CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-860

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

NDA NUMBER
NDA 21,860

NAME OF APPLICANT / NDA HOLDER
Warner Chilcott Company, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
Sarafem®

ACTIVE INGREDIENT(S)
fluoxetine hydrochloride

STRENGTH(S)
10 mg, 15 mg and 20 mg

DOSAGE FORM
Tablets

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number
4,971,998

b. Issue Date of Patent
November 20, 1990

c. Expiration Date of Patent
May 20, 2008

d. Name of Patent Owner
Indevus Pharmaceuticals, Inc. (formerly known as Interneuron Pharmaceuticals, Inc.)

Address *(of Patent Owner)*
99 Hayden Avenue

City/State
Lexington, Massachusetts

ZIP Code
02421

FAX Number *(if available)*
781.861.3830

Telephone Number
781.861.8444

E-Mail Address *(if available)*

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Warner Chilcott (US), Inc.

Address *(of agent or representative named in 1.e.)*
100 Enterprise Drive

City/State
Rockaway, New Jersey

ZIP Code
07866

FAX Number *(if available)*
973.442.3280

Telephone Number
973.442.3200

E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☒ No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1	Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.2	Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3	If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4	Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3**.		
2.5	Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6	Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7	If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1	Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
3.2	Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3	If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1	Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2	Patent Claim Number *(as listed in the patent)* 2	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No	
4.2a	If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* Treatment of premenstrual dysphoric disorder	

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☐ Yes	

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
	5/19/05

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☒ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Alvin Howard	
Address 100 Enterprise Drive	City/State Rockaway, New Jersey
ZIP Code 07866	Telephone Number 973.442.3200
FAX Number *(if available)* 973.442.3280	E-Mail Address *(if available)*

Addendum to Form FDA 3542a

Patent 4,971,998

4.2 Patent Claim Number: 3	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment or supplement? _X_ Yes ___ No
4.2a If the answer to 4.2 is Yes, identify with specificity the use with reference to the proposed labeling for the drug product.	Use: Treatment of premenstrual dysphoric disorder

14. PATENT CERTIFICATION

Not applicable for a 505(b)(1) Application in accordance with 21 CFR 314.50(i).

EXCLUSIVITY SUMMARY

NDA # 21-860 SUPPL # HFD # 580

Trade Name Sarafem®

Generic Name (fluoxetine hydrochloride) Tablets

Applicant Name Warner Chilcott, Inc.

Approval Date, If Known May 19, 2006

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

b) 505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☐ NO ☒

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

The study submitted was a single dose bioequivalence study to show that the proposed 20 mg Sarafem tablets are bioequivalent to the currently-marketed 20 mg Sarafem pulvules.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☐ NO ☒

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 18-936 Prozac® (fluoxetine hydrochloride) capsules
Sarafem® (fluoxetine hydrochloride) capsules
NDA# 20-974 Prozac® (fluoxetine hydrochloride) capsules

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical

investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☐ NO ☒

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☐ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # YES ☐ NO ☐

Explain:

Investigation #2

IND # YES ☐ NO ☐

Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain:

==========

Name of person completing form: Nenita Crisostomo, R.N.
Title: Regulatory Health Project Manager
Date: May 15, 2006

Name of Office/Division Director signing form: Scott Monroe, M.D.
Title: Deputy Director, Division of Reproductive and Urologic Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

Scott Monroe
5/19/2006 03:32:51 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA # : 21-860 **Supplement Type (e.g. SE5):** _____ **Supplement Number:**

Stamp Date: May 20, 2005: Original submission Action Date: March 20, 2006

March 22, 2006: Resubmission for 2nd cycle Action Date: May 19, 2006

HFD 580 **Trade and generic names/dosage form:** Sarafem® (fluoxetine hydrochloride) tablets

Applicant: Warner Chilcott Company, Inc.

Therapeutic Class: 3S

Indication(s) previously approved:
1. Antidepressant

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Treatment of Premenstrual Dysphoric Disorder

Is there a full waiver for this indication (check one)?

☑ **Yes: Please proceed to Section A.**

☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

☐ **Products in this class for this indication have been studied/labeled for pediatric population**
☐ **Disease/condition does not exist in children**
☐ **Too few children with disease to study**
☐ **There are safety concerns**
☑ **Other:** Sarafem is indicated for the treatment of certain premenstrual symptoms in postmenarcheal females. It is not indicated before menarche regardless of the age of the adolescent. The onset of menarche in an adolescent and not her actual age is the factor that defines the characteristics of this population. It is therefore expected that the efficacy of Sarafem in postpubertal females under the age of 18 would be the same as or similar to that established in women 18 and over.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min____	**kg**____	**mo.**____	**yr.**____	**Tanner Stage**____
Max____	**kg**____	**mo.**____	**yr.**____	**Tanner Stage**____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Nenita Crisostomo, R.N.
Regulatory Project Manager

cc: **NDA 21-860**
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**
- ☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:** _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:** _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

cc: **NDA21-860**
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 10-14-03)

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

/s/

Jennifer L. Mercier
5/22/2006 09:30:46 AM

REQUEST FOR FULL WAIVER OF PEDIATRIC STUDIES

Application:	NDA 21,860
Drug:	Sarafem® (fluoxetine hydrochloride tablets)
Sponsor:	Warner Chilcott Company, Inc.
Indication:	Treatment of premenstrual dysphoric disorder

In accordance with 21 CFR 314.55(c)(2), Warner Chilcott requests a full waiver of the requirement for pediatric studies associated with the submission of this NDA. Thus, the waiver applies to all pediatric ages. Specifically, a disease-specific waiver is requested.

Sarafem is not approved for use in pediatric patients.[1] Sarafem is indicated for the treatment of certain premenstrual symptoms in postmenarcheal females. It is not indicated before menarche regardless of the age of the adolescent. It is Warner Chilcott's belief that the onset of menarche in an adolescent and not her actual age is the factor that defines the characteristics of this population. It is therefore expected that the efficacy of Sarafem in postpubertal females under the age of 18 would be the same as or similar to that established in women 18 and over. Suicidality is a known additional safety consideration with the use of selective serotonin reuptake inhibitors (SSRIs) in adolescent patients with psychiatric disorders.

Per the provisions of the November 2000 draft *Guidance to Industry: Recommendations for Complying With the Pediatric Rule (21 CFR 314.55(a) and 601.27(a))*, a justification for waiving pediatric studies is not included since a disease-specific waiver is being requested.

Furthermore, please note that on May 11, 2005 the Division of Reproductive and Urologic Drug Products (DRUDP) released Eli Lilly from the postmarketing study commitment listed in the July 6, 2000 approval letter for NDA 18-936 Supplement 058 to conduct a study of the effect of Sarafem in adolescent girls with premenstrual dysphoric disorder (PMDD). DRUDP acknowledged that a successful completion of the clinical trial is not likely due to the rarity of PMDD in adolescents and to increased complications in recruitment due to the recent concern with the use of SSRI drugs and suicidality in this population.

[1] Currently approved Prescribing Information for Eli Lilly's Sarafem (fluoxetine hydrochloride) Pulvules®.

ITEM 16. CERTIFICATION ABOUT THE USE OF A DEBARRED PERSON

I hereby certify that Warner Chilcott Company, Inc. did not and will not use in any capacity the services of any person debarred under section 306(a) and (b) of the Federal Food, Drug and Cosmetic Act in connection with this New Drug Application for Sarafem® (fluoxetine hydrochloride tablets).

Alvin Howard
Vice President, Regulatory Affairs
Warner Chilcott (US), Inc.

5/19/05
Date

Mercier, Jennifer L

From: Ileana Brown [IBrown@wcrx.com]
Sent: Thursday, May 18, 2006 1:53 PM
To: Crisostomo, Nenita
Cc: Mercier, Jennifer L; Furlong, Lesley-Anne; Kaufman, Martin
Subject: Re: NDA 21860 Sarafem

Attachments: WC PI_Med Guide May 18 06.doc

WC PI_Med Guide May 18 06.doc ...

Hi Nita,

The recommendations are acceptable to us. Attached please find our clean copy (i.e., FDA's clean copy renamed with the WC filename). I will be in the office tonight until at least 6:00 pm.

Ileana

(See attached file: WC PI_Med Guide May 18 06.doc)

"Crisostomo, Nenita" <nenita.crisostomo@fda.hhs.gov>
05/18/2006 12:21 PM

To: "Ileana Brown" <IBrown@wcrx.com>
cc: "Furlong, Lesley-Anne" <lesleyanne.furlong@fda.hhs.gov>, "Mercier, Jennifer L" <jennifer.mercier@fda.hhs.gov>, "Kaufman, Martin" <martin.kaufman@fda.hhs.gov>
Subject: NDA 21860 Sarafem

<<FDA clean copy 18May2006.doc>> <<FDA clean copy 18May2006.pdf>> <<FDA marked copy 18May2006.pdf>>
Hi Ileana,

Attached are our recommendations to the labeling. Please send your responses by COB today, to include all of those included in the CC line above.

Thanks so much,
Nita

Nenita Crisostomo, RN
Regulatory Health Project Manager
U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Products
Telephone: 301-796-0875
Fax: 301-796-9897 [attachment "FDA clean copy 18May2006.doc" deleted by Ileana Brown/WCLABS] [attachment "FDA clean copy 18May2006.pdf" deleted by Ileana Brown/WCLABS] [attachment "FDA marked copy 18May2006.pdf" deleted by Ileana Brown/WCLABS]

M E M O R A N D U M

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

DATE: May 3, 2006
FROM: Maria Elena Ysern, MSc, Review Chemist, DPMA II
SUBJECT: Sponsor's responses to Division request dated April 28, 2006.
THROUGH: Moo Jhong Rhee, PhD, Branch Chief.
TO: NDA 21-860

From a CMC perspective there is no additional reviews for this second cycle.

CC:
HFD-180/ MYsern
HFD-180NCCrisostomo
HFD-180/MRhee
HFD-180/Division Files

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

/s/

Maria Ysern
5/3/2006 12:26:10 PM
CHEMIST

Moo-Jhong Rhee
5/4/2006 04:32:09 PM
CHEMIST
Chief, Branch III

WARNER CHILCOTT

May 3, 2006

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Central Document Room (CDR)
5901-B Ammendale Road
Beltsville, Maryland 20705-1266

Re: NDA 21-860 – Sarafem® (fluoxetine hydrochloride tablets), Amendment No. 17
Requested Labeling Revisions – Blister Cards and Trade Cartons

Dear Sir or Madam:

Reference is made to the March 20, 2006 Action Letter (approvable) for Sarafem® (fluoxetine hydrochloride tablets) and to the request forwarded by the Division by facsimile on April 28, 2006. The following labeling components have been revised and are herein provided.

The above labeling components are herein provided in the enclosed CD-ROM in accordance to the guidance document titled *"Providing Regulatory Submissions in Electronic Format - General Considerations"*. These files were scanned with VirusScan Enterprise and Anti Spyware Module 8.0.0. A paper copy of the revised proposed labeling is also included.

Please contact the undersigned at 973.442.3229 if there are any questions stemming from this submission.

Sincerely,

Ileana Brown
Director
Regulatory Affairs

Enclosure

100 Enterprise Drive ■ Rockaway, NJ 07866 ■ Phone: 973-442-3200 ■ Fax: 973-442-3280

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-860 Supplement # Efficacy Supplement Type SE-

Trade Name: Sarafem®
Established Name: fluoxetine hydrochloride
Strengths: 10 mg, 15 mg, 20 mg

Applicant: Warner Chilcott (US), Inc.
Agent for Applicant: Warner Chilcott (US), Inc.

Date of Application: March 22, 2006, Class 1 resubmission; complete response to 3/20/06 Approvable Action
Date of Receipt: March 23, 2006
Date clock started after UN: Not Applicable
Date of Filing Meeting:
Filing Date:
Action Goal Date (optional): May 16, 2006 User Fee Goal Date: May 23, 2006

Indication(s) requested: Pre-menstrual dysphoric disorder

Type of Original NDA: (b)(1) ☑ (b)(2) ☐
OR
Type of Supplement: (b)(1) ☐ (b)(2) ☐

NOTE:

(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2), complete Appendix B.

(2) If the application is a supplement to an NDA, please indicate whether the NDA is a (b)(1) or a (b)(2) application:

☐ NDA is a (b)(1) application OR ☐ NDA is a (b)(2) application

Therapeutic Classification: S ☑ P ☐
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐
Chemical Classification: (1,2,3 etc.) 3
Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted: YES ☑ NO ☐

User Fee Status: Paid ☑ Exempt (orphan, government) ☐
Waived (e.g., small business, public health) ☐

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the*

product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the user fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application? YES ☐ NO ☑
  If yes, explain:

- Does another drug have orphan drug exclusivity for the same indication? YES ☐ NO ☑

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES ☐ NO ☐

  If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES ☐ NO ☑
  If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES ☐ NO ☐

- Does the submission contain an accurate comprehensive index? YES ☑ NO ☐

- Was form 356h included with an authorized signature? YES ☑ NO ☐
  If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES ☑ NO ☐
  If no, explain:

- If an electronic NDA, does it follow the Guidance? N/A ☑ YES ☐ NO ☐
  If an electronic NDA, all forms and certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format?

  Additional comments:

- If an electronic NDA in Common Technical Document format, does it follow the CTD guidance? N/A ☑ YES ☐ NO ☐

- Is it an electronic CTD (eCTD)? N/A ☑ YES ☐ NO ☐
  If an electronic CTD, all forms and certifications must either be in paper and signed or be electronically signed.

  Additional comments:

- Patent information submitted on form FDA 3542a? YES ☑ NO ☐

- Exclusivity requested? YES, _____ Years NO ☑
  ***NOTE:** An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*

- Correctly worded Debarment Certification included with authorized signature? YES ☑ NO ☐
  If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

  NOTE: *Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . . ."*

- Financial Disclosure forms included with authorized signature? YES ☑ NO ☐
  (Forms 3454 and 3455 must be included and must be signed by the APPLICANT, not an agent.)
  NOTE: *Financial disclosure is required for bioequivalence studies that are the basis for approval.*

- Field Copy Certification (that it is a true copy of the CMC technical section)? Y ☑ NO ☐

- PDUFA and Action Goal dates correct in COMIS? YES ☑ NO ☐
  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

- List referenced IND numbers: **68,098**

- End-of-Phase 2 Meeting(s)? Date(s) _____ NO ☑
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) **December 9, 2004** NO ☐
  If yes, distribute minutes before filing meeting.

Project Management

- Was electronic "Content of Labeling" submitted? YES ☑ NO ☐
  If no, request in 74-day letter.

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? YES ☑ NO ☐

- Risk Management Plan consulted to ODS/IO? N/A ☑ YES ☐ NO ☐

- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? Y ☐ NO ☑

- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A ☐ YES ☐ NO ☑

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted? N/A ☑ YES ☐ NO ☐

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A ☐ YES ☐ NO ☐

- Has DOTCDP been notified of the OTC switch application? YES ☐ NO ☐

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? YES ☐ NO ☐

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES ☑ NO ☐
  If no, did applicant submit a complete environmental assessment? YES ☑ NO ☐
  If EA submitted, consulted to Florian Zielinski (HFD-357)? YES ☐ NO ☐

- Establishment Evaluation Request (EER) submitted to DMPQ? YES ☑ NO ☐

- If a parenteral product, consulted to Microbiology Team (HFD-805)? YES ☐ NO ☑

ATTACHMENT

MEMO OF FILING MEETING

DATE:

BACKGROUND:
(Provide a brief background of the drug, e.g., it is already approved and this NDA is for an extended-release formulation; whether another Division is involved; foreign marketing history; etc.)

ATTENDEES:

ASSIGNED REVIEWERS (including those not present at filing meeting) :

Discipline	**Reviewer**
Medical:	
Secondary Medical:	
Statistical:	
Pharmacology:	
Statistical Pharmacology:	
Chemistry:	
Environmental Assessment (if needed):	
Biopharmaceutical:	
Microbiology, sterility:	
Microbiology, clinical (for antimicrobial products only):	
DSI:	
Regulatory Project Management:	
Other Consults:	

Per reviewers, are all parts in English or English translation? YES ☐ NO ☐
If no, explain:

CLINICAL FILE ☐ REFUSE TO FILE ☐

- Clinical site inspection needed? YES ☐ NO ☐
- Advisory Committee Meeting needed? YES, date if known _____ NO ☐
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? N/A ☐ YES ☐ NO ☐

CLINICAL MICROBIOLOGY N/A ☐ FILE ☐ REFUSE TO FILE ☐

STATISTICS N/A ☐ FILE ☐ REFUSE TO FILE ☐

BIOPHARMACEUTICS FILE ☐ REFUSE TO FILE ☐

- Biopharm. inspection needed? YES ☐ NO ☐

PHARMACOLOGY N/A ☐ FILE ☐ REFUSE TO FILE ☐

- GLP inspection needed? YES ☐ NO ☐

CHEMISTRY FILE ☐ REFUSE TO FILE ☐

- Establishment(s) ready for inspection? YES ☐ NO ☐
- Microbiology YES ☐ NO ☐

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

☐ The application is unsuitable for filing. Explain why:

☐ The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.

- ☐ No filing issues have been identified.
- ☐ Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. ☐ If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
2. ☐ If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
3. ☐ Convey document filing issues/no filing issues to applicant by Day 74.

Nenita Crisostomo, R.N.
Regulatory Health Project Manager, HFD-580

Appendix A to NDA Regulatory Filing Review

An application is likely to be a 505(b)(2) application if:

(1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
(2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
(4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications

1. Does the application reference a listed drug (approved drug)? YES ☐ NO ☐

   *If "**No**," skip to question 3.*

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):

3. The purpose of this and the questions below (questions 3 to 5) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval and that should be referenced as a listed drug in the pending application.

   (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?

   YES ☐ NO ☐

   (***Pharmaceutical equivalents*** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

   *If "**No**," skip to question 4. Otherwise, answer part (b).*

   (b) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES ☐ NO ☐
   (The approved pharmaceutical equivalent(s) should be cited as the listed drug(s).)

   *If "**Yes**," skip to question 6. Otherwise, answer part (c).*

   (c) Have you conferred with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007)? YES ☐ NO ☐

   *If "**No**," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.*

4. (a) Is there a pharmaceutical alternative(s) already approved? YES ☐ NO ☐

   (***Pharmaceutical alternatives*** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

   *If "**No**," skip to question 5. Otherwise, answer part (b).*

   (b) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES ☐ NO ☐
   (The approved pharmaceutical alternative(s) should be cited as the listed drug(s).)

NOTE: *If there is more than one pharmaceutical alternative approved, consult the Director, Division of*

Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007) to determine if the appropriate pharmaceutical alternatives are referenced.

*If "**Yes**," skip to question 6. Otherwise, answer part (c).*

(c) Have you conferred with the Director, Division of Regulatory Policy II, ORP? YES ☐ NO ☐

*If "**No**," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.*

5. (a) Is there an approved drug product that does not meet the definition of "pharmaceutical equivalent" or "pharmaceutical alternative," as provided in questions 3(a) and 4(a), above, but that is otherwise very similar to the proposed product?

YES ☐ NO ☐

*If "**No**," skip to question 6.*

*If "**Yes**," please describe how the approved drug product is similar to the proposed one and answer part (b) of this question. Please also contact the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007), to further discuss.*

(b) Is the approved drug product cited as the listed drug? YES ☐ NO ☐

6. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

7. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). YES ☐ NO ☐

8. Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 21 CFR 314.101(d)(9)). YES ☐ NO ☐

9. Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application should be refused for filing under 21 CFR 314.101(d)(9). YES ☐ NO ☐

10. Are there certifications for each of the patents listed for the listed drug(s)? YES ☐ NO ☐

11. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):

NOTE: *IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must* ***subsequently*** *submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)].*

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):

☐ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):

12. Did the applicant:

- Identify which parts of the application rely on information (e.g. literature, prior approval of another sponsor's application) that the applicant does not own or to which the applicant does not have a right of reference?

  YES ☐ NO ☐

- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

  YES ☐ NO ☐

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

  N/A ☐ YES ☐ NO ☐

- Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?

  N/A ☐ YES ☐ NO ☐

13. If the (b)(2) applicant is requesting 3-year exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

    - Certification that at least one of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

      YES ☐ NO ☐

    - A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

      YES ☐ NO ☐

    - EITHER

      The number of the applicant's IND under which the studies essential to approval were conducted.

      IND# _____ NO ☐

      OR

      A certification that the NDA sponsor provided substantial support for the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

      YES ☐ NO ☐

14. Has the Associate Director for Regulatory Affairs, OND, been notified of the existence of the (b)(2) application?

    YES ☐ NO ☐

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

/s/

Nenita Crisostomo
5/1/2006 12:33:03 PM
CSO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODEIII

FACSIMILE TRANSMITTAL SHEET

DATE: April 28, 2006

To: Ileana Brown	**From:** Nenita Crisostomo, R.N.
Company: Warner Chilcott, Inc.	Division of Reproductive and Urologic Products
Fax number: 973-442-3280	**Fax number:** 301-796-9897
Phone number: (973) 442-3229	**Phone number:** 301-796-0875

Subject: Discipline Review Completed for NDA 21-860
NDA 21860 Sarafem: INformation Request

Total no. of pages including cover: 2

Comments:

Disclaimer: We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

Document to be mailed: ☐YES ☑NO

1 Page(s) Withheld

_____ Trade Secret / Confidential

✓ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Administrative- 1

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

/s/

Nenita Crisostomo
4/28/2006 01:21:12 PM
CSO

WARNER CHILCOTT

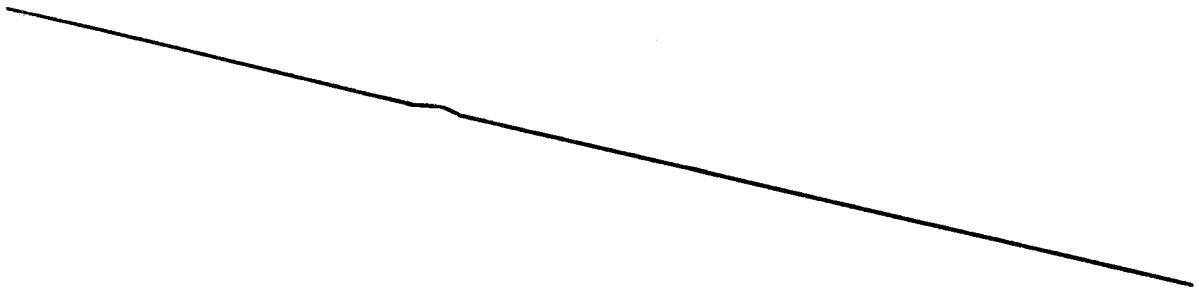
April 3, 2006

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Central Document Room (CDR)
5901-B Ammendale Road
Beltsville, Maryland 20705-1266

Re: NDA 21-860 – Sarafem® (fluoxetine hydrochloride tablets), Amendment No. 16
Requested Labeling Revisions

Dear Sir or Madam:

Reference is made to the March 20, 2006 Action Letter (approvable) for Sarafem® (fluoxetine hydrochloride tablets) and to the request forwarded by the Agency by e-mail on March 29, 2006. The following labeling components have been revised per the Division's request and are herein provided.



The above labeling components are herein provided in the enclosed CD-ROM. In accordance to the guidance document titled *"Providing Regulatory Submissions in Electronic Format - General Considerations"*, January 1999, the prescribing information is provided in MS WORD files as a 'clean copy' and showing the 'tracked changes'. These files were scanned with VirusScan Enterprise and Anti Spyware Module 8.0.0. A paper copy of the revised proposed labeling with tracked changes shown is also included.

Please contact the undersigned at 973.442.3229 if there are any questions stemming from this submission.

Sincerely,

Ileana Brown
Director
Regulatory Affairs

Enclosure

100 Enterprise Drive ■ Rockaway, NJ 07866 ■ Phone: 973-442-3200 ■ Fax: 973-442-3280

Crisostomo, Nenita

m: Crisostomo, Nenita
t: Friday, March 31, 2006 8:32 AM
: 'Ileana Brown'
Cc: 'Alvin Howard'
Subject: RE: FW: NDA 21860: Correction--Blister card recommendations

Hi Ileana,

Thank you so much for also recognizing the need for uniformity of the wordings to the Trade Cartons. Yes, to all 3 items

Best Regards!

nita

Nenita Crisostomo, RN
Regulatory Health Project Manager
Division of Reproductive and Urologic Products
Ph.301-796-0875
Fax: 301-796-9897

Original Message-----
: Ileana Brown [mailto:IBrown@wcrx.com]
Sent: Thursday, March 30, 2006 1:51 PM
To: Crisostomo, Nenita
Cc: Alvin Howard
Subject: Re: FW: NDA 21860: Correction--Blister card recommendations

Hi Nita,

We wish to submit the requested changes quickly but I think I should first clarify what the changes are since in the e-mail there seemed to be swapping of wording between what the PI and the sample carton should say (besides the issue of the number of blister cards). So, please confirm that what I say below is correct:

nks very much.

Ileana

Crisostomo, Nenita

`m: Crisostomo, Nenita
t: Thursday, March 23, 2006 2:30 PM
To: 'Ileana Brown'
Subject: RE: Sarafem tablets RESUBMISSION Amendment 14

Follow Up Flag: Follow up
Due By: Friday, March 24, 2006 12:00 AM
Flag Status: Flagged

Ileana,

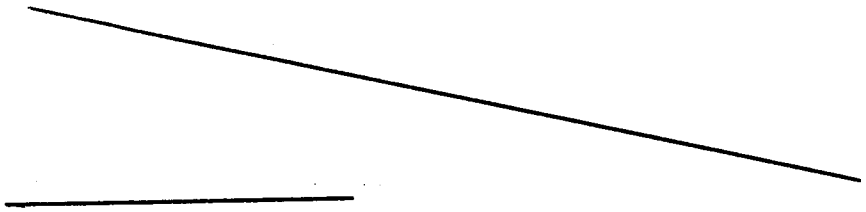
The description of the blister to be used needs to be included & (not only by reference to the pulvules NDA).

Thanks,
nita

-----Original Message-----
From: Ileana Brown [mailto:IBrown@wcrx.com]
Sent: Wednesday, March 22, 2006 5:08 PM
To: Crisostomo, Nenita
Subject: Sarafem tablets RESUBMISSION Amendment 14

Dear Nita,

nt today via FedEx the Resubmission (Amendment 14) with complete responses to the March 20, 2006 Action Letter (approvable). I am e-mailing the components of the submission (see attached). The submission to the CDR included the CD-ROM with all the required electronic files.



The submission should arrive at the CDR no later than 10:30 am tomorrow. Please let me know if there are any questions.

Thanks

Ileana

(See attached file: Amendment 14 Mar 22 06 cover letter.doc)(See attached file: Form FDA 356h Amendment 14.doc)(See attached file: NDA 21-860 blister SAMPLE 10, 15 and 20 mg Mar 22 06.pdf)(See attached file: NDA 21-860 blister TRADE 10, 15 and 20 mg Mar 22 06.pdf)(See attached file: NDA 21-860 sample carton 10mg Mar 22 06.pdf)(See attached file: NDA 21-860 sample carton 15 mg Mar 22 06.pdf)
(See attached file: NDA 21-860 sample carton 20 mg Mar 22 06.pdf)(See attached file: NDA 21-860 sample tray 10 mg Mar 22 06.pdf)(See attached file: NDA 21-860 sample tray 15 mg Mar 22 06.pdf)(See attached file: NDA 21-860 sample tray 20 mg Mar 22 06.pdf)(See attached file: NDA 21-860 trade

cartons 10, 15 and 20 mg Mar 22 06.pdf)(See attached file: NDA 21-860 WC Draft PI Mar 22 06 CLEAN COPY.doc)
(See attached file: NDA 21-860 WC Draft PI Mar 22 06 CLEAN COPY.pdf)(See attached file: NDA 21-860 WC Draft PI Mar 22 06 TRACKED CHANGES.doc)(See attached file: NDA 21-860 WC Draft PI Mar 22 06 TRACKED CHANGES.pdf)

Tracking:	**Recipient**	**Read**
	'Ileana Brown'	
	Ysern, Maria E	Read: 3/24/2006 7:07 AM

Crisostomo, Nenita

m: Crisostomo, Nenita
t: Tuesday, March 07, 2006 5:23 PM
To: 'Ileana Brown'
Subject: NDA 21860 Sarafem: FDA Review Draft March 7 06

Follow Up Flag: Follow up
Due By: Wednesday, March 08, 2006 3:30 PM
Flag Status: Flagged

Attachments: FDA.NDA 21-860 Draft PI Med Guide with track changes Mar 7 06.pdf; FDA.NDA 21-860 Draft PI Med Guide with track changes Mar 7 06.doc


FDA.NDA
60 Draft PI Med


FDA.NDA
60 Draft PI Med

Hi Ileana,

All of your changes were accepted, with additional FDA edits in Track Changes. Please send your response on/before COB tomorrow 3/8/06.

Thank you very much,
Nita

Nenita Crisostomo, RN
Regulatory Health Project Manager
U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Products
Telephone: 301-796-0875
Fax: 301-796-9897

Tracking:

Recipient	Read
'Ileana Brown'	
Soule, Lisa	
Apparaju, Sandhya	Read: 3/8/2006 8:51 AM
Ysern, Maria E	Read: 3/8/2006 6:52 AM
Furlong, Lesley-Anne	
McKinney, Leslie	Read: 3/7/2006 6:23 PM
Monroe, Scott	Read: 3/10/2006 6:50 PM

Crisostomo, Nenita

m: Crisostomo, Nenita
t: Friday, March 03, 2006 4:59 PM
:o: 'Ileana Brown'
Subject: NDA 21860 Sarafem: FDA PI Draft

Attachments: PI 3.3.06to sponsor.pdf; PI 3 3 06to sponsor.revised.doc


PI 3.3.06to
onsor.pdf (128


PI 3 3 06to
onsor.revised.dc

Hi Ileana,

Here are our recommendations for the Package Insert/MedGuide. Please provide your responses on/before COB March 6, 2006, and do not hesitate to call me if you have any questions/problems.

Thank you and have a nice weekend,
Nita

Nenita Crisostomo, RN
Regulatory Health Project Manager
U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Products
Telephone: 301-796-0875
Fax: 301-796-9897

cking:

Recipient	Read
'Ileana Brown'	
Monroe, Scott	Read: 3/3/2006 8:03 PM
Soule, Lisa	
Furlong, Lesley-Anne	

MEMORANDUM

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

DATE: February 28, 2006

TO: Daniel A. Shames, M.D.
Director
Division of Reproductive and Urologic Products, DRUP

FROM: Michael F. Skelly, Ph.D.
Division of Scientific Investigations (HFD-48)

THROUGH: C.T. Viswanathan, Ph.D.
Associate Director - Bioequivalence
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of EIRs Covering NDA 21-860, Sarafem®, (fluoxetine hydrochloride tablets), Sponsored by Warner Chilcott

At the request of DRUP, the clinical and analytical portions of the following bioequivalence study, performed at _____ _____ and _____ _____ respectively, were audited. Please note that DSI scientists did not attend these inspections.

Study PR-10603.1: "A Study to Examine Fluoxetine Bioavailability Following Oral Administration of Sarafem Tablets, 20 mg Relative to that of Sarafem Pulvules®, 20 mg"

Following the inspection at _____ (February 6-10, 2006) there were no objectionable observations and no Form 483 was issued. Following the inspection at _____ (December 13-15, 2005), 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 LC/MS/MS ————on 7/29/04.**

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.

2. **There is no precision test in the system suitability used in the procedure for "The Determination of Fluoxetine and Norfluoxetine in Human Plasma by LC/MS/MS" ————————Job Number: 165162/Protocol PR-10603).**

The FDA ORA inspection team apparently believed that HPLC ———————— reproducibility was expected for this work. It is not expected for these bioanalyses. ———————— correctly demonstrated the suitability of the system for such bioanalytical runs, and accepted or rejected individual runs, by using the performance of quality control (QC) samples in each run. Observation 2 has no adverse consequence to data acceptability.

Conclusions:

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

After you have reviewed this transmittal memo, please append it to the original NDA submission.

Michael F. Skelly, Ph.D.
Pharmacologist

Final Classification:

NAI -
VAI -

Recommendation: Pharmacokinetic data from study PR-10603 are acceptable for review, after excluding the data from Subject #12.

cc:
HFA-224
HFD-45/RF
HFD-48/Himaya
HFD-48/CF
DRUP (formerly HFD-580)/Kirchberg/NDA 21-860
HFR-CE450/Nojek
HFR-NE3550/Davis/Greco
Drafted: MFS 2/27/06
Edits: SS, CTV, MFS 2/28
DSI: 5634; O:\BE\EIRCover\21860warflu.doc
FACTS: 651767 and 653722

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/s/

Amalia Himaya
2/28/2006 02:21:53 PM
CSO
Paper copy signed by Dr. Viswanathan on 2/28/06 and available upon request.

Crisostomo, Nenita

m: Crisostomo, Nenita
.: Wednesday, January 18, 2006 5:32 PM
To: 'Ileana Brown'
Subject: NDA 21-860 Sarafem: Blister Card & Carton Labeling--DMETS comments

Follow Up Flag: Follow up
Due By: Tuesday, January 24, 2006 12:00 AM
Flag Status: Flagged

Attachments: PI revised DMETS comments.1.11.06.doc

PI revised
TS comments.1.

Hi Ileana,

Please send us revised blister card and carton labeling after you have considered the advice, as attached. The advice is the result of our review of an internal consultation from FDA's Division of Medication Errors and Technical Support (DMETS). DMETS suggested changes in labeling to minimize user error. We would appreciate your response on or before January 23, 2006.

Please call me if you have any questions.

Thank you very much,
Nita

'ita Crisostomo, RN
ulatory Health Project Manager
U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Products
Telephone: 301-796-0875
Fax: 301-796-9897

2 Page(s) Withheld

_____ Trade Secret / Confidential

✓ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Administrative- 2

Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; White Oak Bldg #22, Mailstop 4447
Center for Drug Evaluation and Research

LABEL AND LABELING REVIEW

DATE OF REVIEW: December 2, 2005

NDA #: 21-860

NAME OF DRUG: Sarafem®
(Fluoxetine Hydrochloride Tablets)
10 mg, 15 mg, and 20 mg

NDA HOLDER: Warner Chilcott (US), Inc.

I. INTRODUCTION:

This consult was written in response to a request from the Division of Reproductive and Urologic Products to review the physician sample, container labels and carton labeling of Sarafem® submitted on October 31, 2005 and the package insert labeling submitted on August 30, 2005. Sarafem® capsules (NDA 18-936) were approved on July 6, 2000 for the treatment of premenstrual dysphoric disorder (PMDD). At that time, Sarafem® was approved with 10 mg and 20 mg dosages, using continuous and intermittent dosing regimens. Warner Chilcott has submitted NDA 21-860 which provides for a new dosage form, tablet, and the addition of a new 15 mg dose for the treatment of PMDD. The proposed new dose is intermediate to those already marketed and will be prescribed using the same dosing regimens.

PRODUCT INFORMATION

Sarafem® tablets contain fluoxetine hydrochloride equivalent to 10 mg, 15 mg, or 20 mg of fluoxetine. Sarafem® is a selective serotonin reuptake inhibitor (SSRI) for oral administration. It is indicated for the treatment of premenstrual dysphoric disorder. The recommended dose for the treatment of PMDD is 20 mg per 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 dosing regimen should be determined by the physician based on individual patient characteristics. A lower or less frequent dosage should be considered in patients with hepatic impairment, concurrent disease, or on multiple concomitant medications. Dosage adjustments for renal impairment are not routinely necessary. Sarafem® is supplied in [redacted]

2 Page(s) Withheld

_____ Trade Secret / Confidential

✓ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Administrative- 3

D. CARTON LABELING—TRAY (10 mg, 15 mg, 20 mg: tray for physician's sample)

1. See General Comments A-1 through A-3 and Comments C-2 and C-3.

2. [redacted]

E. INSERT LABELING

DMETS recommmends the Medication Guide be submitted to the Division of Surveillance, Research, and Communication Support (DSRCS) for review and comment.

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

/s/

Loretta Holmes
1/5/2006 12:27:53 PM
DRUG SAFETY OFFICE REVIEWER

Kristina Arnwine
1/5/2006 03:27:15 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
1/5/2006 03:40:35 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
1/5/2006 03:44:11 PM
DRUG SAFETY OFFICE REVIEWER

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-860

Warner Chilcott (US), Inc.
Attention: Alvin D. Howard
Vice President, Regulatory Affairs
100 Enterprise Way
Rockaway, New Jersey 07866

Dear Mr. Howard

Please refer to your May 19, 2005, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sarafem® (fluoxetine hydrochloride) Tablets.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application was filed under section 505(b) of the Act on July 19, 2005 in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues:

Chemistry

- The proposed expiration dating period for the drug product should be supported by additional stability data. We request that you submit this additional stability data when it is available. Submission of stability data during the final three months of review may warrant a major amendment to the NDA.

- Comparative *in-vitro* dissolution data should be provided for the clinical, stability, and to-be-marketed formulations. We request that you submit comparative dissolution profiles and calculated f_2 values for the clinical batch versus the stability and proposed commercial formulations, for all three dosage strengths.

Clinical Pharmacology

- Pharmacokinetic data generated using the new tablet dosage form in Study PR-10603 should be included in the proposed labeling. We request that you submit updated labeling for review.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, call Karen Kirchberg, N.P., Regulatory Project Manager, at (301) 827-4254.

Sincerely,

{See appended electronic signature page}

Donna Griebel, M.D.
Deputy Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

Donna Griebel
7/27/05 03:10:24 PM

Memorandum of Consultation
Statistical Review

Date: July 8, 2005

From: Katherine B. Meaker, M.S. (HFD-715)

To: Lesley Furlong, M.D. (HFD-580)

Subject: NDA 21-860 (SN 000); No statistical review needed

NDA 21-860, submitted May 19, 2005, does not contain any new clinical data. The basis for the application is bioequivalence studies. Therefore no statistical review is needed for this NDA.

Katherine B. Meaker, M.S.
Mathematical Statistician

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

/s/

Katherine Meaker
7/8/05 07:46:28 PM
BIOMETRICS

Mike Welch
7/11/05 11:36:23 AM
BIOMETRICS

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-860 Supplement # Efficacy Supplement Type SE-

Trade Name: Sarafem®
Established Name: Fluoxetine hydrochloride
Strengths: 10 mg, 15 mg, 20 mg

Applicant: Warner Chilcott
Agent for Applicant: same

Date of Application: May 19, 2005
Date of Receipt: May 20, 2005
Date clock started after UN:
Date of Filing Meeting: July 7, 2005
Filing Date: July 19, 2005

Action Goal Date (optional): March 20, 2006 User Fee Goal Date: March 20, 2006

Indication(s) requested: Pre-menstrual dysphoric disorder

Type of Original NDA: (b)(1) ☒ (b)(2) ☐
OR
Type of Supplement: (b)(1) ☐ (b)(2) ☐

NOTE:

(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2), complete Appendix B.

(2) If the application is a supplement to an NDA, please indicate whether the NDA is a (b)(1) or a (b)(2) application:

☒ NDA is a (b)(1) application OR ☐ NDA is a (b)(2) application

Therapeutic Classification: S ☒ P ☐
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐
Chemical Classification: (1,2,3 etc.)
Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted: YES ☒ NO ☐

User Fee Status: Paid ☒ Exempt (orphan, government) ☐
Waived (e.g., small business, public health) ☐

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the*

product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the user fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application? YES ☐ NO ☒
  If yes, explain:

- Does another drug have orphan drug exclusivity for the same indication? YES ☐ NO ☒

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES ☐ NO ☐

  If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES ☐ NO ☒
  If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES ☐ NO ☐

- Does the submission contain an accurate comprehensive index? YES ☒ NO ☐

- Was form 356h included with an authorized signature? YES ☒ NO ☐
  If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES ☒ NO ☐
  If no, explain:

- If an electronic NDA, does it follow the Guidance? N/A ☒ YES ☐ NO ☐
  If an electronic NDA, all forms and certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format?

  Additional comments: SAS data and labeling were submitted electeronically

- If an electronic NDA in Common Technical Document format, does it follow the CTD guidance? N/A ☒ YES ☐ NO ☐

- Is it an electronic CTD (eCTD)? N/A ☒ YES ☐ NO ☐
  If an electronic CTD, all forms and certifications must either be in paper and signed or be electronically signed.

  Additional comments:

- Patent information submitted on form FDA 3542a? YES ☒ NO ☐

- Exclusivity requested? YES, _____ Years NO ☒
  NOTE: *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*

- Correctly worded Debarment Certification included with authorized signature? YES ☒ NO ☐
  If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: *Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . . ."*

- Financial Disclosure forms included with authorized signature? YES ☒ NO ☐
  (Forms 3454 and 3455 must be included and must be signed by the APPLICANT, not an agent.)
  NOTE: *Financial disclosure is required for bioequivalence studies that are the basis for approval.*

- Field Copy Certification (that it is a true copy of the CMC technical section)? Y ☒ NO ☐

- PDUFA and Action Goal dates correct in COMIS? YES ☒ NO ☐
  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

- List referenced IND numbers: 68,098

- End-of-Phase 2 Meeting(s)? Date(s) _____ NO ☒
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) _____ NO ☒
  If yes, distribute minutes before filing meeting.

Project Management

- Was electronic "Content of Labeling" submitted? YES ☒ NO ☐
  If no, request in 74-day letter.

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?
  YES ☐ NO ☒

- Risk Management Plan consulted to ODS/IO? N/A ☒ YES ☐ NO ☐

- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? Y ☐ NO ☒

- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A ☐ YES ☐ NO ☐

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted?
  N/A ☒ YES ☐ NO ☐

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A ☐ YES ☐ NO ☐

- Has DOTCDP been notified of the OTC switch application? YES ☐ NO ☐

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? YES ☐ NO ☒

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES ☒ NO ☐
  If no, did applicant submit a complete environmental assessment? YES ☐ NO ☐
  If EA submitted, consulted to Florian Zielinski (HFD-357)? YES ☐ NO ☐
- Establishment Evaluation Request (EER) submitted to DMPQ? YES ☒ NO ☐
- If a parenteral product, consulted to Microbiology Team (HFD-805)? YES ☐ NO ☒

ATTACHMENT

MEMO OF FILING MEETING

DATE: July 6, 2005

BACKGROUND: The product was bought from Lilly by Warner chilcott. The current approved product is Sarafem® (fluoxetine hydrocholide)10 mg and 20 mg Puvules.The sponsor is proposing to change the Puvules to Tablets and add an 3rd 15mg dose.
(Provide a brief background of the drug, e.g., it is already approved and this NDA is for an extended-release formulation; whether another Division is involved; foreign marketing history; etc.)

ATTENDEES: listed below.

ASSIGNED REVIEWERS (including those not present at filing meeting) :

Discipline	**Reviewer**
Medical:	Scott Monroe, MD.
Secondary Medical:	Lesley Furlong, MD
Statistical:	Kate Meaker, M.S.
Pharmacology:	Leslie Leonard, PhD
Statistical Pharmacology:	NA
Chemistry:	Sarah Pope, PhD
Environmental Assessment (if needed):	NA
Biopharmaceutical:	Sandhya Apparaju, PhD
Microbiology, sterility:	NA
Microbiology, clinical (for antimicrobial products only):	NA
DSI:	Michael Skelly
Regulatory Project Management:	Karen Kirchberg, NP
Other Consults:	

Per reviewers, are all parts in English or English translation? YES ☒ NO ☐
If no, explain:

CLINICAL FILE ☒ REFUSE TO FILE ☐

- Clinical site inspection needed? YES ☐ NO ☒
- Advisory Committee Meeting needed? YES, date if known _____ NO ☒
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?
  N/A ☒ YES ☐ NO ☐

CLINICAL MICROBIOLOGY N/A ☒ FILE ☐ REFUSE TO FILE ☐

STATISTICS N/A ☐ FILE ☒ REFUSE TO FILE ☐

BIOPHARMACEUTICS FILE ☒ REFUSE TO FILE ☐

- Biopharm. inspection needed? YES ☒ NO ☐

PHARMACOLOGY N/A ☐ FILE ☒ REFUSE TO FILE ☐

- GLP inspection needed? YES ☐ NO ☒

CHEMISTRY FILE ☒ REFUSE TO FILE ☐

- Establishment(s) ready for inspection? YES ☒ NO ☐
- Microbiology YES ☐ NO ☒

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

☐ The application is unsuitable for filing. Explain why:

☒ The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.

☐ No filing issues have been identified.

☒ Filing issues to be communicated by Day 74. List (optional): CMC and BioPharm comments

ACTION ITEMS:

1.☐ If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.

2.☐ If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

3.☒ Convey document filing issues/no filing issues to applicant by Day 74.

Karen Kirchberg, NP
Regulatory Project Manager, HFD-580

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

/s/

Karen Kirchberg
7/7/05 05:01:51 PM
CSO

Karen Kirchberg
7/7/05 05:11:44 PM
CSO

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-860 Supplement # Efficacy Supplement Type SE-

Trade Name: Sarafem®
Established Name: Fluoxetine hydrochloride
Strengths: 10 mg, 15 mg, 20 mg

Applicant: Warner Chilcott
Agent for Applicant: same

Date of Application: May 19, 2005
Date of Receipt: May 20, 2005
Date clock started after UN:
Date of Filing Meeting: July 7, 2005
Filing Date: July 19, 2005

Action Goal Date (optional): March 20, 2006 User Fee Goal Date: March 20, 2006

Indication(s) requested: Pre-menstrual dysphoric disorder

Type of Original NDA: (b)(1) ☒ (b)(2) ☐
OR
Type of Supplement: (b)(1) ☐ (b)(2) ☐

NOTE:

(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2), complete Appendix B.

(2) If the application is a supplement to an NDA, please indicate whether the NDA is a (b)(1) or a (b)(2) application:

☒ NDA is a (b)(1) application OR ☐ NDA is a (b)(2) application

Therapeutic Classification: S ☒ P ☐
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐
Chemical Classification: (1,2,3 etc.)
Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted: YES ☒ NO ☐

User Fee Status: Paid ☒ Exempt (orphan, government) ☐
Waived (e.g., small business, public health) ☐

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the*

product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the user fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application? YES ☐ NO ☒
  If yes, explain:

- Does another drug have orphan drug exclusivity for the same indication? YES ☐ NO ☒

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES ☐ NO ☐

  If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES ☐ NO ☒
  If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES ☐ NO ☐

- Does the submission contain an accurate comprehensive index? YES ☒ NO ☐

- Was form 356h included with an authorized signature? YES ☒ NO ☐
  If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES ☒ NO ☐
  If no, explain:

- If an electronic NDA, does it follow the Guidance? N/A ☒ YES ☐ NO ☐
  If an electronic NDA, all forms and certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format?

  Additional comments: SAS data and labeling were submitted electeronically

- If an electronic NDA in Common Technical Document format, does it follow the CTD guidance? N/A ☒ YES ☐ NO ☐

- Is it an electronic CTD (eCTD)? N/A ☒ YES ☐ NO ☐
  If an electronic CTD, all forms and certifications must either be in paper and signed or be electronically signed.

  Additional comments:

- Patent information submitted on form FDA 3542a? YES ☒ NO ☐

- Exclusivity requested? YES, _____ Years NO ☒
  NOTE: *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*

- Correctly worded Debarment Certification included with authorized signature? YES ☒ NO ☐
  If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: *Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . . ."*

- Financial Disclosure forms included with authorized signature? YES ☒ NO ☐
  (Forms 3454 and 3455 must be included and must be signed by the APPLICANT, not an agent.)
  NOTE: *Financial disclosure is required for bioequivalence studies that are the basis for approval.*

- Field Copy Certification (that it is a true copy of the CMC technical section)? Y ☒ NO ☐

- PDUFA and Action Goal dates correct in COMIS? YES ☒ NO ☐
  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

- List referenced IND numbers: 68,098

- End-of-Phase 2 Meeting(s)? Date(s) _____ NO ☒
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) _____ NO ☒
  If yes, distribute minutes before filing meeting.

Project Management

- Was electronic "Content of Labeling" submitted? YES ☒ NO ☐
  If no, request in 74-day letter.

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?
  YES ☐ NO ☒

- Risk Management Plan consulted to ODS/IO? N/A ☒ YES ☐ NO ☐

- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? Y ☐ NO ☒

- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A ☐ YES ☐ NO ☐

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted?
  N/A ☒ YES ☐ NO ☐

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A ☐ YES ☐ NO ☐

- Has DOTCDP been notified of the OTC switch application? YES ☐ NO ☐

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
  YES ☐ NO ☒

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES ☒ NO ☐
  If no, did applicant submit a complete environmental assessment? YES ☐ NO ☐
  If EA submitted, consulted to Florian Zielinski (HFD-357)? YES ☐ NO ☐
- Establishment Evaluation Request (EER) submitted to DMPQ? YES ☒ NO ☐
- If a parenteral product, consulted to Microbiology Team (HFD-805)? YES ☐ NO ☒

ATTACHMENT

MEMO OF FILING MEETING

DATE: July 6, 2005

BACKGROUND: The product was bought from Lilly by Warner chilcott. The current approved product is Sarafem® (fluoxetine hydrocholide)10 mg and 20 mg Puvules.The sponsor is proposing to change the Puvules to Tablets and add an 3rd 15mg dose.
(Provide a brief background of the drug, e.g., it is already approved and this NDA is for an extended-release formulation; whether another Division is involved; foreign marketing history; etc.)

ATTENDEES: listed below.

ASSIGNED REVIEWERS (including those not present at filing meeting) :

Discipline	**Reviewer**
Medical:	Scott Monroe, MD.
Secondary Medical:	Lesley Furlong, MD
Statistical:	Kate Meaker, M.S.
Pharmacology:	Leslie Leonard, PhD
Statistical Pharmacology:	NA
Chemistry:	Sarah Pope, PhD
Environmental Assessment (if needed):	NA
Biopharmaceutical:	Sandhya Apparaju, PhD
Microbiology, sterility:	NA
Microbiology, clinical (for antimicrobial products only):	NA
DSI:	Michael Skelly
Regulatory Project Management:	Karen Kirchberg, NP
Other Consults:	

Per reviewers, are all parts in English or English translation? YES ☒ NO ☐
If no, explain:

CLINICAL FILE ☒ REFUSE TO FILE ☐

- Clinical site inspection needed? YES ☐ NO ☒
- Advisory Committee Meeting needed? YES, date if known _____ NO ☒
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? N/A ☒ YES ☐ NO ☐

CLINICAL MICROBIOLOGY N/A ☒ FILE ☐ REFUSE TO FILE ☐

STATISTICS N/A ☐ FILE ☒ REFUSE TO FILE ☐

BIOPHARMACEUTICS FILE ☒ REFUSE TO FILE ☐

- Biopharm. inspection needed? YES ☒ NO ☐

PHARMACOLOGY N/A ☐ FILE ☒ REFUSE TO FILE ☐

- GLP inspection needed? YES ☐ NO ☒

CHEMISTRY FILE ☒ REFUSE TO FILE ☐

- Establishment(s) ready for inspection? YES ☒ NO ☐
- Microbiology YES ☐ NO ☒

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

☐ The application is unsuitable for filing. Explain why:

☒ The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.

- ☐ No filing issues have been identified.
- ☒ Filing issues to be communicated by Day 74. List (optional): CMC and BioPharm comments

ACTION ITEMS:

1. ☐ If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
2. ☐ If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
3. ☒ Convey document filing issues/no filing issues to applicant by Day 74.

Karen Kirchberg, NP
Regulatory Project Manager, HFD-580

Appendix A to NDA Regulatory Filing Review

An application is likely to be a 505(b)(2) application if:

(1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
(2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
(4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications

1. Does the application reference a listed drug (approved drug)? YES ☐ NO ☐

   *If "**No**," skip to question 3.*

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):

3. The purpose of this and the questions below (questions 3 to 5) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval and that should be referenced as a listed drug in the pending application.

   (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?

   YES ☐ NO ☐

   (***Pharmaceutical equivalents*** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

   *If "**No**," skip to question 4. Otherwise, answer part (b).*

   (b) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES ☐ NO ☐
   (The approved pharmaceutical equivalent(s) should be cited as the listed drug(s).)

   *If "**Yes**," skip to question 6. Otherwise, answer part (c).*

   (c) Have you conferred with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007)? YES ☐ NO ☐

   *If "**No**," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.*

4. (a) Is there a pharmaceutical alternative(s) already approved? YES ☐ NO ☐

   (***Pharmaceutical alternatives*** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

   *If "**No**," skip to question 5. Otherwise, answer part (b).*

   (b) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES ☐ NO ☐
   (The approved pharmaceutical alternative(s) should be cited as the listed drug(s).)

NOTE: *If there is more than one pharmaceutical alternative approved, consult the Director, Division of*

Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007) to determine if the appropriate pharmaceutical alternatives are referenced.

*If "**Yes**," skip to question 6. Otherwise, answer part (c).*

(c) Have you conferred with the Director, Division of Regulatory Policy II, ORP? YES ☐ NO ☐

*If "**No**," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.*

5. (a) Is there an approved drug product that does not meet the definition of "pharmaceutical equivalent" or "pharmaceutical alternative," as provided in questions 3(a) and 4(a), above, but that is otherwise very similar to the proposed product?

YES ☐ NO ☐

*If "**No**," skip to question 6.*

*If "**Yes**," please describe how the approved drug product is similar to the proposed one and answer part (b) of this question. Please also contact the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007), to further discuss.*

(b) Is the approved drug product cited as the listed drug? YES ☐ NO ☐

6. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

7. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). YES ☐ NO ☐

8. Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 21 CFR 314.101(d)(9)). YES ☐ NO ☐

9. Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application should be refused for filing under 21 CFR 314.101(d)(9). YES ☐ NO ☐

10. Are there certifications for each of the patents listed for the listed drug(s)? YES ☐ NO ☐

11. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):

NOTE: *IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must* ***subsequently*** *submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)].*

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):

☐ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):

12. Did the applicant:

- Identify which parts of the application rely on information (e.g. literature, prior approval of another sponsor's application) that the applicant does not own or to which the applicant does not have a right of reference?

  YES ☐ NO ☐

- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

  YES ☐ NO ☐

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

  N/A ☐ YES ☐ NO ☐

- Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?

  N/A ☐ YES ☐ NO ☐

13. If the (b)(2) applicant is requesting 3-year exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

- Certification that at least one of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

  YES ☐ NO ☐

- A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

  YES ☐ NO ☐

- EITHER

  The number of the applicant's IND under which the studies essential to approval were conducted.

  IND# _____ NO ☐

  OR

  A certification that the NDA sponsor provided substantial support for the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

  YES ☐ NO ☐

14. Has the Associate Director for Regulatory Affairs, OND, been notified of the existence of the (b)(2) application?

YES ☐ NO ☐

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

/s/

Karen Kirchberg
7/7/05 05:01:51 PM
CSO

Karen Kirchberg
7/7/05 05:11:44 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-860

Warner Chilcott, Inc.
Attention: Alvin Howard
Vice President, Regulatory Affairs
100 Enterprise Drive
Rockaway, NJ 07866

Dear Mr. Howard:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Sarafem® (fluoxetine hydrochloride) Tablets
Review Priority Classification:	Standard (S)
Date of Application:	May 19, 2005
Date of Receipt:	May 20, 2005
Our Reference Number:	NDA 21-860

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on July 19, 2005 in accordance with 21 CFR 314.101(a). If we file the application, the user fee goal date will be March 20, 2006.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. We are waiving the requirement for pediatric studies for this application.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Send all electronic or mixed electronic and paper submissions to the Central Document Room at the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room (CDR)
5901-B Ammendale Road
Beltsville, MD 20705-1266

If your submission only contains paper, send it to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room, 8B45
5600 Fishers Lane

If you have any questions, call me at (301) 827-4254.

Sincerely,

{See appended electronic signature page}

Karen Kirchberg, N.P.
Regulatory Project Manager
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

Karen Kirchberg
5/25/05 04:21:19 PM

CONSULTATION RESPONSE

DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; White Oak Bldg #22, Mailstop 4447)

DATE RECEIVED: November 8, 2005 **DATE OF DOCUMENT:** May 19, 2005	**DESIRED COMPLETION DATE:** January 10, 2006 **PDUFA DATE:** March 20, 2006	**ODS CONSULT #:** 05-0258

TO: Daniel Shames, MD
Director, Division of Reproductive and Urologic Products

THROUGH: Kristina C. Arnwine, PharmD, Acting Team Leader
Denise P. Toyer, PharmD, Deputy Director
Carol Holquist, RPh, Director
Division of Medication Errors and Technical Support

From: Loretta Holmes, PharmD, Safety Evaluator
Division of Medication Erors and Technical Support

PRODUCT NAME: **Sarafem®**
(Fluoxetine Hydrochloride Tablets) 10 mg, 15 mg, 20 mg

)A #: 21-860

NDA Sponsor: Warner Chilcott (US), Inc.

RECOMMENDATIONS:

DMETS recommends implementation of the professional sample, container label, carton labeling, and package insert labeling revisions outlined in Section II of this review in order to minimize potential user error.

26 Page(s) Withheld

_____ Trade Secret / Confidential

✓ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Administrative- 4

Form Approved: OMB No. 0910 - 0297 Expiration Date: December 31, 2006 See instructions for OMB Statement.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

PRESCRIPTION DRUG USER FEE COVERSHEET

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS

WARNER CHILCOTT COMPANY INC
Alvin Howard
100 ENTERPRISE DR SUITE 280
ROCKAWAY NJ 07866
US

2. TELEPHONE NUMBER
973-442-3233

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER
21-860

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?
[X] YES [ ] NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:

[ ] THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION

[X] THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

18-936 058 and 067

3. PRODUCT NAME
Serafem (fluoxetine hydrochloride tablets)

6. USER FEE I.D. NUMBER
PD3006078

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

[ ] A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)

[ ] A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE

[ ] THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food,Drug, and Cosmetic Act

[ ] THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? [ ] YES [X] NO

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewinginstructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information.Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
[signature]	SVP	5/13/05

9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION
$336,000.00

Form FDA 3397 (12/03)

MEMORANDUM OF MEETING MINUTES

The Pre-NDA meeting scheduled for December 6, 2004 was cancelled. The following are the official Division of Reproductive and Urologic Drug Products (DRUDP) responses to the questions in the meeting package.

SPONSOR: Warner Chilcott
APPLICATION: IND 68,098
DRUG NAME: Sarafem® (fluoxetine hydrochloride) Tablets

BACKGROUND: Warner Chilcott has acquired the sales and marketing rights from Eli Lily for Sarafem Pulvules®, 10 mg and 20 mg. The product is approved for the treatment of premenstrual dysphoric disorder (PMDD) in both continuous and intermittent dosing regimes. Warner Chilcott is developing a 15 mg dose and changing the drug product from pulvules to tablets.

MEETING OBJECTIVES: Discussion of the proposed content and format of the New Drug Application for Sarafem Tablets to be submitted under 505(b)2 of the Food, Drug and Cosmetic Act.

SPONSOR'S QUESTIONS AND DIVISION'S (DRUDP's) RESPONSES

General

1. *Does the Agency concur that the information to be included in the NDA in support of Sarafem tablets, 10 mg, [15 mg], and 20 mg, in the treatment of PMDD is adequate and sufficient for the evaluation of the NDA under Section 505(b)(2)?*

DRUDP Response:
Yes, the information described in the meeting package should be sufficient for submission of the proposed NDA if the issues raised by the chemistry and biopharmaceutical reviewers (see below) are adequately addressed.

Item 4. Chemistry, Manufacturing and Controls

2. *Does the Agency concur that the chemistry, manufacturing and controls information proposed for the 15 mg tablet is adequate and sufficient for the evaluation of this tablet strength, and that the limited stability data on the 15 mg tablet which would be further supported with stability data for the 10 and 20 mg tablets can be considered sufficient in determining the stability of the 15 mg tablet?*

DRUDP Response:
Considering the similarity of the formulation of 15 mg Sarafem tablets to those for the 10 mg and 20 mg tablets, the sponsor's proposal of providing limited data for the 15 mg Sarafem tablets is acceptable. However, the sponsor needs to specify the amount of stability data (one batch) that will be provided for the 15 mg Sarafem tablets. It is recommended that the sponsor provide at least 6-months accelerated and long term stability data.

3. *Does the Agency concur with the content and outline proposed for Item 4?*

DRUDP Response:

The drug substance content section should include the following additional information:

- Drug substance testing sites
- Packaging information, if changed from the supplier's (DMF holder) packaging.
- Validation reports for the drug substance test methods
- Storage conditions and retest period

The drug product content section should include the following additional information:

- "Specifications and Test Methods for Non-Compendial Components" of the drug product [redacted] as a subsection. However, if authorization letters from the DMF holders of [redacted] are included, that will suffice.
- The overview of stability program should include a subsection "General Product Information" to include information on the specific formulations, size & type of container closure etc.

Other comments:

- Acceptance criterion for water content of the drug products should be established (specification section).
- The related substances should include "specified identified," "specified unidentified," "unspecified" and total degradation products (specification section).
- The stability section should contain "Stressed or other Stability Studies."

Item 5. Nonclinical Pharmacology and Toxicology

4. *Does the Agency concur that the nonclinical pharmacology and toxicology of fluoxetine hydrochloride is well established and that no further information on fluoxetine hydrochloride is required in Item 5?*

DRUDP Response: Yes.

5. *Does the Agency concur that a demonstration that the quantity of each inactive ingredient found in Sarafem tablets is below the maximum potency provided in FDA's database is adequate and sufficient in the evaluation of the product?*

DRUDP Response: Yes.

6. *Does the Agency concur with the extent of the content proposed for Item 5?*

DRUDP Response: Yes

Item 6. Human Pharmacokinetics and Bioavailability

7. *Does the Agency concur that the absorption, distribution, metabolism and excretion of fluoxetine hydrochloride is well established and can be addressed in Item 6 with only a reference to Lilly's NDA 18-963?*

DRUDP Response: Yes.

8. *Does the Agency concur with the approach in requesting the waiver of evidence of in vivo bioavailability/bioequivalence for the two lower strength (10 and 15 mg) tablets, and the waiver for the food-effect study?*

DRUDP Response:
Your approach in requesting an in vivo bioavailability/bioequivalence (BA/BE) study waiver for the 10 mg tablet strength is appropriate. Similar data (in vitro dissolution profile comparisons, formulation similarity, etc.) should be submitted in requesting a BA/BE study waiver for the 15 mg tablet strength. The waiver for the food effect study will be considered upon the Division's thorough review of the fasted BE study results and in vitro dissolution comparisons of the pulvules versus tablets in different pH media (pH 1.2, 4.5, and 6.8).

9. *In the event that a response to the requests for the biowaiver and the food-effect study waiver submitted to IND 68,098 on October 29, 2004 (Amendment 3) has not been received at the time of the NDA filing, does the Agency concur that a copy of the request should be included in Item 6 rather than a cross-reference to the IND?*

DRUDP Response:
The agency will respond to the waiver requests during the NDA review cycle following a thorough review of the BE study results and the in vitro dissolution testing comparisons. Include the waiver requests with appropriate data in the NDA.

10. Does the Agency concur with the content and outline proposed for Item 6?

DRUDP Response:
Yes. Also include electronic data sets in SAS transport files for drug levels for both the BE study and in vitro dissolution testing results.

Item 8. Clinical

11. Does the Agency concur that no further information is needed in Item 8 besides the single-dose bioavailability study and reference to Lilly's NDA 18-936 Supplements 058 and 067?

DRUDP Response: Yes.

12. Does the Agency concur with the content and outline proposed for Item 8?

DRUDP Response: Yes

Item 10. Statistical

13. Does the Agency concur that Item 10 is not applicable and can be omitted? Item 1 (index) will reflect that Item 10 is "not applicable."

DRUDP Response: Yes.

Electronic Components of the NDA

14. Does the agency concur that only draft labeling (prescribing information and container labeling) provided in MS WORD 2000 and PDF files need to be submitted in the NDA in electronic format?

DRUDP Response:
The Division requests that the Sponsor also provides the pharmacokinetic data and dissolution data in both paper format as well as electronic data sets in SAS transport format (see response to Question 10).

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/s/

Scott Monroe
12/9/04 05:54:56 PM

MEETING MINUTES

Date: February 18, 2004 **Time:** 8:30 – 9:15 am **Location:** Conf Rm C

IND: 68,098

Drug Name: Sarafem® (fluoxetine hydrochloride)

Sponsor: Galen Holdings

Indication: PMDD (premenstrual dysphoric disorder)

Type of Meeting: Pre-IND

Meeting Chair: Scott Monroe, M.D.

Meeting Recorder: Dale Cutright

FDA Attendees:
Scott Monroe, M.D., Medical Team Leader, Division of Reproductive and Urologic Drug Products (HFD-580)
Lesley Furlong, M.D., Medical Officer, DRUDP
Dale Cutright, Regulatory Project Manager, DRUDP
Swapan De, Ph.D., Chemistry Reviewer, Division of New Drugs II @ DRUDP
Ameeta Parekh, Ph.D., Clinical Pharmacology Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP
Sandhya Apparaju, Ph.D., Clinical Pharmacology Reviewer, OCPB @ DRUDP
Suzanne Thornton Ph.D., Pharmacology/Toxicology Reviewer, DRUDP
Lynnda Reid, Ph.D., Pharmacology/Toxicology Team Leader, DRUDP

Galen Holdings Attendees:
Ileana Brown, Director, Regulatory Affairs
Tina deVries, Ph.D., Vice President, Pharmaceutics
Herman Ellman, M.D., Senior Vice President, Clinical Development
Alvin Howard, Vice President, Regulatory Affairs
Katie MacFarlane, Pharm.D., Vice President, Marketing and Product Planning

Background:
Sarafem® Capsules (fluoxetine hydrochloride) are currently approved and marketed by Eli Lilly and Company for the treatment of premenstrual dysphoric disorder (PMDD) in both continuous and intermittent dosing regimens. Galen (the sponsor) has acquired from Eli Lilly "the sales and marketing rights to Sarafem inclusive of patent, technology and trademark/trade dress rights." The Sponsor is planning the filing of a NDA under Section 505(b)(2) for a new formulation (tablets) of fluoxetine and a new packaging configuration.

Question:

1. **Does the Agency concur that a relative bioavailability study comparing Sarafem tablets to be manufactured by Galen to the currently approved Sarafem capsules manufacture by Eli Lilly in a single-dose, two sequence crossover study is sufficient and adequate in support of the future filing of a Sarafem tablets NDA under section 505 (b)(2) for the currently approved indication and dosing regimens?**

   - We concur that the proposed single-dose, crossover, fasting study in healthy adults is acceptable (21 CFR 320.26). We recommend assessing bioequivalence of the test and reference products (the defined regulatory criteria for bioequivalence is that the 90% CI falls within 80-125%). The study report should include acceptable bioanalytical method validation.
   - We also request that you provide in the NDA supportive information in the form of comparative *in vitro* dissolution profiles for Sarafem tablets (proposed product) and Sarafem capsules (pulvules).
   - In order to obtain an *in vivo* biowaiver for the lower strength Sarafem tablets (10 mg), a biowaiver should be requested under 21 CFR 320.22(d)(2). In support of this request, *in vitro* release comparisons as well as information on formulation proportionality/similarity should be provided [see conditions (d)(2)(i), (ii) and (iii)].

2. **Does the Agency concur that a food effect study is not required in support of the future NDA filing?**

   - We request that you address food effects issue because of the proposed change in the formulation (capsule to tablet). If a food effect study for Sarafem tablets is not conducted, we request that you provide in your NDA adequate justification for this decision. (Justification can be in the form of comparative *in vitro* dissolution profiles in different pH conditions, outcome of the proposed *in vivo* bioequivalence study, published literature, BCS classification, results of any food effect bioavailability study conducted on Sarafem pulvules by previous sponsor, or any relevant information contained in the currently approved labels for fluoxetine).

3. **Does the Agency concur with the concept of** _____

[redacted]

4. Do all the reviewing disciplines concur with the proposed abbreviated content and outline of the IND application?

- The reviewing disciplines concur with the abbreviated content and outline of the proposed IND application.

Additional comments

1. Clinical Comments and Discussion

[redacted]

2. Chemistry Comments

- Galen inquired as to how much stability data should be provided for an NDA submission. The Division requested stability data at the time of submission of the NDA from at least three lots representative of the product to be marketed. The Division also recommended that Galen submit stability data for at least 12 months at long-term storage conditions and 6 month at accelerated storage conditions.

Dale Cutright
Project Manager

Scott Monroe, M.D.
Medical Team Leader

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/s/

Scott Monroe
3/10/04 12:24:36 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 68,098

Warner Chilcott Company, Inc.
Attention: Ileana Brown
Director, Regulatory Affairs
100 Enterprise Drive
Rockaway, NJ 07866

Dear Ms. Brown:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Sarafem® (fluoxetine hydrochloride) Tablets.

We also refer to the meeting request dated September 23, 2004 and the Pre-NDA meeting that was scheduled for December 6, 2004. The preliminary responses to your meeting questions were faxed to you on December 3, 2004. Since you agreed to accept the Division's responses, the meeting was canceled. Enclosed are the finalized responses. This correspondence serves as the official minutes of that meeting.

If you have any questions, call Karen Kirchberg, Regulatory Project Manager, at (301) 827-4254.

Sincerely,

{See appended electronic signature page}

Scott Monroe, M.D.
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure