

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-860

CHEMISTRY REVIEW(S)

NDA 21-860

Sarafem® (fluoxetine hydrochloride tablets)

Warner Chilcott Company, Inc.

**Maria Ysern, MSc.
Pre-Marketing Assessment Division II, Branch III
Office of New Drug Quality Assessment.**



Table of Contents

Table of Contents	2
Chemistry Review Data Sheet.....	3
The Executive Summary	8
I. Recommendations.....	8
A. Recommendation and Conclusion on Approvability	8
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	8
II. Summary of Chemistry Assessments.....	8
A. Description of the Drug Product(s) and Drug Substance(s)	8
B. Description of How the Drug Product is Intended to be Used.....	9
C. Basis for Approvability or Not-Approval Recommendation.....	10
III. Administrative.....	10
A. Reviewer's Signature.....	10
B. Endorsement Block.....	10
C. CC Block	10
Chemistry Assessment	11
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data.....	11
S DRUG SUBSTANCE [Name, Manufacturer].....	11
P DRUG PRODUCT [Name, Dosage form].....	11
A APPENDICES	13
R REGIONAL INFORMATION	13
II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1	13
A. Labeling & Package Insert	14
B. Environmental Assessment Or Claim Of Categorical Exclusion	15
III. List Of Deficiencies To Be Communicated.....	15



Chemistry Review Data Sheet

1. NDA: 21-860

2. REVIEW # 3:

3. REVIEW DATE: April 6, 2006

4. REVIEWER: Maria E. Ysern, MSc.

5. PREVIOUS DOCUMENTS: None

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original NDA (Paper)	19-May-2005
Original NDA(EDR)	19-May-2005
BC Amendment	14-Aug-2005
BZ Amendment	30-Aug-2005
BC Amendment	15-Sep-2005
BL Amendment	31-Oct-2005
BC Amendment	2-Dec-2005
BL Amendment	26-Jan-2006
BL Amendment	02-Feb-2006
BL Amendment	20-Feb-2006
BL Amendment	28-Feb-2006
BL Amendment	Mar 3, 2006
BL Amendment	Mar 23, 2006
BL Amendment	April 3, 2006

7. NAME & ADDRESS OF APPLICANT:



Chemistry Review Data Sheet

Name: Warner Chilcott
Address: 100 Enterprise Drive, Rockaway, NJ 07866
Representative: Alvin Howard, Vicepresident of Regulatory Affairs
Telephone: 973-442-3280

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Sarafem
b) Non-Proprietary Name (USAN): Fluoxetine hydrochloride
c) Code Name/# (ONDC only): none
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Selective serotonin inhibitor (SSRI). For treatment of premenstrual dysphoric disorder

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 10, 15 and 20 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

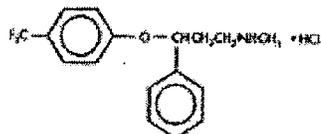
_____ SPOTS product – Form Completed

 x Not a SPOTS product

Chemistry Review Data Sheet

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

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



Molecular Weight: 345.79
 $C_{17}H_{18}F_3NO \cdot HCl$

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
/	II	/	/	1	Adequate	July 07, 2005	Chem Review #2
	II			1	Adequate	July 19, 2004	Chem. Review #6
	III			4			
	III			4			
	IV			4			
	IV			4			
	IV			4			



CHEMISTRY REVIEW



Chemistry Review Data Sheet

—	IV			4			

¹ Action codes for DMF Table:

1 – DMF Reviewed.

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

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	68,098	Sarafem (fluoxetine)
NDA	18-936 Supplements 058 and 067	Sarafem (fluoxetine)

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Compliance Acceptable recommendation	28-Feb-2006	Shawante Adams
Pharm/Tox			
Biopharm			
LNC			
Methods Validation	To be done		
DMETS	Revisions recommended and accepted by the sponsor	Jan 10, 2006	
EA	N/A		
Microbiology	N/A		
Microbiology			
EES			



CHEMISTRY REVIEW



Chemistry Review Data Sheet

Methods Validation			
--------------------	--	--	--

*Appears This Way
On Original*

The Chemistry Review for A/NDA ##-###

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

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

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

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance:

The drug substance used in the manufacture of Sarafem Tablets, 10 mg, 15 mg and 20 mg is fluoxetine hydrochloride, USP, a selective serotonin reuptake inhibitor (SSRI) for oral administration.

Fluoxetine hydrochloride, ((±)-N-methyl-3-phenyl-3-[(α,α,α-trifluoro-*p*-tolyl)oxy]propylamine hydrochloride), is a white or almost white, crystalline powder, sparingly soluble in water, _____

_____ Its molecular weight is 345.79.

Detailed information relating about manufacturing and controls, including stability of the drug substance at _____, is contained in Type II DMFs # _____

Fluoxetine hydrochloride, USP is tested in compliance with the current USP monograph. The test methods include visual description, identification by IR and chloride test, water content by KF (NMT 0.5%), heavy metals (NMT 0.003%), Assay (98.0%-102.0% on the anhydrous base).

The related compounds are tested for α-[2-(Methylamino)ethyl benzenemethanol (NMT 0.25%), fluoxetine related compound B (NMT 0.25%), fluoxetine related compound A (NMT 0.15%), other individual impurities (NMT 0.1%), and total impurities (NMT 0.5%).

The Chemistry Review for NDA 21-860

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Based on the information provided, this NDA can be approved pending and acceptable report from the cGMP inspections.

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

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance:

The drug substance used in the manufacture of Sarafem Tablets, 10 mg, 15 mg and 20 mg is fluoxetine hydrochloride, USP, a selective serotonin reuptake inhibitor (SSRI) for oral administration.

Fluoxetine hydrochloride, ((±)-N-methyl-3-phenyl-3-[(α,α,α-trifluoro-*p*-tolyl)oxy]propylamine hydrochloride), is a white or almost white, crystalline powder, sparingly soluble in water, _____

_____ Its molecular weight is 345.79.

Detailed information relating to manufacture and control, including stability of the drug substance at _____ contained in Type II DMFs # _____ and # _____

Fluoxetine hydrochloride, USP is tested in compliance with the current USP monograph. The test methods include visual description, identification by IR and chloride test, water content by KF (NMT 0.5%), heavy metals (NMT 0.003%), Assay (98.0%-102.0% on the anhydrous base).

The related compounds tested for are α-[2-(Methylamino)ethyl benzenemethanol (NMT 0.25%), fluoxetine related compound B (NMT 0.25%), fluoxetine related compound A (NMT 0.15%) , other individual impurities (NMT 0.1%), total impurities (NMT 0.5%).



Executive Summary Section

Drug Product:

Warner Chilcott Company, Inc., located in Fajardo, Puerto Rico, has submitted this NDA under section 505(b)(1) of the FDCA for a new tablet dosage form for Sarafem at 10 & 20 mg as well as a new 15 mg tablet strength.

Sarafem® (fluoxetine hydrochloride) tablets are manufactured in three dosage strengths: 10 mg (32.3 µmol), 15 mg (48.5 µmol) and 20 mg (64.7 µmol) of fluoxetine.

The release specifications include the description for each strength of tablet, identification by IR, uniformity of dosage (according to USP <905>), assay (90.0-110.0% of the label claim), related substance (NMT _____ fluoxetine related compound _____) and dissolution (USP<711>, _____ (Q) in 15 minutes)

With the exception of the colorant _____ all inactive drug product components are compendial (NF) including microcrystalline cellulose _____ croscarmellose sodium _____ colloidal silicone dioxide _____ and magnesium stearate _____

Sarafem® (fluoxetine hydrochloride tablets) is supplied as follows:

The 10 mg tablet is a cream, round tablet embossed with S10 on one side:

N 0430-0210-14 - _____

The 15 mg tablet is a white, round tablet embossed with S15 on one side:

N 0430-0215-14 - _____

The 20 mg tablet is a yellow, round tablet embossed with S20 on one side:

N 0430-0220-14 - _____

¹ Equivalent to fluoxetine base.

Six months of stability data for accelerated conditions and 18 months for intermediate and long term room temperature conditions were submitted and they met specifications. The test data for the stability pilot batch of Sarafem tablets, 15 mg through 9 months also meet specifications. (Refer to Amendment dated Dec 06, 2005).

The stability data supports the proposed 24 month shelf life for all three strengths of Sarafem.



Executive Summary Section

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

The proposed dose of Sarafem is 20 mg/day given either continuously (everyday of the menstrual cycle) _____

or intermittently (for 14 days prior to the onset of menstruation, through the first full day of menstruation repeating each cycle).

The new 15 mg tablet was developed to allow prescribers the option of an intermediate dose.

C. Basis for Approvability or Not-Approval Recommendation

The manufacturing of the drug substance, fluoxetine hydrochloride has been provided through cross reference to two DMFs _____ which have been reviewed and found adequate.

The manufacturing of the Sarafem® (fluoxetine hydrochloride) tablets 10, 15 and 20 mg tablets, using a conventional _____ described adequately through the application and master batch formulae have been provided for each of the dosage strengths.

The new child resistant packaging is deemed comparable to the original packaging without compromising stability data.

Based on the information provided, including adequate cGMP status, this NDA is recommended for approval.

III. Administrative**A. Reviewer's Signature****B. Endorsement Block**

Maria Ysern/ March 23, 2006

Moo Jhong Rhee

NChrisostomo/ProjectManagerName/Date

C. CC Block In DFS

12 Page(s) Withheld

Trade Secret / Confidential

Draft Labeling

Deliberative Process

**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
4/20/2006 01:40:50 PM
CHEMIST
Additional labeling changes

Moo-Jhong Rhee
4/20/2006 03:22:47 PM
CHEMIST
Chief, Branch III

NDA 21-860

Sarafem® (fluoxetine hydrochloride tablets)

Warner Chilcott Company, Inc.

**Maria Ysern, MSc
Pre-Marketing Assessment Division II, Branch III
Office of New Drug Quality Assessment**

Table of Contents

Table of Contents	2
Chemistry Review Data Sheet.....	3
The Executive Summary	7
I. Recommendations.....	7
A. Recommendation and Conclusion on Approvability	7
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	7
II. Summary of Chemistry Assessments.....	7
A. Description of the Drug Product(s) and Drug Substance(s)	7
B. Description of How the Drug Product is Intended to be Used.....	9
C. Basis for Approvability or Not-Approval Recommendation.....	9
III. Administrative.....	9
A. Reviewer's Signature.....	9
B. Endorsement Block.....	9
C. CC Block	9
Chemistry Assessment.....	9
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data.....	10
S DRUG SUBSTANCE [Name, Manufacturer].....	10
P DRUG PRODUCT [Name, Dosage form].....	10
A APPENDICES	15
R REGIONAL INFORMATION	15
II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1	15
A. Labeling & Package Insert	15
B. Environmental Assessment Or Claim Of Categorical Exclusion	17
III. List Of Deficiencies To Be Communicated.....	17



Chemistry Review Data Sheet

1. NDA: 21-860
2. REVIEW #:2 (Change in Packaging and Overall cGMP Compliance report).
3. REVIEW DATE: March 3, 2006
4. REVIEWER: Maria E. Ysem, MSc.
5. PREVIOUS DOCUMENTS: None
6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original NDA (Paper)	19-May-2005
Original NDA(EDR)	19-May-2005
BC Amendment	14-Aug-2005
BZ Amendment	30-Aug-2005
BC Amendment	15-Sep-2005
BL Amendment	31-Oct-2005
BC Amendment	2-Dec-2005
BL Amendment	26-Jan-2006
BL Amendment	02-Feb-2006
BL Amendment	20-Feb-2006
BL Amendment	28-Feb-2006
BL Amendment	Mar 3, 2006

7. NAME & ADDRESS OF APPLICANT:



CHEMISTRY REVIEW TEMPLATE



Chemistry Assessment Section

Name: Warner Chilcott
Address: 100 Enterprise Drive, Rockaway, NJ 07866
Representative: Alvin Howard, Vicepresident of Regulatory Affairs
Telephone: 973-442-3280

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Sarafem
b) Non-Proprietary Name (USAN): Fluoxetine hydrochloride
c) Code Name/# (ONDC only): none
d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 3
 - Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Selective serotonin inhibitor (SSRI)
For treatment of premenstrual dysphoric disorder.

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 10, 15 and 20 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

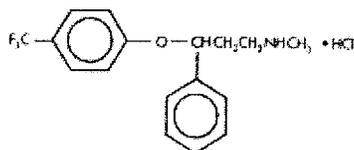
_____ SPOTS product – Form Completed

 x Not a SPOTS product

Chemistry Assessment Section

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

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



Molecular Weight: 345.79

$C_{17}H_{18}F_3NO \cdot HCl$

17. RELATED/SUPPORTING DOCUMENTS:
A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
	II			1	Adequate	July 07, 2005	Chem Review #2
	II			1	Adequate	July 19, 2004	Chem. Review #6
	III			4			
	III			4			
	IV			4			
	IV			4			
	IV			4			



CHEMISTRY REVIEW TEMPLATE



Chemistry Assessment Section

	IV			4			

¹ Action codes for DMF Table:

1 – DMF Reviewed.

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

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	68,098	Sarafem (fluoxetine hydrochloride)
NDA	18-936 Supplements 058 and 067	Sarafem (fluoxetine hydrochloride)

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Compliance recommendation	28-Feb-2006	Shawante Adams
Pharm/Tox			
Biopharm			
LNC			
Methods Validation	To be done		
DMETS	Revisions recommended and accepted by the sponsor	Jan 10, 2006	
EA	N/A		
Microbiology	N/A		

The Chemistry Review for NDA 21-860

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

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

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

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance:

The drug substance used in the manufacture of Sarafem Tablets, 10 mg, 15 mg and 20 mg is fluoxetine hydrochloride, USP, a selective serotonin reuptake inhibitor (SSR) for oral administration.

Fluoxetine hydrochloride, ((±)-N-methyl-3-phenyl-3-[(α,α,α-trifluoro-*p*-tolyl)oxy]propylamine hydrochloride), is a white or almost white, crystalline powder, sparingly soluble in water, _____

_____ Its molecular weight is 345.79.

Detailed information relating about manufacturing and controls, including stability of the drug substance at _____ is contained in Type II DMFs # _____

Fluoxetine hydrochloride, USP is tested in compliance with the current USP monograph. The test methods include visual description, identification by IR and chloride test, water content by KF (NMT 0.5%), heavy metals (NMT 0.003%), Assay (98.0%-102.0% on the anhydrous base).

The related compounds are tested for α-[2-(Methylamino)ethyl benzenemethanol (NMT 0.25%), fluoxetine related compound B (NMT 0.25%), fluoxetine related compound A (NMT 0.15%) , other individual impurities (NMT 0.1%),and total impurities (NMT 0.5%).



Chemistry Assessment Section

The primary Reference Standard for testing fluoxetine hydrochloride, USP are sourced from the USP.

Drug Product:

Warner Chilcott Company, Inc., located in Fajardo, Puerto Rico, has submitted this NDA under section 505(b)(1) of the FDCA for a new tablet dosage form for Sarafem at 10 & 20 mg as well as a new 15 mg tablet strength.

Sarafem® (fluoxetine hydrochloride) tablets are manufactured in three dosage strengths: 10 mg (32.3 μmol), 15 mg (48.5 μmol) and 20 mg (64.7 μmol) of fluoxetine.

The release specifications include the description for each strength of tablet, identification by IR, uniformity of dosage (according to USP <905>), assay (90.0-110.0% of the label claim), related substance (NMT _____

_____ fluoxetine related compound B, _____ and dissolution (USP<711> _____ (Q) in 15 minutes)

The 10 mg tablet is a cream, round tablet embossed with S10 on one side:

N 0430-0210-14 - _____

The 15 mg tablet is a white, round tablet embossed with S15 on one side:

N 0430-0215-14 - _____

The 20 mg tablet is a yellow, round tablet embossed with S20 on one side:

N 0430-0220-14 - _____

With the exception of the colorant _____ all inactive drug product components are compendial (NF) including microcrystalline cellulose _____, croscarmellose sodium _____ colloidal silicone dioxide _____ and magnesium stearate _____

Sarafem Tablets are packaged in unit-dose blisters composed of _____

_____ incorporates a peel-push opening feature and is recommended for child resistant applications.

Six months of stability data for accelerated conditions and 18 months for intermediate and long term room temperature conditions were submitted and they met specifications. The test data for the stability pilot batch of Sarafem tablets, 15 mg through 9 months also meet specifications. (Refer to Amendment dated Dec 06, 2005).

The stability data supports the proposed 24 month shelf life for all three strengths of Sarafem.



Chemistry Assessment Section

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

The proposed dose of Sarafem is 20 mg/day given either continuously (everyday of the menstrual cycle) or _____ or intermittently (for 14 days prior to the onset of menstruation, through the first full day of menstruation repeating each cycle).
The new 15 mg tablet was developed to allow prescribers the option of an intermediate dose.

C. Basis for Approvability or Not-Approval Recommendation

The manufacturing of the drug substance, fluoxetine hydrochloride has been provided through cross reference to two DMFs _____ which have been reviewed and found adequate.

The manufacturing of the Sarafem® (fluoxetine hydrochloride) tablets 10, 15 and 20 mg tablets, using a conventional _____ described adequately through the application and master batch formulae have been provided for each of the dosage strengths.

Sufficient stability data for Sarafem packaged for commerce in blister packages (tablets/blister) was provided, to support the proposed 24 month expiry (controlled room temperature for the drug product).

The new child resistant packaging is deemed comparable to the original packaging without compromising stability data.

Based on the information provided, including adequate cGMP status, this NDA is recommended for approval

III. Administrative

A. Reviewer's Signature in DFS

B. Endorsement Block

Maria Ysern/Mar 1, 2006
Moo Jhong Rhee/
NChrisostomo/Date

C. CC Block

12 Page(s) Withheld

Trade Secret / Confidential

Draft Labeling

Deliberative Process

**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
3/7/2006 10:52:02 AM
CHEMIST

Moo-Jhong Rhee
3/7/2006 01:39:23 PM
CHEMIST
Chief, Branch III

NDA 21-860

Sarafem® (fluoxetine Hydrochloride tablets)

Warner Chilcott Company, Inc.

**Maria Ysern, MSc
Pre-Marketing Assessment Division II, Branch III
Office of New Drug Quality Assessment**



Table of Contents

Table of Contents	2
Chemistry Review Data Sheet.....	3
The Executive Summary	7
I. Recommendations	7
A. Recommendation and Conclusion on Approvability	7
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	7
II. Summary of Chemistry Assessments.....	7
A. Description of the Drug Product(s) and Drug Substance(s)	7
B. Description of How the Drug Product is Intended to be Used.....	9
C. Basis for Approvability or Not-Approval Recommendation.....	9
III. Administrative.....	9
A. Reviewer's Signature.....	9
B. Endorsement Block.....	9
C. CC Block	9
Chemistry Assessment.....	10
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data.....	10
S DRUG SUBSTANCE [Name, Manufacturer].....	10
P DRUG PRODUCT [Name, Dosage form].....	13
A APPENDICES	45
R REGIONAL INFORMATION	45
II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1	46
A. Labeling & Package Insert	46
B. Environmental Assessment Or Claim Of Categorical Exclusion	47
III. List Of Deficiencies To Be Communicated.....	47



Chemistry Review Data Sheet

1. NDA: 21-860
2. REVIEW #:1
3. REVIEW DATE: Jan 12, 2005
4. REVIEWER: Maria E. Ysern, MSc.
5. PREVIOUS DOCUMENTS: None

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original NDA (Paper)	19-May-2005
Original NDA(EDR)	19-May-2005
BC Amendment	14-Aug-2005
BZ Amendment	30-Aug-2005
BC Amendment	28 -Sep- 2005
BL Amendment	31-Oct-2005
BL Amendment	10-Nov-2005

7. NAME & ADDRESS OF APPLICANT:



Chemistry Assessment Section

Name: Warner Chilcott
Address: 100 Enterprise Drive, Rockaway, NJ 07866
Representative: Alvin Howard, Vicepresident of Regulatory Affairs
Telephone: 973-442-3280

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Sarafem
- b) Non-Proprietary Name (USAN): Fluoxetine hydrochloride
- c) Code Name/# (ONDC only): none
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 3
 - Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Selective serotonin inhibitor (SSRI)
For treatment of premenstrual dysphoric disorder.

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 10, 15 and 20 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

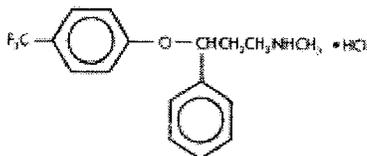
_____ SPOTS product – Form Completed

 x Not a SPOTS product

Chemistry Assessment Section

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

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



Molecular Weight: 345.79
 $C_{17}H_{18}F_3NO \cdot HCl$

17. RELATED/SUPPORTING DOCUMENTS:
A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
	II			1	Adequate	July 07, 2005	Chem Review #2
	II			1	Adequate	July 19, 2004	Chem. Review #6
	III			4			
	III			4			
	IV			4			
	IV			4			
	IV			4			

Chemistry Assessment Section

	IV		4			

¹ Action codes for DMF Table:

1 – DMF Reviewed.

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

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	68,098	Sarafem (fluoxetine hydrochloride)
NDA	18-936 Supplements 058 and 067	Sarafem (fluoxetine hydrochloride)

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Inspection request submitted Aug, 2005 Overall results pending		S. Pope
Pharm/Tox			
Biopharm			
LNC			
Methods Validation	Pending		
DMETS	Revisions recommended	Jan 10, 2006	
EA	N/A		
Microbiology	N/A		



Chemistry Assessment Section

The primary Reference Standard for testing fluoxetine hydrochloride, USP are sourced from the USP.

Drug Product:

Warner Chilcott Company, Inc., located in Fajardo, Puerto Rico, has submitted a NDA under section 505(b)(1) of the FDCA for a new tablet dosage form for Sarafem at 10 & 20 mg as well as a new 15 mg tablet strength.

Sarafem® (fluoxetine hydrochloride) tablets are manufactured in three dosage strengths: 10 mg (32.3 µmol), 15 mg (48.5 µmol) and 20 mg (64.7 µmol) of fluoxetine.

The release specifications include the description for each strength of tablet, identification by IR, uniformity of dosage (according to USP <905>), assay (90.0-110.0% of the label claim), related substance (NMT _____)

_____ fluoxetine related compound _____
_____ dissolution (USP<711>), _____ (Q) in 15 minutes)

The 10 mg tablet is a cream, round tablet embossed with S10 on one side:

N 0430-0210-14 - _____

The 15 mg tablet is a white, round tablet embossed with S15 on one side:

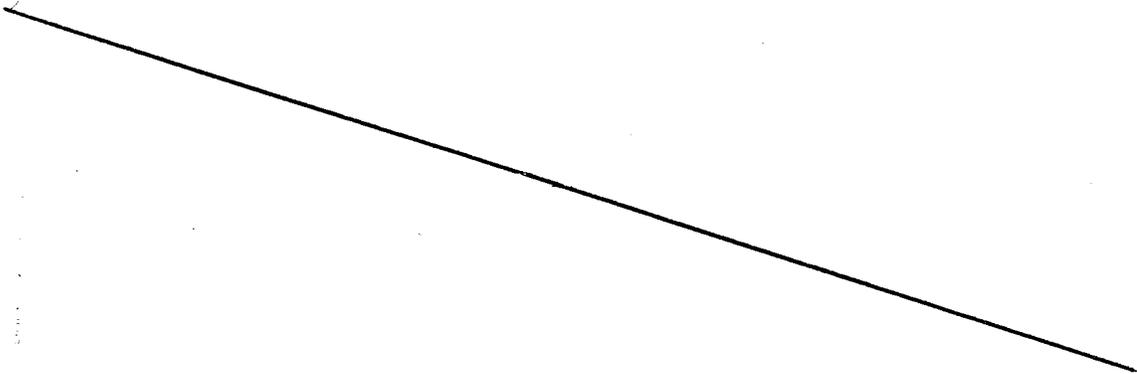
N 0430-0215-14 - _____

The 20 mg tablet is a yellow, round tablet embossed with S20 on one side:

N 0430-0220-14 - _____

With the exception of the colorant _____ all inactive drug product components are compendial (NF) and include microcrystalline cellulose _____ croscarmellose sodium _____, colloidal silicone dioxide _____ and magnesium stearate _____

Sarafem Tablets are packaged in unit-dose blisters composed of



Stability studies on Sarafem tablets, 10 and 20 mg, packaged in the commercial containers closures are on-going. Six months of data for Accelerated conditions and 18 months for intermediate conditions and long term conditions is available and all data meets specifications. The test data for the stability pilot batch of Sarafem tablets, 15 mg through 9 months also meets specifications. (Refer to Amendment dated Dec 06, 2005).

Chemistry Assessment Section

The stability data supports a request for 24 month shelf life for all three strengths of Sarafem.

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

The proposed dose of Sarafem is 20 mg/day given either continuously (everyday of the menstrual cycle) _____ or intermittently (for 14 days prior to the onset of menstruation, through the first full day of menstruation repeating each cycle).

The new 15 mg tablet was developed to allow prescribers the option of an intermediate dose.

C. Basis for Approvability or Not-Approval Recommendation

The manufacturing of the drug substance, fluoxetine hydrochloride has been provided through cross reference to two DMFs _____ which have been reviewed and found Adequate.

The manufacturing of the Sarafem® (fluoxetine hydrochloride) tablets 10, 15 and 20 mg tablets, using a conventional _____ described adequately though the application and master batch formulae have been provided for each of the dosage strengths.

Sufficient stability data for Sarafem packaged for commerce in blister packages (tablets/blister) was provided, including additional data Dec 06, 2005 to support the proposed 24 month expiry (controlled room temperature for the drug product).

Based on the information provided this NDA is recommended for approval under 5050(b)(1) if an acceptable overall evaluation from the cGMP inspections is received.

III. Administrative**A. Reviewer's Signature in DFS****B. Endorsement Block**

Maria Ysern/Jan 12, 2006
Moo Jhong Rhee/
NChrisostomo/Date

C. CC Block

38 Page(s) Withheld

Trade Secret / Confidential

Draft Labeling

Deliberative Process

Withheld Track Number: Chemistry-3

**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
1/25/2006 03:17:29 PM
CHEMIST

Moo-Jhong Rhee
1/30/2006 02:53:43 PM
CHEMIST
Chief, Branch III

NDA FILEABILITY CHECKLIST

NDA Number: 21-860

Applicant: Warner-Chilcott Company, Inc.

Stamp Date: 20-MAY-2005

Drug Name: Sarafem® (fluoxetine hydrochloride tablets)

IS THE CMC SECTION OF THE APPLICATION FILEABLE? (Yes or No) Yes

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

	<i>Parameter</i>	<i>Yes</i>	<i>No</i>	<i>Comment</i>
1	On its face, is the section organized adequately?	√		
2	Is the section indexed and paginated adequately?	√		
3	On its face, is the section legible?	√		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	√		Drug substance manufacture is referenced to DMF _____
5	Is confirmation provided that all facilities are ready for GMP inspection?	√		Requested 08-JUL-2005. In a follow-up teleconference held on 13-JUL-2005, the Sponsor confirmed that a statement would be submitted to the Agency by the filing date of 19-JUL-2005.
6	Has an environmental assessment report or categorical exclusion been provided?	√		Reference to CFR 25.31(1) – the Sponsor has filed a claim for categorical exclusion.
7	Does the section contain controls for the drug substance?	√		See DMF _____
8	Does the section contain controls for the drug product?	√		
9	Has stability data and analysis been provided to support the requested expiration date?	√		Additional data requested during review clock.
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	√		
11	Have draft container labels been provided?	√		
12	Has the draft package insert been provided?	√		
13	Has an investigational formulations section been provided?	√		
14	Is there a Methods Validation package?	√		
15	Is a separate microbiological section included?		√	Not necessary, since this is a solid oral dosage form (tablet).

Review Chemist: Sarah C. Pope, Ph.D.

Date: 12-JUL-2005

Team Leader: Moo-Jhong Rhee, Ph.D.

Date: 12-JUL-2005

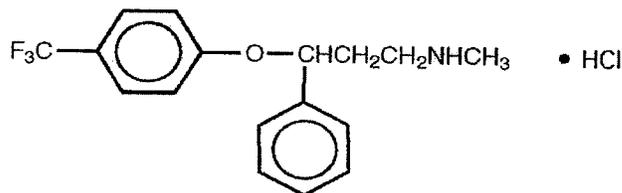
Inclusive DMF References

<i>DMF Number</i>	<i>DMF Holder</i>	<i>Description</i>	<i>LOA Included</i>	<i>Status</i>
			Yes	Under review.
			Yes	Under Review
			Yes	Under Review.
			Yes	Under Review.
			Yes	Under review.
			Yes	Under review.
			Yes	Under review.
			Yes	Under review.

**Appears This Way
On Original**

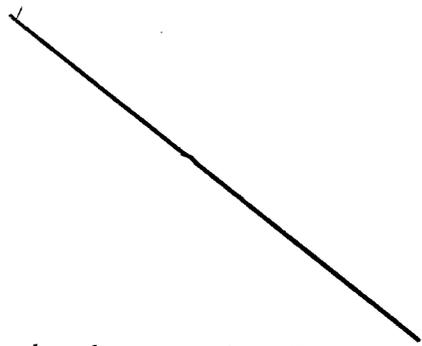
Drug Substances

Fluoxetine hydrochloride is a compendial (USP) compound. All Chemistry, Manufacturing, and Controls information for fluoxetine hydrochloride has been cross-referenced to DMF _____ letters of Authorization have been provided for these references, and the cross-referenced information will be reviewed under separate cover.



(±)-N-methyl-3-phenyl-3-[(α),(α),(α)-trifluoro-p-tolyl]oxypropylamine hydrochloride
MW = 345.79 g/mole
C₁₇H₁₈F₃NO (free base)

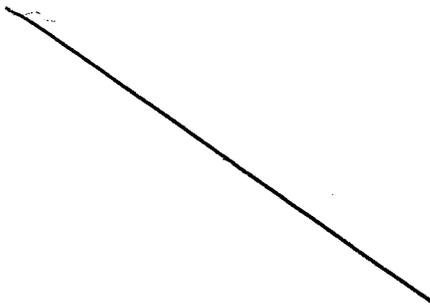
The Sponsor has listed the following sites for drug substance manufacturing:



Both sites have been entered into EES.

Drug Product

Sarafem® (fluoxetine hydrochloride) tablets are manufactured in three dosage strengths: 10 mg, 15 mg, and 20 mg. The three tablet formulations are listed in the tables below. Clinical trial and pilot-scale stability supplies included the _____ and the final commercial formulations were adjusted to include a different coloring component _____. Due to this revision, the Sponsor should provide comparative dissolution data for all clinical, stability, and proposed commercial formulations.



All sites have been entered into EES. In a 12-JUL-2005 teleconference (Karen Kirchberg), the Sponsor confirmed that a statement certifying the GMP readiness for all drug substance and drug product sites would be forthcoming prior to the filing date of 19-MAY-2005.

Release specifications include methods and criteria for description, identification (IR), water content, content uniformity, assay, related substances, and dissolution.

Once manufactured, Sarafem will be packaged for commerce in blister packages (_____ blister). The physician's sample package will also be packaged as _____

As agreed in the pre-NDA meeting (see meeting minutes from 09-DEC-2004 teleconference), the Sponsor has provided six (6) months of accelerated stability data and twelve (12) months of intermediate and real time stability data for three pilot-scale _____ batches for the 10- and 20-mg tablets. Three (3) months of accelerated, intermediate, and real time data have also been provided for one commercial-scale batch of the proposed 10- and 20-mg tablet. Three (3) months of accelerated, intermediate, and real time stability data have been provided for one pilot scale batch of the 15-mg tablet. Additional stability data will be provided during the review cycle.

The Sponsor has proposed a 24-month expiry (controlled room temperature) for the drug product.

With the exception of the colorant, all tablet components are compendial (USP or NF).

10 mg fluoxetine hydrochloride

Component	Compendial Status	Function	Amount per Tablet (mg)	
			Clinical Supplies	Proposed Commercial
Fluoxetine hydrochloride	USP DMF DMF	API	/	/
Microcrystalline cellulose	NF	/		
Croscarmellose sodium	NF			
Magnesium stearate	NF			
	Non-compendial			
	Non-compendial			
Colloidal silicon dioxide	NF			
Total				

15 mg fluoxetine hydrochloride

Component	Compendial Status	Function	Amount per Tablet (mg)	
			Clinical Supplies	Proposed Commercial
Fluoxetine hydrochloride	USP DMF DMF	API	/	/
Microcrystalline cellulose	NF	/		
Croscarmellose sodium	NF			
Magnesium stearate	NF			
	Non-compendial			
	Non-compendial			
Colloidal silicon dioxide	NF			
Total				

20 mg fluoxetine hydrochloride

Component	Compendial Status	Function	Amount per Tablet (mg)	
			Clinical Supplies	Proposed Commercial
Fluoxetine hydrochloride	USP DMF DMF	API	/	/
Microcrystalline cellulose	NF	/		
Croscarmellose sodium	NF			
Magnesium stearate	NF			
	Non-compendial			
	Non-compendial			
Colloidal silicon dioxide	NF			
Total				

Each dosage strength is manufactured using a conventional _____
 _____ Master batch formulae have been provided for each of the dosage strengths. The proposed
 commercial scale of manufacture is _____

The manufacturing sites are listed below, with the specific functions outlined:

Manufacturing
 Pharmaceuticals International, Inc.
 10819 Gilroy Road
 Hunt Valley, MD 21031

Comments (non-filing review issues, for 74-day letter)

1. Provide additional stability data when available. Be advised that the submission of stability data during the final three months of review would potentially warrant a major amendment to the NDA.
2. Provide comparative dissolution profiles and calculated f_2 values for the clinical batch versus the stability and proposed commercial formulations for all three dosage strengths.

**Appears This Way
On Original**

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

/s/

Sarah Pope
7/14/05 10:10:09 AM
CHEMIST

Moo-Jhong Rhee
7/14/05 01:47:46 PM
CHEMIST
I concur