CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-860

MEDICAL REVIEW(S)

MEMORANDUM

TO: FILE

FROM: LESLEY FURLONG, MD

SUBJECT: FINAL LABELING FOR NDA 21-860, SARAFEM

DATE: 5/19/2006

CC: SCOTT MONROE, MD AND LISA SOULE, MD

ADDENDUM TO CLINICAL REVIEW

Final labeling negotiations included

1. minor editorial changes
2. removal of a redundant section of preclinical data for consistency with the labeling approved by FDA's Division of Psychiatry Products in a supplement letter for the Prozac and Sarafem NDAs (18-936,20-101, 20-974, and 21-235), dated 11-April-2006

The labeling proposed by the sponsor on 18-May-06 was satisfactory.

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/s/

Lesley-Anne Furlong
5/19/2006 10:12:50 AM
MEDICAL OFFICER

Scott Monroe
5/19/2006 11:38:49 AM
MEDICAL OFFICER

DIVISION OF REPRODUCTIVE AND UROLOGIC PRODUCTS
CLINICAL TEAM LEADER MEMORANDUM

NDA	NDA 21-860
Type of Application	Complete Response
Applicant	Warner Chilcott (US), Inc.
Proprietary Drug Name	Sarafem
Established Drug Name	Fluoxetine hydrochloride
Drug Class	Selective serotonin reuptake inhibitor
Indications	Treatment of premenstrual dysphoric disorder
Route of Administration	Oral
Dosage Form	Tablet
Dosage Strength	Fluoxetine 10, 15 and 20 mg
Dosing Regimen	10, 15 or 20 mg daily in continuous or intermittent luteal phase dosing regimens
CDER Receipt Date	March 23, 2006
PDUFA Goal Date	May 23, 2006
Date of Memorandum	May 3, 2006
Reviewer	Lisa M. Soule, M.D.

1 RECOMMENDATIONS

1.1 RECOMMENDATION REGARDING APPROVABILITY

I recommend that NDA 21-860, 10, 15 and 20 mg fluoxetine hydrochloride oral tablets, be approved for the indication of treatment of premenstrual dysphoric disorder (PMDD).

1.2 BASIS FOR RECOMMENDATION REGARDING APPROVABILITY [RISK/BENEFIT ANALYSIS]

This NDA is submitted to support marketing approval for a new tablet formulation and for a new intermediate dose of 15 mg, in addition to the 10 and 20 mg doses already approved in pulvule formulation. A single dose bioequivalence study in healthy women was conducted to compare the new 20 mg tablets to the existing 20 mg pulvules, and bioequivalence was demonstrated. These data, and comparative dissolution profiles for all three strengths, support waivers for bioequivalence studies of lower dose strengths and for a food-effect study.

The safety profile demonstrated in the bioequivalence study of 26 women did not suggest any new safety signals for the new fluoxetine formulation and intermediate dose. The risk/benefit ratio for the new formulation is expected to be the same as that for the previously approved pulvule formulation, and is therefore acceptable for this indication.

1.3 RECOMMENDATION ON RISK MANAGEMENT STEPS AND/OR PHASE 4 STUDIES

1.3.1 Risk Management Steps

No risk management steps are planned by the Applicant or recommended by the Division. Labeling, included a bolded warning concerning risk of suicidality, will be consistent with that used for the current approved formulation of Sarafem®.

1.3.2 Phase 4 Studies

No phase 4 clinical studies are recommended.

2 BACKGROUND

2.1 DESCRIPTION OF PRODUCT

Fluoxetine hydrochloride is an antidepressant in the selective serotonin reuptake inhibitor (SSRI) class. The mechanism of action is believed to involve the inhibition of neuronal reuptake of the neurotransmitter serotonin in the central nervous system.

2.2 REGULATORY HISTORY

Fluoxetine (Prozac®) was initially approved for major depressive disorder in 1987, under NDA 18-936, submitted by Eli Lilly. The indication for PMDD was approved (Sarafem®) in 2000 as a continuous dosing regimen (efficacy supplement 058), and as an intermittent dosing regimen in 2002 (efficacy supplement 067).

A pre-IND meeting was held with DRUP on February 18, 2004 to discuss plans for a new formulation (tablets) and new packaging, to include [redacted] intended to improve compliance by [redacted] At that time, the Division concurred that a single-dose relative bioavailability study comparing the currently approved Sarafem pulvules to the proposed Sarafem tablets would be acceptable to support an NDA. Submission of comparative *in vitro* dissolution profiles, requests for biowaivers for lower strength Sarafem doses, and justification of a food effects study waiver were recommended.

Subsequent to this, the Applicant decided not to pursue [redacted] A pre-NDA meeting was scheduled for December 2004 with the Applicant, Warner Chilcott, which had acquired sales and marketing rights from Eli Lilly. This meeting was cancelled after receipt of DRUP responses to the Applicant's questions. The Division agreed that nonclinical pharmacology and toxicology of fluoxetine was well-established and did not need to be addressed further in the NDA, and that information on absorption, distribution, metabolism and excretion of fluoxetine could be addressed by reference to NDA 18-936. The Division further concurred that no further clinical information beyond the bioequivalence study would be necessary.

The Applicant submitted an NDA for a new tablet formulation and for a new intermediate dose of 15 mg on May 19, 2005. Due to unaddressed labeling issues relating to a change in packaging submitted on the action date, an approvable action was taken on March 20, 2006. The Applicant then submitted the Complete Response that is the subject of this review on March 22, 2006.

2.3 PRIMARY MEDICAL REVIEWER'S RECOMMENDATION FOR APPROVABILITY

In her first cycle review, dated March 2, 2006, the primary medical reviewer, Dr. Lesley Furlong, recommended:

From a clinical perspective, I recommend approval of this application for

- *a new formulation (tablets) of Sarafem*

- *a new, intermediate dosage strength (15-mg), in addition to the existing dosage strengths (10-mg and 20-mg)*

pending satisfactory inspections of the clinical study and manufacturing sites, and pending completion of labeling negotiations.

The Applicant demonstrated bioequivalence between the new tablet formulation and the existing pulvule formulation through a single-dose study comparing the 20-mg dose of the new tablet to the 20-mg dose of the approved pulvule. Furthermore, the Applicant acceptably met FDA requirements for a food effects waiver. In addition, the Applicant acceptably met FDA requirements for a bioavailability waiver for the lower doses. No unexpected safety issues arose in the only clinical study, a small bioequivalence study involving 26 subjects. The introduction of an intermediate dosage strength necessitated no substantive changes in labeling, including no changes in the dosing instructions. The addition of an intermediate dosage strength confers no apparent health benefit and no apparent health risk to the already-marketed regimen.

In her review of the Complete Response, dated April 26, 2006, Dr. Furlong recommended:

From a clinical perspective, I recommend approval of the application.

Team Leader Comment

- I concur with the recommendation of the primary medical reviewer that the application be approved. Acceptable labeling has been negotiated in this review cycle.

3 INDICATION OF PREMENSTRUAL DYSPHORIC DISORDER

3.1 OVERVIEW OF CLINICAL PROGRAM

The primary efficacy study, Protocol PR 10603.1, was a randomized, non-blinded, single dose, two-period crossover study to assess the bioavailability of fluoxetine following administration of 20 mg Sarafem tablets as compared to 20 mg Sarafem pulvules. The study enrolled 26 healthy, nonsmoking, nonpregnant women aged 18-45. Subjects received a single dose of either tablet or pulvule formulation, then received the alternate formulation after a 56-day washout. Treatment sequence was randomized. Noncompartmental pharmacokinetic parameters for fluoxetine and the active metabolite, norfluoxetine, were calculated for both tablets and pulvules, based on a validated LC-MS/MS technique. Bioavailability measures were compared between the test (tablet) and reference (pulvule) treatment using the average bioequivalence approach, where treatments are defined as bioequivalent if the ratios of the test: reference AUC and C_{max} values fall between 80-125%.

3.2 DEMOGRAPHICS

The median age of the subjects enrolled was 27 (20-45) years, with median weight of 65.7 (47.6-85.5) kg. Twenty-four subjects were Caucasian, one was African American and one was Asian.

3.3 DISPOSITION OF SUBJECTS

Twenty-four subjects completed the trial, and all completers provided evaluable data. No subject was withdrawn due to an adverse event; however, one subject (#20) was withdrawn after she vomited within 16 hours after dosing in Period 1. A second subject (#25) withdrew for personal reasons several weeks after Period 1.

3.4 EFFICACY FINDINGS

The Clinical Pharmacology and Biopharmaceutics reviewer confirmed the data submitted by the Applicant, verifying that bioequivalence was demonstrated for both fluoxetine and norfluoxetine

(Table 1). The data on fluoxetine alone was considered adequate to demonstrate bioequivalence, with the data on norfluoxetine merely supportive.

Table 1 Geometric Means, Bioequivalence Ratios and 90% Confidence Intervals (CI)

Parameter	Test (Tablet)	Reference (Pulvule)	Ratio (T/R)	Lower 90% CI	Upper 90% CI
Fluoxetine					
C_{max}	12.85	13.06	98.08	95.22	101.02
AUC_{0-t}	454.23	480.99	94.74	91.47	98.14
AUC_{inf}	524.40	553.56	94.92	90.98	99.02
Norfluoxetine					
C_{max}	8.69	9.1	95.69	93.57	106.43
AUC_{0-t}	1952.2	2039.05	95.95	92.94	99.06
AUC_{inf}	2315.3	2383.70	96.16	92.13	100.36

Source: Based on Synopsis Table 1, Volume 9, p 34

Upon receipt of the report by the Division of Scientific Investigation (see Section 5.5) indicating inadvertent switching of the first and second treatment period data for one subject, the Clinical Pharmacology and Biopharmaceutics reviewer reanalyzed the bioequivalence data with removal of all data on the affected subject, and with the data from the first and second periods reversed for that subject. By either method, the bioequivalence criteria were met within the 80-125% bounds.

The Clinical Pharmacology and Biopharmaceutics reviewer concluded in her first cycle review, dated March 2, 2006, that requests for biowaivers for demonstrating bioequivalence of the 10 and 15 mg tablets were justified based on

- demonstration of bioequivalence for the highest dose
- proportionally similar composition of the new 10 and 15 mg tablets in relation to the 20 mg tablet, whose bioavailability has been demonstrated
- comparable dissolution profiles of the lower strength tablets to the 20 mg tablet

The food effect waiver was also deemed to be justified, based on

- establishment of bioequivalence to the reference pulvule under fasted conditions
- comparable dissolution profiles for the tablets under three different pH media
- lack of significant food effect for the currently marketed pulvule and resultant labeling language in the current approved Sarafem label.

Thus, efficacy, as determined by bioequivalence of the proposed 20 mg tablet to the currently marketed 20 mg pulvule has been adequately demonstrated. Waivers for additional bioequivalence studies on the two lower doses and for a food effects study have been justified.

3.5 SAFETY FINDINGS

3.5.1 Deaths and Serious Adverse Events

There were no deaths or serious adverse events.

3.5.2 Other Adverse Events

A total of 21 subjects experienced 55 adverse events following dosing. Twenty-one adverse events occurred in 11 subjects after receiving the test article (Sarafem tablets); 30 occurred in 18 subjects after receiving Sarafem pulvules. Four laboratory adverse events occurring in four subjects were detected at the end of the trial; therefore association with a particular treatment could not be determined. The most common adverse event was headache, which affected 11 subjects, with eight events following pulvule treatment and six events following tablet treatment.

Laboratory testing was done at baseline and end of study. Five subjects experienced out-of-range laboratory values. The three laboratory abnormalities considered severe all involved leukocytosis

on urinalysis. One subject experienced elevated AST and ALT, which was considered a moderate adverse event, with post-study values of 47 U/L for AST and 87 U/L for ALT.

Team Leader Comment

- The significance of one case of elevated transaminases cannot be determined. Due to the schedule for laboratory testing, it cannot be stated whether this event followed tablet or pulvule administration. Transaminase elevation is a labeled event in the current label.

Review of physical examination findings and vital signs did not reveal any clinically significant abnormal findings. ECGs conducted at screening and end of the study were all normal.

3.5.3 Overall Assessment of Safety Findings

No change in the safety profile of the existing formulation of Sarafem was demonstrated using the new tablet formulation. Only two adverse events not currently labeled (genital pruritis and vaginal burning) occurred following tablet administration; both were considered unlikely to be related to drug administration.

Safety updates were submitted on September 12, 2005 and on February 24, 2006 for the first cycle review. No clinical or nonclinical studies were ongoing. Prescribing Information for Eli Lilly's Sarafem Pulvules was revised on January 26, 2006 and reviewed by the Division of Neuropharmacologic Products; the draft labeling for Sarafem tablets was updated in accord with this, and submitted to the Division on February 20, 2006. The updates pertain to a new drug interaction with pimozide and to juvenile animal toxicology, and affect the Contraindications and Precautions sections of the proposed label.

A safety update was submitted with the Complete Response of March 22, 2006. Again, the Applicant affirmed that no clinical or nonclinical studies were ongoing or being initiated, that Sarafem is not marketed outside the US, that the proposed labeling is based upon the approved Sarafem pulvules labeling, and that no new safety information that may affect labeling has been obtained.

3.6 RISK/BENEFIT ANALYSIS OF SARAFEM TABLETS FOR PMDD

This NDA is submitted to support marketing approval for a new tablet formulation and for a new intermediate dose of 15 mg, in addition to the 10 and 20 mg doses already approved in pulvule formulation. A single dose bioequivalence study in healthy women was conducted to compare the new 20 mg tablets to the existing 20 mg pulvules, and bioequivalence was demonstrated. These data, and comparative dissolution profiles for all three strengths, support waivers for bioequivalence studies of lower dose strengths and for a food-effect study.

The safety profile demonstrated in the bioequivalence study of 26 women did not suggest any new safety signals for the new fluoxetine formulation and intermediate dose. The risk/benefit ratio for this new formulation and new intermediate dosage strength for the indication of PMDD is acceptable.

4 LABELING ISSUES

Negotiations on labeling issues aside from those pertaining to packaging and carton and container labeling were concluded successfully during the first cycle review. The Applicant has submitted final packaging and carton and container labeling in this complete response, and has adopted the requested FDA revisions:

All submitted labeling and packaging is now acceptable.

5 RECOMMENDATIONS OF OTHER DISCIPLINES AND DIVISIONS

5.1 TOXICOLOGY AND PRECLINICAL PHARMACOLOGY

The primary Toxicology Reviewer (Leslie McKinney) made the following recommendations in her first cycle review (October 20, 2005):

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

No new pharmacology/toxicology issues arose in review of the Complete Response. Dr. McKenney's memorandum dated April 26 2006 stated:

> *The major amendment to NDA 21-860, submitted 3-23-2006, does not contain any new pharm/tox data. I have reviewed the label and find it acceptable.*

5.2 CMC AND PRODUCT MICROBIOLOGY

The primary Chemistry Reviewer (Maria Ysern) made the following recommendations in her review of the Complete Response (April 20, 2006):

> *The new child-resistant packaging is acceptable. The cGMP status is now acceptable. Therefore this NDA can be approved from a CMC perspective.*

No phase IV commitments or risk management steps were recommended.

5.3 CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

The primary Clinical Pharmacology and Biopharmaceutics Reviewer (Sandhya Apparaju) stated the following in her first cycle review (March 2, 2006):

> *NDA 21-860 is acceptable from a clinical pharmacology and biopharmaceutics perspective.*

No phase IV commitments were recommended.

Dr. Apparaju's Complete Response review (May 1, 2006) concluded that:

> *The resubmitted label has been reviewed and found acceptable from a clinical pharmacology perspective.*

5.4 STATISTICS

The Statistical Reviewer (Kate Meaker) stated the following (July 8, 2005) during the first cycle review:

> *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.*

No new clinical data were submitted in the Complete Response.

5.5 DIVISION OF SCIENTIFIC INVESTIGATION

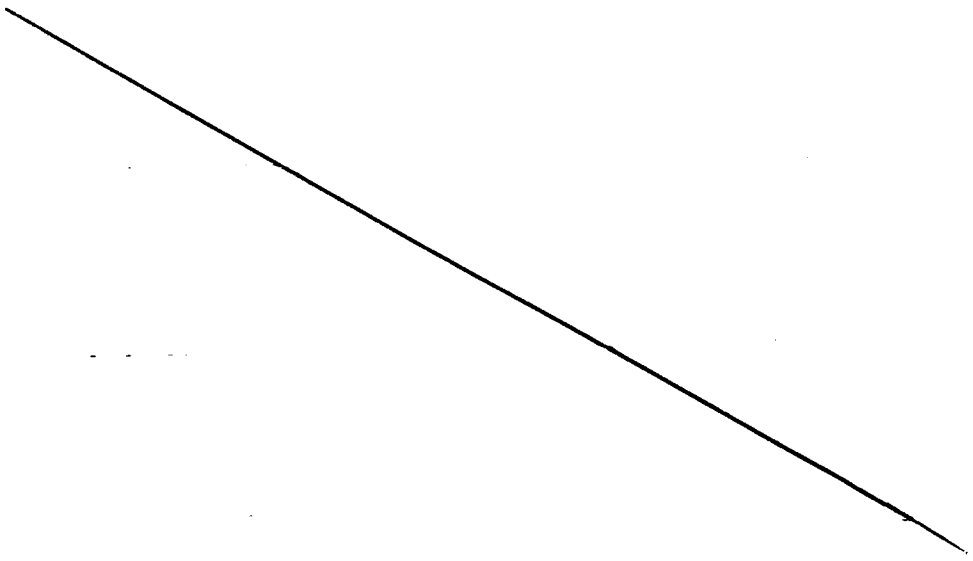
During the first cycle review, the Division of Scientific Investigation (DSI) inspected two sites for the NDA [redacted] Michael Skelly, Ph.D. from

DSI made the following overall assessment and general recommendations in his review dated February 28, 2006:

> *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.* [Period 1 and 2 samples for a single subject were switched. DSI's evaluation supported the hypothesis of accidental exchange.]
> 2. *There is no precision test in the system suitability used in the procedure for the "The Determination of Fluoxetine and Norfluoxetine in Human Plasma by LC/MS/MS"...* [DSI's subsequent evaluation was that HPLC ——— reproducibility is, in fact, not expected for these bioanalysis, the suitability of the system was correctly demonstrated, and that the objectionable observation above has no adverse consequences to data acceptability.]
>
> *DSI recommends that the clinical and analytical data from study PR-10603 are acceptable for review, after excluding the data from Subject #12.* (See Section 3.4)

5.6 DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT

Loretta Holmes, Pharm.D., of the Division of Medication Errors and Technical Support (DMETS) made recommendations in her first cycle review (January 5, 2006) concerning container, carton and package insert labeling. Specific recommendations were conveyed to the Applicant and satisfactory resolution was reached. Two DMETS recommendations were not adopted:



5.7 DIVISION OF DRUG MARKETING, ADVERTISING AND COMMUNICATIONS AND DIVISION OF SURVEILLANCE, RESEARCH AND COMMUNICATION SUPPORT

Consults were not requested of these two divisions because this NDA utilizes existing approved labeling for Sarafem, with revisions limited to those pertaining to the change from pulvule to tablet formulation and the addition of an intermediate dose.

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/s/

Lisa Soule
5/15/2006 01:52:43 PM
MEDICAL OFFICER

Scott Monroe
5/15/2006 03:02:39 PM
MEDICAL OFFICER
I concur that NDA 21-860 (10, 15 and 20 mg fluoxetine hydrochloride oral tablets) be approved for the indication of treatment of premenstrual dysphoric disorder.

CLINICAL REVIEW

Application Type	NDA
Submission Number	21-860
Submission Code	AZ
Letter Date	22-Mar-2006
Stamp Date	23-Mar-2006
PDUFA Goal Date	23-May-2006
Reviewer Name	L. Furlong
Review Completion Date	26-Apr-2006
Established Name	fluoxetine hydrochloride tablets
Trade Name	Sarafem
Therapeutic Class	antidepressant
Applicant	Warner Chilcott (US), Inc.
Priority Designation	S
Formulation	tablets
Dosing Regimen	10 mg, 15 mg, or 20 mg daily in continuous or intermittent dosing regimens
Indication	premenstrual dysphoric disorder
Intended Population	women of reproductive age

Table of Contents

1 EXECUTIVE SUMMARY

From a clinical perspective, I recommend approval of the application.

The submission is a complete response to an approvable action issued on 20-March-2006. FDA issued an approvable action because the Applicant submitted a change in packaging (blister packs) on the action date. Other labeling had not been updated to reflect the change in the blister packs. The new blister packs contained seven tablets [redacted] The blister packs had been reconfigured in response to an earlier request from the chemistry review team to meet requirements for child-resistant packaging. FDA's approvable letter requested acceptable labeling and a routine safety update.

Three days later, the Applicant responded with a resubmission.

The Applicant amended only the sections of labeling that applied to the new blister packs. FDA had concurred with the remaining labeling before the approvable action.

The safety update consisted of two paragraphs detailing that

- No studies are underway
- Sarafem tablets are not marketed elsewhere
- The proposed labeling is consistent with currently approved labeling for Sarafem Pulvules
- There is no new safety information that may affect labeling since the last safety update

Comment: FDA requested the addition of the word "tablets" to descriptive phrases that appear on the cartons and in the "How Supplied" section of the package insert. The Applicant concurred. For example, the phrase [redacted] was amended to read [redacted] on the trade cartons.

The Applicant's resubmission was acceptable to me from a clinical perspective.

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/s/

Lesley-Anne Furlong
4/27/2006 02:49:56 PM
MEDICAL OFFICER

Lisa Soule
4/27/2006 02:58:04 PM
MEDICAL OFFICER

DIVISION OF REPRODUCTIVE AND UROLOGIC PRODUCTS
CLINICAL TEAM LEADER MEMORANDUM

NDA	NDA 21-860
Type of Application	Original NDA
Applicant	Warner Chilcott (US), Inc.
Proprietary Drug Name	Sarafem
Established Drug Name	Fluoxetine hydrochloride
Drug Class	Selective serotonin reuptake inhibitor
Indications	Treatment of premenstrual dysphoric disorder
Route of Administration	Oral
Dosage Form	Tablet
Dosage Strength	Fluoxetine 10, 15 and 20 mg
Dosing Regimen	10, 15 or 20 mg daily in continuous or intermittent luteal phase dosing regimens
CDER Receipt Date	May 20, 2005
PDUFA Goal Date	March 20, 2006
Date of Memorandum	March 20, 2006
Reviewer	Lisa M. Soule, M.D. Clinical Team Leader, Division of Reproductive and Urologic Products (DRUP)

1 RECOMMENDATIONS

1.1 RECOMMENDATION REGARDING APPROVABILITY

I recommend that NDA 21-860, 10, 15 and 20 mg fluoxetine hydrochloride oral tablets, be approved for the indication of treatment of premenstrual dysphoric disorder (PMDD, pending submission of final packaging and acceptable labeling (physician insert, carton and container labels).

1.2 BASIS FOR RECOMMENDATION REGARDING APPROVABILITY [RISK/BENEFIT ANALYSIS]

This NDA is submitted to support marketing approval for a new tablet formulation and for a new intermediate dose of 15 mg, in addition to the 10 and 20 mg doses already approved in pulvule formulation. A single dose bioequivalence study in healthy women was conducted to compare the new 20 mg tablets to the existing 20 mg pulvules, and bioequivalence was demonstrated. These data, and comparative dissolution profiles for all three strengths, support waivers for bioequivalence studies of lower dose strengths and for a food-effect study.

The safety profile demonstrated in the bioequivalence study of 26 women did not suggest any new safety signals for the new fluoxetine formulation and intermediate dose. The risk/benefit ratio for this indication is acceptable.

1.3 RECOMMENDATION ON RISK MANAGEMENT STEPS AND/OR PHASE 4 STUDIES

1.3.1 Risk Management Steps

No risk management steps are planned by the Applicant or recommended by the Division. Labeling, included a bolded warning concerning risk of suicidality, will be consistent with that used for the current approved formulation of Sarafem®.

1.3.2 Phase 4 Studies

No phase 4 clinical studies are recommended.

2 BACKGROUND

2.1 DESCRIPTION OF PRODUCT

Fluoxetine hydrochloride is an antidepressant in the selective serotonin reuptake inhibitor (SSRI) class. The mechanism of action is believed to involve the inhibition of neuronal reuptake of the neurotransmitter serotonin in the central nervous system.

2.2 REGULATORY HISTORY

Fluoxetine (Prozac®) was initially approved for major depressive disorder in 1987, under NDA 18-936, submitted by Eli Lilly. The indication for PMDD was approved (Sarafem®) in 2000 as a continuous dosing regimen (efficacy supplement 058), and later, as an intermittent dosing regimen, in 2002 (efficacy supplement 067).

A pre-IND meeting was held with DRUP on February 18, 2004 to discuss plans for a new formulation (tablets) and new packaging, to include [redacted] intended to improve compliance [redacted] At that time, the Division concurred that a single-dose relative bioavailability study comparing the currently approved Sarafem capsules to the proposed Sarafem tablets would be acceptable to support an NDA. Submission of comparative *in vitro* dissolution profiles, requests for biowaivers for lower strength Sarafem doses, and justification of a food effects study waiver were recommended.

Subsequent to this, the Applicant decided not to pursue the [redacted] A pre-NDA meeting was scheduled for December 2004 with the Applicant, Warner Chilcott, which had acquired sales and marketing rights from Eli Lilly. This meeting was cancelled after receipt of DRUP responses to the Applicant's questions. The Division agreed that nonclinical pharmacology and toxicology of fluoxetine was well-established and did not need to be addressed further in the NDA, and that information on absorption, distribution, metabolism and excretion of fluoxetine could be addressed by reference to NDA 18-936. The Division further concurred that no further clinical information beyond the bioequivalence study would be necessary.

2.3 PRIMARY MEDICAL REVIEWER'S RECOMMENDATION FOR APPROVABILITY

The primary medical reviewer, Dr. Lesley Furlong, recommended:

From a clinical perspective, I recommend approval of this application for

- *a new formulation (tablets) of Sarafem*
- *a new, intermediate dosage strength (15-mg), in addition to the existing dosage strengths (10-mg and 20-mg)*

pending satisfactory inspections of the clinical study and manufacturing sites, and pending completion of labeling negotiations.

The Applicant demonstrated bioequivalence between the new tablet formulation and the existing pulvule formulation through a single-dose study comparing the 20-mg dose of

the new tablet to the 20-mg dose of the approved pulvule. Furthermore, the Applicant acceptably met FDA requirements for a food effects waiver. In addition, the Applicant acceptably met FDA requirements for a bioavailability waiver for the lower doses. No unexpected safety issues arose in the only clinical study, a small bioequivalence study involving 26 subjects. The introduction of an intermediate dosage strength necessitated no substantive changes in labeling, including no changes in the dosing instructions. The addition of an intermediate dosage strength confers no apparent health benefit and no apparent health risk to the already-marketed regimen.

Team Leader Comment

- I concur with the recommendation of the primary medical reviewer that the application be approved.

3 INDICATION OF PREMENSTRUAL DYSPHORIC DISORDER

3.1 OVERVIEW OF CLINICAL PROGRAM

The primary efficacy study, Protocol PR 10603.1, was a randomized, non-blinded, single dose, two-period crossover study to assess the bioavailability of fluoxetine following administration of 20 mg Sarafem tablets as compared to 20 mg Sarafem pulvules. The study enrolled 26 healthy, nonsmoking, nonpregnant women aged 18-45. Subjects received a single dose of either tablet or pulvule formulation, then received the alternate formulation after a 56-day washout. Treatment sequence was randomized. Noncompartmental pharmacokinetic parameters for fluoxetine and the active metabolite, norfluoxetine, were calculated for both tablets and pulvules, based on a validated LC-MS/MS technique. Bioavailability measures were compared between the test (tablet) and reference (pulvule) treatment using the average bioequivalence approach, where treatments are defined as bioequivalent if the ratios of the test: reference AUC and C_{max} values fall between 80-125%.

3.2 DEMOGRAPHICS

The median age of the subjects enrolled was 27 (20-45) years, with median weight of 65.7 (47.6-85.5) kg. Twenty-four subjects were Caucasian, one was African American and one was Asian.

3.3 DISPOSITION OF SUBJECTS

Twenty-four subjects completed the trial, and all completers provided evaluable data. No subject was withdrawn due to an adverse event; however, one subject (#20) was withdrawn after she vomited within 16 hours after dosing in Period 1. A second subject (#25) withdrew for personal reasons several weeks after Period 1.

3.4 EFFICACY FINDINGS

The Clinical Pharmacology and Biopharmaceutics reviewer confirmed the data submitted by the Applicant, verifying that bioequivalence was demonstrated for both fluoxetine and norfluoxetine (Table 1). The data on fluoxetine alone was considered adequate to demonstrate bioequivalence, with the data on norfluoxetine merely supportive.

Table 1 Geometric Means, Bioequivalence Ratios and 90% Confidence Intervals (CI)

Parameter	Test (Tablet)	Reference (Pulvule)	Ratio (T/R)	Lower 90% CI	Upper 90% CI
Fluoxetine					
C_{max}	12.85	13.06	98.08	95.22	101.02
AUC_{0-t}	454.23	480.99	94.74	91.47	98.14
AUC_{inf}	524.40	553.56	94.92	90.98	99.02
Norfluoxetine					
C_{max}	8.69	9.1	95.69	93.57	106.43
AUC_{0-t}	1952.2	2039.05	95.95	92.94	99.06
AUC_{inf}	2315.3	2383.70	96.16	92.13	100.36

Source: Based on Synopsis Table 1, Volume 9, p 34

Upon receipt of the report by the Division of Scientific Investigation (see Section 5.5) indicating inadvertent switching of the first and second treatment period data for one subject, the Clinical Pharmacology and Biopharmaceutics reviewer reanalyzed the bioequivalence data with removal of all data on the affected subject, and with the data from the first and second periods reversed for that subject. By either method, the bioequivalence criteria were met within the 80-125% bounds.

The Clinical Pharmacology and Biopharmaceutics reviewer concluded that requests for biowaivers for demonstrating bioequivalence of the 10 and 15 mg tablets were justified based on

- demonstration of bioequivalence for the highest dose
- proportionally similar composition of the new 10 and 15 mg tablets in relation to the 20 mg tablet, whose bioavailability has been demonstrated
- comparable dissolution profiles of the lower strength tablets to the 20 mg tablet

The food effect waiver was also deemed to be justified, based on

- establishment of bioequivalence to the reference pulvule under fasted conditions
- comparable dissolution profiles for the tablets under three different pH media
- lack of significant food effect for the currently marketed pulvule and resultant labeling language in the current approved Sarafem label.

Thus, efficacy, as determined by bioequivalence of the proposed 20 mg tablet to the currently marketed 20 mg pulvule has been adequately demonstrated. Waivers for additional bioequivalence studies on the two lower doses and for a food effects study have been justified.

3.5 SAFETY FINDINGS

3.5.1 Deaths and Serious Adverse Events

There were no deaths or serious adverse events.

3.5.2 Other Adverse Events

A total of 21 subjects experienced 55 adverse events following dosing. Twenty-one adverse events occurred in 11 subjects after receiving the test article (Sarafem tablets); 30 occurred in 18 subjects after receiving Sarafem pulvules. Four laboratory adverse events occurring in four subjects were detected at the end of the trial; therefore association with a particular treatment could not be determined. The most common adverse event was headache, which affected 11 subjects, with eight events following pulvule treatment and six events following tablet treatment.

Laboratory testing was done at baseline and end of study. Five subjects experienced out-of-range laboratory values. The three laboratory abnormalities considered severe all involved leukocytosis on urinalysis. One subject experienced elevated AST and ALT, which was considered a moderate adverse event, with post-study values of 47 U/L for AST and 87 U/L for ALT.

Team Leader Comment

- The significance of one case of elevated transaminases cannot be determined. Due to the schedule for laboratory testing, it cannot be stated whether this event followed tablet or pulvule administration. Transaminase elevation is a labeled event in the current label.

Review of physical examination findings and vital signs did not reveal any clinically significant abnormal findings. ECGs conducted at screening and end of the study were all normal.

3.5.3 Overall Assessment of Safety Findings

No change in the safety profile of the existing formulation of Sarafem was demonstrated using the new tablet formulation. Only two adverse events not currently labeled (genital pruritis and vaginal burning) occurred following tablet administration; both were considered unlikely to be related to drug administration.

Safety updates were submitted on September 12, 2005 and on February 24, 2006. No clinical or nonclinical studies were ongoing. Prescribing Information for Eli Lilly's Sarafem Pulvules was revised on January 26, 2006 and reviewed by the Division of Neuropharmacologic Products; the draft labeling for Sarafem tablets was updated in accord with this, and submitted to the Division on February 20, 2006. The updates pertain to a new drug interaction with pimozide and to juvenile animal toxicology, and affect the Contraindications and Precautions sections of the proposed label.

3.6 RISK/BENEFIT ANALYSIS OF SARAFEM TABLETS FOR PMDD

This NDA is submitted to support marketing approval for a new tablet formulation and for a new intermediate dose of 15 mg, in addition to the 10 and 20 mg doses already approved in pulvule formulation. A single dose bioequivalence study in healthy women was conducted to compare the new 20 mg tablets to the existing 20 mg pulvules, and bioequivalence was demonstrated. These data, and comparative dissolution profiles for all three strengths, support waivers for bioequivalence studies of lower dose strengths and for a food-effect study.

The safety profile demonstrated in the bioequivalence study of 26 women did not suggest any new safety signals for the new fluoxetine formulation and intermediate dose. The risk/benefit ratio for this indication is acceptable.

4 LABELING ISSUES

The Applicant has not yet submitted final packaging and carton and container labeling. Negotiations on labeling issues aside from those pertaining to packaging and carton and container labeling have been concluded successfully. The physician insert is acceptable, pending submission of final packaging and acceptable labeling with regard to the packaging.

5 RECOMMENDATIONS OF OTHER DISCIPLINES AND DIVISIONS

5.1 TOXICOLOGY AND PRECLINICAL PHARMACOLOGY

The primary Toxicology Reviewer (Leslie McKinney) made the following recommendations in her review (October 20, 2005):

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

5.2 CMC AND PRODUCT MICROBIOLOGY

The primary Chemistry Reviewer (Maria Ysern) made the following recommendations in her review (March 3, 2006):

> *The new child-resistant packaging is acceptable. The cGMP status is now acceptable. Therefore this NDA can be approved from a CMC perspective.*

No phase IV commitments or risk management steps were recommended.

5.3 CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

The primary Clinical Pharmacology and Biopharmaceutics Reviewer (Sandhya Apparaju) stated the following in her review (March 2, 2006):

> *NDA 21-860 is acceptable from a clinical pharmacology and biopharmaceutics perspective.*

No phase IV commitments were recommended.

5.4 STATISTICS

The Statistical Reviewer (Kate Meaker) stated the following (July 8, 2005):

> *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.*

5.5 DIVISION OF SCIENTIFIC INVESTIGATION

The Division of Scientific Investigation (DSI) inspected two sites for the NDA [redacted] Michael Skelly, Ph.D. from DSI made the following overall assessment and general recommendations in his review dated February 28, 2006:

> *Following the inspection at [redacted] February 6-10, 2006) there were no objectionable observations and no Form 483 was issued. Following the inspection at [redacted] (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.* [Period 1 and 2 samples for a single subject were switched. DSI's evaluation supported the hypothesis of accidental exchange.]
> 2. *There is no precision test in the system suitability used in the procedure for the "The Determination of Fluoxetine and Norfluoxetine in Human Plasma by LC/MS/MS"...* [DSI's subsequent evaluation was that HPLC [redacted] reproducibility is, in fact, not expected for these bioanalysis, the suitability of the system was correctly demonstrated, and that the objectionable observation above has no adverse consequences to data acceptability.]
>
> *DSI recommends that the clinical and analytical data from study PR-10603 are acceptable for review, after excluding the data from Subject #12.*

5.6 DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT

Loretta Holmes, Pharm.D. of the Division of Medication Errors and Technical Support (DMETS) made recommendations in her review (January 5, 2006) concerning container, carton and package insert labeling. Final packaging and carton and container labeling have not yet been submitted by the Applicant.

5.7 DIVISION OF DRUG MARKETING, ADVERTISING AND COMMUNICATIONS AND DIVISION OF SURVEILLANCE, RESEARCH AND COMMUNICATION SUPPORT

Consults were not requested of these two divisions because this NDA utilizes existing approved labeling for Sarafem, with revisions limited to those pertaining to the change from pulvule to tablet formulation and the addition of an intermediate dose.

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/s/

Lisa Soule
3/20/2006 04:33:59 PM
MEDICAL OFFICER

Scott Monroe
3/20/2006 04:54:11 PM
MEDICAL OFFICER
I concur with Dr. Soule that this Application can be approved, subject to the Applicant's submitting final packaging and acceptable labeling (i.e., physician insert and carton and container labeling).

CLINICAL REVIEW

Application Type	NDA
Submission Number	21-860/000
Submission Code	N
Letter Date	19-May-2005
Stamp Date	20-May-2005
PDUFA Goal Date	20-Mar-2006
Reviewer Name	Lesley-Anne Furlong
Review Completion Date	2-Mar-06
Established Name	fluoxetine hydrochloride
(Proposed) Trade Name	Sarafem
Therapeutic Class	antidepressant
Applicant	Warner Chilcott (US), Inc.
Priority Designation	S
Formulation	tablets
Dosing Regimen	10 mg, 15 mg, or 20 mg daily in continuous or intermittent dosing regimens
Indication	Premenstrual Dysphoric Disorder
Intended Population	women of reproductive age

Table of Contents

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

From a clinical perspective, I recommend approval of this application for

- a new formulation (tablets) of Sarafem
- a new, intermediate dosage strength (15-mg), in addition to the existing dosage strengths (10-mg and 20-mg)

pending satisfactory inspections of the manufacturing site, and pending completion of labeling negotiations.

The Applicant demonstrated bioequivalence between the new tablet formulation and the existing pulvule formulation through a single-dose study comparing the 20-mg dose of the new tablet to the 20-mg dose of the approved pulvule. Furthermore, the Applicant acceptably met FDA requirements for a food effects waiver. In addition, the Applicant acceptably met FDA requirements for a bioavailability waiver for the lower doses. No unexpected safety issues arose in the only clinical study, a small bioequivalence study involving 26 subjects. The introduction of an intermediate dosage strength necessitated no substantive changes in labeling, including no changes in the dosing instructions. The addition of an intermediate dosage strength confers no apparent health benefit and no apparent health risk to the already-marketed regimen.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

Standard risk management activity includes postmarketing reporting of adverse drug experiences, as delineated in the Code of Federal Regulations (21CFR 314.80). No exceptional risk management activity is recommended.

1.2.2 Required Phase 4 Commitments

There are no clinical Phase 4 studies required.

1.2.3 Other Phase 4 Requests

There are no other Phase 4 requests.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

The clinical program consisted of a single dose, non-blinded, two-sequence, two-treatment, crossover study of 26 subjects. The primary goal of the study was to show bioequivalence between the new tablet formulation (20-mg) and the approved pulvule formulation (20-mg.)

1.3.2 Efficacy

According to the biopharmaceutical reviewer, bioequivalence was shown "between the two formulations as seen from the ratio of the log-transformed systemic exposure parameters and the 90 % CI surrounding these estimates that are completely within the 80-125 % bounds." In addition, the Applicant also showed bioequivalence between the two formulations with respect to the active metabolite, norfluoxetine. The biopharmaceutical reviewer agreed that biowaivers for the lower dosages and a food-effect study were adequately justified by composition and dissolution profile data.

1.3.3 Safety

The small trial to show bioequivalence did not uncover any unexpected safety issues.

1.3.4 Dosing Regimen and Administration

The approved dosing instructions do not change. The new dosage strength, 15 mg, is bracketed by the existing dosage strengths, 10 mg and 20 mg.

1.3.5 Drug-Drug Interactions

The approved label addresses drug-drug interactions. During the course of the review, a new drug-drug interaction was added to the label as a contraindication because of an update to fluoxetine labeling approved by FDA's Division of Neuropharmacologic Drug Products in December 2005. The new interaction related to the use of the antipsychotic pimozide. Text was added contraindicating the concomitant use of fluoxetine and pimozide because of potential for QTc prolongation observed in studies of pimozide with other antidepressants.

1.3.6 Special Populations

The approved label addresses special populations.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Sarafem (fluoxetine hydrochloride) is currently marketed as a *pulvule* for the treatment of premenstrual dysphoric disorder (PMDD). The pulvule is available in 10-mg and 20-mg strengths. Sarafem is an antidepressant that is thought to act through inhibition of neuronal re-uptake of serotonin (a selective serotonin re-uptake inhibitor, or SSRI).

The Applicant developed a new *tablet* formulation and a new intermediate strength (15-mg) in addition to the 10-mg and 20-mg strengths.

The proposed indication and dosing instructions remain the same as those on the already-approved label for Sarafem. The addition of an intermediate dosage does not require any change in the current dosing instructions, which are:

> "20 mg/day given continuously (every day of the menstrual cycle) or intermittently (defined as starting a daily dose 14 days prior to the anticipated onset of menstruation through the first full day of menses and repeating with each new cycle.) The dosing regimen should be determined by the physician based on individual patient characteristics. In a study comparing continuous dosing of fluoxetine 20 and 60 mg/day to placebo, both doses were proven to be effective, but there was no statistically significant added benefit for the 60 mg/day compared with the 20 mg/day dose. Fluoxetine doses above 60 mg/day have not been systematically studied in patients with PMDD. The maximum fluoxetine dose should not exceed 80 mg/day."

2.2 Currently Available Treatment for Indications

Other antidepressants approved for the indication PMDD include Paxil and Zoloft. A variety of drug products and nutritional supplements are used off-label for the indication.

2.3 Availability of Proposed Active Ingredient in the United States

Fluoxetine hydrochloride was approved in the United States in 1987 for depression, and in 2000 for premenstrual dysphoric disorder (PMDD). It is available under the brand names Prozac for depression and Sarafem for PMDD. There are numerous generic versions for depression, but, according to *The Orange Book*, the patent for Sarafem (the PMDD indication) is still in effect. The patent for Sarafem will expire on November 20, 2007.

2.4 Important Issues With Pharmacologically Related Products

In 2004 the FDA promulgated standardized labeling for all antidepressants used in children. The main change was a Black Box Warning describing an increased risk of suicidal thinking and suicidal behavior in children with major depressive disorder and other psychiatric disorders during the first few months of treatment. The change in labeling was based on a pooled analysis of nine antidepressant drugs, including SSRIs and others. Current Sarafem labeling includes the FDA-recommended changes.

2.5 Presubmission Regulatory Activity

Regulatory activity started with a preIND meeting in January 2004, during which the Applicant proposed a new formulation (tablet) and new packaging [redacted] FDA also requested a food-effect study, or justification for not doing one.

IND 68,098 was opened in April 2004 with a PK study comparing a single 20-mg dose of the approved Sarafem pulvule with a single 20-mg dose of test product. In October 2004, the Applicant submitted information to support a food effects waiver and a waiver of an in vivo bioavailability study for the lower dose strengths (10-mg and 15-mg). The Applicant requested a preNDA meeting for December 2004, but cancelled it after receiving the FDA's responses to their questions in a fax. The Applicant had decided against the blister pack [redacted]

2.6 Other Relevant Background Information

In 1987 FDA approved fluoxetine (brand name Prozac) for depression (NDA 18-936). In July 2000, FDA approved a continuous dosing regimen of fluoxetine (brand name Sarafem) for treatment of PMDD (efficacy supplement 058). In June 2002, FDA approved an intermittent dosing regimen for the treatment of PMDD (efficacy supplement (067).

In January 2003, the Applicant became the distributor for Sarafem in the U.S. and obtained certain marketing rights as a result of an agreement between the Applicant and the NDA holder (Eli Lilly and Co.).

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

In February, 2006, the FDA's project manager noted that the Applicant had not planned on packaging the new formulation in child resistant packaging, and informed the review team that this plan did not conform to regulations. The chemistry team discussed the problem with the Applicant who agreed to meet regulations for packaging in a child-resistant package.

At the time this review was finalized, the application was acceptable to the chemistry reviewer pending a satisfactory inspection of the manufacturing site.

3.2 Animal Pharmacology/Toxicology

The application contained no new nonclinical data.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

Clinical data came from a single dose bioequivalence study, Study PR-10603.1 (Report RR-09204).

4.2 Tables of Clinical Studies

Table 1. Summary of Study PR-10603.1

Description	Design	N Enrolled/Completed	Objective
Single dose bioequivalence study	Single-center, non-blinded, single dose, two-sequence, two-treatment, two-period crossover	26/24	To show that Sarafem tablets 20 mg are bioequivalent to Sarafem pulvules 20 mg

Source: Modified from NDA Table 14, Volume 1, page 109

4.3 Review Strategy

My review was limited to an evaluation of the single clinical study report from the standpoint of safety. I deferred to the biopharmaceutical reviewer to evaluate whether the Sarafem tablets were shown to be bioequivalent to the approved pulvule formulation.

4.4 Data Quality and Integrity

The review team requested an inspection of the only clinical study site by FDA's Division of Scientific Integrity (DSI). The final report from DSI was received by the review team on February 28, 2006. DSI noted a problem with accidental mix-up of blood samples of a single subject (#12) from Period 1 and Period 2. When FDA's biopharmaceutical reviewer re-analyzed the data, first by removing Subject #12's data and then by reversing Subject #12's Period 1 and Period 2 data, the two formulations still demonstrated bioequivalence.

4.5 Compliance with Good Clinical Practices

According to the study report, the study was performed under Good Clinical Practices. The study was approved by the local Institutional Review Board, and detailed consent forms were provided to subjects.

4.6 Financial Disclosures

The submission contains financial disclosures for the investigator and all four subinvestigators. The financial disclosures did not raise questions about the integrity of the data.

5 CLINICAL PHARMACOLOGY

In addition to providing the results of a clinical study to support bioequivalence of the new tablet to the marketed pulvule, the Applicant requested a food effects waiver and a biowaiver for the 10-mg and 15-mg dose. According to the FDA biopharmaceutical reviewer:

- The clinical study supported bioequivalence between the approved 20-mg pulvule and the proposed 20-mg tablet.
- A food effects waiver was acceptable based on the results of the sole clinical study and "dissolution profile comparisons in three different pH media and the food-effect information derived from the approved pulvule formulation."
- The biowaiver for the lower dose strengths was acceptable based on "formulation similarity/proportionality information and comparable dissolution profiles."

6 INTEGRATED REVIEW OF EFFICACY

The submission addressed efficacy by showing bioequivalence of the new formulation to the approved formulation. See Section 5 Clinical Pharmacology.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

Twenty-six subjects were given a single, 20-mg dose of either tablet or pulvule formulation, and then they were given a single dose of the alternate formulation after a 56-day washout period. The treatment sequence was randomized.

The subjects were healthy, non-smoking, non-pregnant women between the ages of 20 and 45. The median age was 27 years old. The median weight (range) was 65.7 kg (47.6 to 85.5 kg). Twenty-four subjects were Caucasian, one was Black, and one was Asian.

7.1.1 Deaths

There were no deaths.

7.1.2 Other Serious Adverse Events

No serious adverse events were detected.

7.1.3 Dropouts and Other Significant Adverse Events

Subject #20 withdrew after vomiting about 2 hours after drug administration, and Subject #25 withdrew for personal reasons.

7.1.5 Common Adverse Events

Headache was the most frequent AE, occurring in 11 subjects. Table 2 shows that the overall incidence of AEs was not higher in the test group (tablets) compared with controls (pulvules). The only other events that occurred in more than one subject included nausea (N=2), white blood cells in urine (N= 3), and appetite decreased (N=2).

Table 2. Summary of AEs

Parameter	Tablets	Pulvules
N	24	26
N reporting at least one AE	12	19
Withdrawals	0	2
Total number of AEs	25	34

Source: Adapted from Text Table 10 of Clinical Study Report

7.1.6 Less Common Adverse Events

The events that occurred in the remaining subjects were either labeled or not clinically important.

7.1.7 Laboratory Findings

The study detected one potentially significant laboratory abnormality: an increase in ALT/AST in Subject 17 at the time of the post-study blood draw. Her AST was 47 U/L (normal 12-36 U/L) and ALT was 87 U/L (normal 12 to 52 U/L). The elevated transaminases were detected 28 days following the second treatment cycle, and the subject was lost to follow up. The subject was not known to be taking concomitant medications.

Comment: I can conclude nothing from the detection of a mild elevation in liver enzymes following exposure to both formulation in a single subject. Whether this had anything to do with drug exposure is unknown. Elevation of transaminases is listed on the approved label as a rare event (that is, occurs in less than 1 in 1,000 subjects.)

7.1.8 Vital Signs

There were no clinically important changes in vital signs.

7.1.9 Electrocardiograms (ECGs)

There were no on-treatment ECGs. Screening and post-study ECGs were normal.

7.2.9 Additional Submissions, Including Safety Update

The Applicant has no ongoing clinical or nonclinical studies of Sarafem. The only notable item in the safety update was revised labeling submitted on February 20, 2006. Two changes in labeling of Sarafem pulvules had been approved by the FDA's Division of Neuropharmacological Drug Products in December 2005.The Applicant revised labeling for the new formulation for consistency with the labeling approved in December 2005. The changes related to a new drug interaction with pimozide and new nonclinical toxicity language related to juvenile animal toxicity.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

There were no unlabelled adverse events.

8.7 Postmarketing Risk Management Plan

The Applicant has no postmarketing risk management plan.

Comment: I do not anticipate any risks related to the change from pulvule to tablet, or from the addition of an intermediate dose strength. Therefore, I do not recommend any risk management beyond current surveillance.

9 OVERALL ASSESSMENT

9.1 Conclusions

According to the biopharmaceutical reviewer, the Applicant showed bioequivalence between the new formulation and the approved formulation. In addition, the Applicant met FDA's guidelines for a bioavailability waiver for the 10-mg and 15-mg doses, and a food effects waiver. No new safety issues were raised by the data, nor are any safety or efficacy issues anticipated by the addition of the intermediate dosage strength.

Comment: It is unclear why the Applicant developed the new formulation. There is neither health benefit nor health risk apparent from the change to tablets and addition of an

intermediate dosage strength. It may be a business decision, possibly intended to impede generic competition.

9.2 Recommendation on Regulatory Action

From a clinical perspective, I recommend approval of this application for

- a new formulation of Sarafem (tablets)
- an intermediate dosage strength (15-mg), in addition to the already approved 10-mg and 20-mg dosage strengths

pending satisfactory inspections and completion of labeling negotiations.

9.3 Recommendation on Postmarketing Actions

Current surveillance should be adequate.

9.4 Labeling Review

The proposed labeling was almost identical to approved labeling for Sarafem pulvules. The changes include

- Change from "pulvule" to "tablet"
- Addition of 15-mg strength
- Minor editorial changes (e.g. change from "health care" to "healthcare")
- Removal of a reference to Prozac in the DESCRIPTION section.

A consult related to the proposed carton and packaging was obtained from FDA's Division of Medication Errors and Technical Support (DMETS). The DMETS' comments were revised slightly in consultation with the chemistry reviewer and sent to the Applicant. I received the Applicant's response, with a stamp date 27-Jan-06, on 8-Feb-06. The response addressed DMETS' carton and packaging issues satisfactorily.

The biopharmaceutical reviewer proposed small changes in the Clinical Pharmacology section of labeling. The changes had not been negotiated with the Applicant when this review was finalized.

Comment: The labeling is acceptable from a clinical standpoint.

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/s/

Lesley-Anne Furlong
3/2/2006 01:26:39 PM
MEDICAL OFFICER

Lisa Soule
3/2/2006 05:25:53 PM
MEDICAL OFFICER
I concur with Dr. Furlong's conclusions and recommendations

NDA: 21-860

45 Day Filing Meeting Checklist
CLINICAL

ITEM	YES	NO	COMMENT
1) On its face, is the clinical section of the NDA organized in a manner to allow substantive review to begin?	x		
2) Is the clinical section of the NDA indexed and paginated in a manner to allow substantive review to begin?	x		
3) On its face, is the clinical section of the NDA legible so that substantive review can begin?	x		
4) If needed, has the sponsor made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)?			Not applicable (NA)
5) On its face, do there appear to be the requisite number of adequate and well controlled studies in the application?	x		
6) Are the pivotal efficacy studies of appropriate design to meet basic requirements for approvability of this product based on proposed draft labeling?	x		The pivotal study is a single bioequivalence study designed to show bioequivalence of the proposed tablet formulation to the approved capsule formulation.
7) Are all data sets for pivotal efficacy studies complete for all indications (infections) requested?	x		
8) Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	x		

ITEM	YES	NO	COMMENT
9) Has the applicant submitted line listings in a format to allow reasonable review of the patient data? Has the applicant submitted line listings in the format agreed to previously by the Division?	x		
10) Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?		x	The study was performed in Canada. There is no reason to think that the findings would not apply to US subjects.
11) Has the applicant submitted all additional required case record forms (beyond deaths and drop-outs) previously requested by the Division		x	There were no CRFs. However, there were no deaths and 2 dropouts. One subject dropped out for personal reasons and the other for emesis. The narrative summaries provided should be adequate for the clinical review.
12) Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously agreed to by the Division?	x		
13) Has the applicant presented safety assessment based on all current world-wide knowledge regarding this product?	x		The Applicant referenced the approved NDA, and provided a copy of the approved drug label.
14) Has the applicant submitted draft labeling consistent with 201.56 and 201.57, current divisional policies, and the design of the development package?	x		
15) Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions with the sponsor?	x		
16) From a clinical perspective, is this NDA fileable? If "no", please state in item #17 below why it is not.	x		

ITEM	YES	NO	COMMENT
17) Reasons for refusal to file: none (from the clinical perspective).			

Lesley Furlong/27-Jun-2005
Reviewing Medical Officer/Date

Supervisory Medical Officer/Date

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/s/

Lesley-Anne Furlong
7/6/05 01:12:14 PM
MEDICAL OFFICER

Scott Monroe
7/11/05 07:05:17 PM
MEDICAL OFFICER
I concur.