.76
10	9.5	72.0	1963.7	2246.9	0.0070	99.13
11	13.4	36.0	2786.1	3075.6	0.0059	117.34
12	10.5	72.0	3659.7	3943.7	0.0047	148.02
13	10.9	36.0	2576.0	2793.3	0.0068	101.74
14	7.4	36.0	1563.1	1769.8	0.0054	127.94
15	10.2	72.0	3542.0	3878.3	0.0043	163.01
16	10.3	48.0	2937.3	3272.6	0.0048	145.25
17	2.9	168.0	1306.6	1840.7	0.0019	356.01
18	10.5	72.0	2553.7	2830.7	0.0058	119.25
19	11.0	48.0	3552.7	3784.9	0.0047	146.32
21	16.6	48.0	3223.6	3491.0	0.0050	139.37
22	9.4	72.0	2076.5	2226.1	0.0068	102.63
23	2.8	96.0	550.9	1190.5	0.0025	277.10
24	2.1	96.0	650.5	1088.3	0.0023	303.48
26	12.8	36.2	1750.9	1919.0	0.0105	65.85
N	24	24	24	24	24	24
Mean	10.1	59.0	2265.7	2550.9	0.0060	140.76
Standard	3.68	33.55	927.76	903.77	0.00237	74.396
%CV	36.47	56.85	40.95	35.43	39.82	52.86
Median	10.4	42.1	2223.8	2486.2	0.0059	118.30
Minimum	2.1	36.0	550.9	1088.3	0.0019	63.76
Maximum	16.6	168.0	3659.7	3943.7	0.0109	356.01
Geometric Mean	9.1	--	2039.0	2383.7	--	--
Harmonic Mean	--	--	--	--	--	116.30

Source data: CR-11804.0; Archived at Warner Chilcott

Individual subject data used for BE analysis:

Fluoxetine data:						
Subject	Period	Sequence	Treatment	Cmax	AUCt	AUCinf
1	1	RT	R	11.4	245.77	295.433
2	2	TR	R	7.25	181.04	238.5958
3	1	RT	R	13.5	275.135	329.7358
4	2	TR	R	13.1	370.96	402.7456
5	1	RT	R	16.4	523.21	568.2963
6	2	TR	R	11.9	488.78	545.7167
7	2	TR	R	14.5	466.82	502.4596
8	1	RT	R	14.1	507.18	555.9501
9	2	TR	R	8.18	185.185	220.3925
10	1	RT	R	19.9	826.81	886.6833
11	2	TR	R	14.1	380.61	414.732

12	1	RT	R	12.7	366.545	434.2565
13	2	TR	R	13.6	425.355	467.7671
14	1	RT	R	11.6	340.65	397.4884
15	1	RT	R	12.9	455.92	513.8371
16	2	TR	R	12.7	463.56	508.0058
17	2	TR	R	18.4	4168.72	5082.047
18	1	RT	R	17.4	607.26	685.1107
19	2	TR	R	10.7	318.445	372.337
21	2	TR	R	12.5	270.75	360.7487
22	1	RT	R	12.8	417.58	481.5138
23	2	TR	R	13.8	1688.71	1900.842
24	1	RT	R	17.3	3736.82	4245.256
26	2	TR	R	10.6	227.295	277.1668
1	2	RT	T	11.9	263.485	326.7613
2	1	TR	T	8.79	147.845	180.3431
3	2	RT	T	11.7	279.54	323.5251
4	1	TR	T	15.3	355.355	391.621
5	2	RT	T	15.9	471.35	512.7305
6	1	TR	T	10.8	414.89	474.3178
7	1	TR	T	14	374.37	408.6196
8	2	RT	T	13.2	424.845	465.8843
9	1	TR	T	8.66	177.59	209.0189
10	2	RT	T	18.5	807.76	898.8022
11	1	TR	T	14.8	315.38	378.0225
12	2	RT	T	12.2	416.925	467.2522
13	1	TR	T	14.5	420.83	463.7479
14	2	RT	T	10.5	386.84	434.873
15	2	RT	T	12.8	500.935	558.6457
16	1	TR	T	12	444.905	618.2356
17	1	TR	T	18.9	3992.89	4985.87
18	2	RT	T	17.7	602.54	665.4096
19	1	TR	T	10.2	305.29	347.2367
21	1	TR	T	11	227.72	265.5506
22	2	RT	T	10.7	336.61	405.2388
23	1	TR	T	13.7	1699.37	1960.461
24	2	RT	T	15.8	3466.74	3913.609
26	1	TR	T	11.9	217.95	246.1502

	Subject	Sequence	R	T	Test-Ref	Ratio{%Ref}
Log10(Cmax)	1	RT	11.4	11.9	0.5	104.39
Log10(Cmax)	2	TR	7.25	8.79	1.54	121.24
Log10(Cmax)	3	RT	13.5	11.7	-1.8	86.67
Log10(Cmax)	4	TR	13.1	15.3	2.2	116.79
Log10(Cmax)	5	RT	16.4	15.9	-0.5	96.95
Log10(Cmax)	6	TR	11.9	10.8	-1.1	90.76
Log10(Cmax)	7	TR	14.5	14	-0.5	96.55
Log10(Cmax)	8	RT	14.1	13.2	-0.9	93.62

Log10(Cmax)	9	TR	8.18	8.66	0.48	105.87
Log10(Cmax)	10	RT	19.9	18.5	-1.4	92.96
Log10(Cmax)	11	TR	14.1	14.8	0.7	104.96
Log10(Cmax)	12	RT	12.7	12.2	-0.5	96.06
Log10(Cmax)	13	TR	13.6	14.5	0.9	106.62
Log10(Cmax)	14	RT	11.6	10.5	-1.1	90.52
Log10(Cmax)	15	RT	12.9	12.8	-0.1	99.22
Log10(Cmax)	16	TR	12.7	12	-0.7	94.49
Log10(Cmax)	17	TR	18.4	18.9	0.5	102.72
Log10(Cmax)	18	RT	17.4	17.7	0.3	101.72
Log10(Cmax)	19	TR	10.7	10.2	-0.5	95.33
Log10(Cmax)	21	TR	12.5	11	-1.5	88
Log10(Cmax)	22	RT	12.8	10.7	-2.1	83.59
Log10(Cmax)	23	TR	13.8	13.7	-0.1	99.28
Log10(Cmax)	24	RT	17.3	15.8	-1.5	91.33
Log10(Cmax)	26	TR	10.6	11.9	1.3	112.26
AUCt						
Log10(AUCt)	1	RT	245.77	263.485	17.715	107.21
Log10(AUCt)	2	TR	181.04	147.845	-33.195	81.66
Log10(AUCt)	3	RT	275.135	279.54	4.405	101.6
Log10(AUCt)	4	TR	370.96	355.355	-15.605	95.79
Log10(AUCt)	5	RT	523.21	471.35	-51.86	90.09
Log10(AUCt)	6	TR	488.78	414.89	-73.89	84.88
Log10(AUCt)	7	TR	466.82	374.37	-92.45	80.2
Log10(AUCt)	8	RT	507.18	424.845	-82.335	83.77
Log10(AUCt)	9	TR	185.185	177.59	-7.595	95.9
Log10(AUCt)	10	RT	826.81	807.76	-19.05	97.7
Log10(AUCt)	11	TR	380.61	315.38	-65.23	82.86
Log10(AUCt)	12	RT	366.545	416.925	50.38	113.74
Log10(AUCt)	13	TR	425.355	420.83	-4.525	98.94
Log10(AUCt)	14	RT	340.65	386.84	46.19	113.56
Log10(AUCt)	15	RT	455.92	500.935	45.015	109.87
Log10(AUCt)	16	TR	463.56	444.905	-18.655	95.98
Log10(AUCt)	17	TR	4168.72	3992.89	-175.83	95.78
Log10(AUCt)	18	RT	607.26	602.54	-4.72	99.22
Log10(AUCt)	19	TR	318.445	305.29	-13.155	95.87
Log10(AUCt)	21	TR	270.75	227.72	-43.03	84.11
Log10(AUCt)	22	RT	417.58	336.61	-80.97	80.61
Log10(AUCt)	23	TR	1688.71	1699.37	10.66	100.63
Log10(AUCt)	24	RT	3736.82	3466.74	-270.08	92.77
Log10(AUCt)	26	TR	227.295	217.95	-9.345	95.89
AUCinf						
Log10(AUCinf)	1	RT	295.433	326.7613	31.3283	110.6
Log10(AUCinf)	2	TR	238.5958	180.3431	-58.2527	75.59
Log10(AUCinf)	3	RT	329.7358	323.5251	-6.2107	98.12

Log10(AUCinf)	4	TR	402.7456	391.621	-11.1246	97.24
Log10(AUCinf)	5	RT	568.2963	512.7305	-55.5658	90.22
Log10(AUCinf)	6	TR	545.7167	474.3178	-71.3989	86.92
Log10(AUCinf)	7	TR	502.4596	408.6196	-93.84	81.32
Log10(AUCinf)	8	RT	555.9501	465.8843	-90.0658	83.8
Log10(AUCinf)	9	TR	220.3925	209.0189	-11.3736	94.84
Log10(AUCinf)	10	RT	886.6833	898.8022	12.1189	101.37
Log10(AUCinf)	11	TR	414.732	378.0225	-36.7095	91.15
Log10(AUCinf)	12	RT	434.2565	467.2522	32.9957	107.6
Log10(AUCinf)	13	TR	467.7671	463.7479	-4.0192	99.14
Log10(AUCinf)	14	RT	397.4884	434.873	37.3846	109.41
Log10(AUCinf)	15	RT	513.8371	558.6457	44.8086	108.72
Log10(AUCinf)	16	TR	508.0058	618.2356	110.2298	121.7
Log10(AUCinf)	17	TR	5082.047	4985.87	-96.1764	98.11
Log10(AUCinf)	18	RT	685.1107	665.4096	-19.7011	97.12
Log10(AUCinf)	19	TR	372.337	347.2367	-25.1003	93.26
Log10(AUCinf)	21	TR	360.7487	265.5506	-95.1981	73.61
Log10(AUCinf)	22	RT	481.5138	405.2388	-76.275	84.16
Log10(AUCinf)	23	TR	1900.842	1960.461	59.6184	103.14
Log10(AUCinf)	24	RT	4245.256	3913.609	-331.646	92.19
Log10(AUCinf)	26	TR	277.1668	246.1502	-31.0166	88.81

BE analysis results for Fluoxetine (parent) bioavailability:

Dependent	Log10(Cmax)	Log10(AUCt)	Log10(AUCinf)
Units			
FormVar	Treatment	Treatment	Treatment
FormRef	R	R	R
RefLSM	1.1191	2.6849	2.7459
RefLSM_SE	0.0193	0.073	0.0725
RefGeoLSM	3.0811	19468.6368	24373.6483
Test	T	T	T
TestLSM	1.1107	2.6615	2.7233
TestLSM_SE	0.0193	0.073	0.0725
TestGeoLSM	2.857	17833.5128	22435.5051
Difference	-0.0084	-0.0235	-0.0227
Diff_SE	0.0075	0.0089	0.0107
Diff_DF	22	22	22
Ratio[%Ref]	98.08	94.74	94.92
CI_80_Lower	95.87	92.21	91.87
CI_80_Upper	100.34	97.34	98.06
WL_80_Lower	96.62	93.09	92.93
WL_80_Upper	103.38	106.91	107.07
CI_90_Lower	95.22	91.47	90.98
CI_90_Upper	101.02	98.14	99.02
WL_90_Lower	95.86	92.21	91.87
WL_90_Upper	104.14	107.79	108.13
CI_95_Lower	94.64	90.8	90.18

CI_95_Upper	101.65	98.86	99.9
WL_95_Lower	95.21	91.47	90.98
WL_95_Upper	104.79	108.53	109.02
Prob<80.00	0	0	0
Prob>125.00	0	0	0
MaxProb	0	0	0
TotalProb	0	0	0
Ahpval	0	0	0
Power	1	1	1

(Note: DSI inspection of the bioanalytical site had revealed that the test and reference samples for subject # 12 were reversed during extraction. DSI recommended that the NDA data should be acceptable after removing data from Subject # 12 from the final BE analysis. OCPB has conducted BE analysis without data from Subject 12 as well as with Subject 12 test and reference PK data reversed (to match the reversal that occurred during the analysis) and found that in all scenarios the two formulations exhibited bioequivalence).

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/s/

Sandhya Apparaju
3/1/2006 05:13:38 PM
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Ameeta Parekh
3/2/2006 01:46:07 PM
BIOPHARMACEUTICS
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Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission			
	Information		Information
NDA Number	21-860	Brand Name	Sarafem
OCPB Division (I, II, III)	DPE II	Generic Name	Fluoxetine Hydrochloride
Medical Division	DRUDP	Drug Class	Selective serotonin reuptake inhibitor (SSRI)
OCPB Reviewer	Sandhya Apparaju, Ph.D.	Indication	Premenstrual dysphoric disorder (PMDD)
OCPB Team Leader	Ameeta Parekh, Ph.D.	Dosage Form	Tablets
		Dosing Regimen	20 mg/day given on a continuous or intermittent regimen.
Date of Submission	05/20/2005	Route of Administration	Oral
Estimated Due Date of OCPB Review	01/15/2006	Sponsor	Warner-Chilcott
PDUFA Due Date	03/20/2006	Priority Classification	Standard
Division Due Date	02/28/2006		

Clinical Pharmacology and Biopharmaceutics Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
<i>Healthy Volunteers-</i>				
single dose:				
multiple dose:				
<i>Patients-</i>				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				

PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single dose:	X	1		20 mg tablets vs. 20 mg pulvules
replicate design; single / multi dose:				
Food-drug interaction studies:	X	Waiver request		Food-effect waiver request
Dissolution:	X	3		Includes comparisons of dissolution profiles as a function of tablet strength, formulation and pH.
(IVIVC):				
Bio-waiver request based on BCS	X	Waiver request		Biowaiver for lower strengths based on in vivo BE study of higher strength, comparable dissolution profiles & BCS class I status etc
BCS class	X	Justification provided		Justification provided to support BCS class I
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		4		

Filability comments:

- Release comparisons of the clinical vs. TBM formulations are needed due to a change in the colorant employed; this however is not a filing issue.
- Pharmacokinetic data generated using the new tablet dosage form in Study PR-10603 should be included in the proposed labeling and the updated labeling should be submitted for review.
- A DSI inspection of the following study site will be requested:


- Other: BE study results are presented in SAS transport file format; Biowaiver and food-effect waiver requests are included along with requested justification including dissolution comparisons as a function of dosage form, strength and pH of the media.

	"X" if yes	Comments
Application filable ?	X	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?	X	Comments have been sent to firm (or attachment included). FDA letter date if applicable. <ul style="list-style-type: none"> Dissolution profile comparisons of the clinical vs. TBM formulations are needed due to a change in the colorant employed. This will be a review issue. 
QBR questions (key issues to be considered)		
Other comments or information not included above		
Primary reviewer Signature and Date	Sandhya Apparaju, 07/05/05	
Secondary reviewer Signature and Date	Ameeta Parekh, 07/05/05	

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Clinical Pharmacology and Biopharmaceutics Review

NDA: 21860
Compound: Sarafem tablets (Fluoxetine Hydrochloride)
Sponsor: Warner Chilcott

Date: 07/05/05
Reviewer: Sandhya Apparaju

Background:

- Sarafem (fluoxetine hydrochloride pulvules) was originally developed and marketed by Eli Lilly as both continuous as well as intermittent regimens for the treatment of premenstrual dysphoric disorder (PMDD). Warner Chilcott (WC) has obtained the rights from Eli Lilly for the manufacture, marketing as well as trade name of Sarafem.
- In this NDA, WC has requested approval of a new 'tablet' dosage form of Sarafem at 10 & 20 mg as well as new 15 mg strength. The proposed dose of Sarafem is 20 mg/day given either continuously (every day of the menstrual cycle) or intermittently (for 14 days prior to the onset of menstruation, through the first full day of menstruation, repeating each cycle). The new 15 mg tablet was developed to allow prescribers the option of an intermediate dose.
- The sponsor has submitted results from a single dose in vivo BE study comparing the new 20 mg tablets to the existing 20 mg pulvules, comparative dissolution profiles and other forms of justification to support biowaivers of lower strengths and food-effect study waiver. In addition, Lilly has granted permission to Warner Chilcott for cross referring supplements 058 & 067 of their original NDA 18-936 and this information is included in the NDA.
- DRUDP had three previous communications with the sponsor during the pre-IND, IND as well as pre-NDA stages. Clinical pharmacology & HPBio issues were discussed/reviewed and comments were conveyed to the sponsor as captured in the DFS reviews dated 02/18/04, 05/10/2004, 11/29/2004 for IND 68098; Primary reviewer: Sandhya Apparaju).
- The submitted NDA 21-860 (Sarafem Tablets for PMDD) contains the following in the human pharmacokinetics, bioavailability & clinical pharmacology section:
 - Drug formulation information; Clinical versus to-be-marketed formulations
 - Bioequivalence study report comparing 20 mg tablets vs. 20 mg pulvules
 - In vitro methodology, conditions and study results of the dissolution profiles of various dose strengths of tablets as well as tablets versus capsules in various pH conditions.
 - Biowaiver requests for the lower strength (10 & 15 mg) tablets
 - Waiver request for a food-effect study for the tablets and supporting justification
 - Bioanalytical methods
 - Summary of Human pharmacokinetic & bioavailability studies from earlier NDA
 - Summary of available fluoxetine ADME information
 - Proposed changes to the existing product label
 - References

- The clinical versus to-be-marketed formulations appear identical except for a colorant _____ instead of _____. Comparative dissolution profiles are not provided for the clinical vs. TBM formulations and may be needed in order to verify that the change in colorant does not alter the release characteristics.
- BE study results obtained from n = 24 individuals, suggests that the 20 mg Sarafem tablets are bioequivalent to the 20 mg Sarafem pulvules. The 90 % CI for the treatment ratios of C_{max} and AUC were within the 80-125 % no effect boundary (pending review). Fluoxetine and norfluoxetine concentrations as well as PK parameters associated with the test and reference formulations are provided for each subject in the NDA.
- Biowaivers for the lower tablet strengths (10 mg and 15 mg) are supported by dissolution profiles that are tested using the f1 criteria (difference factor) and f2 criteria (similarity factor). In addition, the dissolution of 20 mg tablets was compared against the 20 mg pulvule formulation in various dissolution media: 0.1 N HCl, pH 4.5 buffer & water. All results indicate comparable dissolution profiles, with a f1 < 15 and f2 > 50.
- Food study waiver request is supported by dissolution studies conducted on the three proposed strengths of tablets in three different pH conditions (0.1N HCl, pH 4.5 and 6.8); tablet dissolution was almost complete within the first 15 minutes and dissolution profiles were similar in all three pH conditions.
- Justification is also presented for supporting the BCS class I status (based on high solubility, high permeability and rapid dissolution) for fluoxetine, in order to support the food-effect waiver request.
- A request for the inspection of the study site (see filability comments) will be made to DSI.

Recommendation:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II find that the Human Pharmacokinetics and Bioavailability section for NDA 21-860 is fileable.

Sandhya Apparaju, Ph.D., Primary reviewer Date 07/05/2005

Ameeta Parekh, Ph.D., Team Leader Date 07/05/2005

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/s/

Sandhya Apparaju
7/19/05 12:44:59 PM
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Ameeta Parekh
7/28/05 03:17:25 PM
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