CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-807

CHEMISTRY REVIEW(S)

Chemistry Review Data Sheet

NDA 21-807

SOLTAMOX™
(Tamoxifen Citrate oral solution)
(equivalent to 10 mg/5 mL Tamoxifen)

Savient Pharmaceuticals, Inc.

Ruth E. Wager, Ph.D.
Chengyi Liang, PH.D.
HFD-150 Division of Oncology Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA: 21-807

2. REVIEW : #1

3. REVIEW DATE: Aug. 20, 2005

4. REVIEWER: Ruth E. Wager, Ph.D., Chengyi Liang, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original NDA	12-23-2004
Amendment	4/30/2005
Amendment	6/15/2005
Amendment	8/1/2005
Amendment	8/12/2005
Amendment	8/25/2005

7. NAME & ADDRESS OF APPLICANT:

Name:	Savient Pharmaceuticals Inc.
Address:	One Tower Center, 14th Floor East Brunswick, NJ 08816
Representative:	Briti Kundu

Chemistry Review Data Sheet

Telephone: 732-418-9300

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: SOLTAMOX™
b) Non-Proprietary Name (USAN): Tamoxifen citrate
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):
   - Chem. Type: 3
   - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b) (2)
Listed drug: Nolvadex® (Tamoxifen) from AstraZeneca Pharmaceuticals
NDA#17-970

10. PHARMACOL. CATEGORY: Treatment of breast cancer

11. DOSAGE FORM: Solution

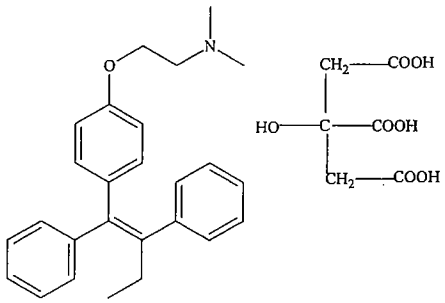
12. STRENGTH/POTENCY: 10 mg/5 mL

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X_ Rx ___ OTC

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

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



Tamoxifen citrate
$C_{32}H_{37}NO_8$
MW=563.62
(Z)-2-[4-(1,2-diphenylbut-1-enyl) phenoxy] ethyldimethylamine citrate

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE [1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	II	[redacted]	[redacted]	1	Adequate	11-DEC-2000	
	III			4	Adequate	2/17/05	Reviewed by Ruth Wager

[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)

Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	67,993	Soltamox-liquid formulation of tamoxifen, CDER date: 12/16/2003

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	9-8-2005	Office of Compliance
Methods Validation	Acceptable	3-8-2005	Ruth E. Wager
DMETS	Acceptable	7-12-2005	Todd Bridges
EA	Acceptable	2-10-2005	Ruth E. Wager
Microbiology	N/A		

The Chemistry Review for NDA 21-807

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 21-807 is recommended for approval from the standpoint of chemistry, manufacture and controls. The applicant has satisfactorily responded to the deficiencies and
the Office of Compliance has provided an overall acceptable recommendation.

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 product:

SOLTAMOX™ (Tamoxifen citrate oral solution) is a liquid formulation developed for use in patients who have difficulty with or dislike of taking solid oral dosage forms. The commercial tablet of tamoxifen citrate (Nolvadex®) was approved in the US on 12/30/77, under NDA 17-970.

Each 5 mL of the finished drug product, SOLTAMOX™ contains 15.2 mg of tamoxifen citrate, equivalent to 10 mg of tamoxifen. Inactive ingredients in SOLTAMOX™ include ethanol, glycerol, and propylene glycol [redacted] sorbitol [redacted] licorice flavor, aniseed flavor and water [redacted] Ethanol also serves as a preservative/antimicrobial agent. The drug product is filled to 150 mL in amber bottles.

Tamoxifen citrate is a nonsteroidal agent that has demonstrated antiestrogenic properties, probably resulting from its ability to compete with estradiol for binding to the estrogen receptor. Tamoxifen citrate has shown efficacy in the treatment of metastatic breast cancer in women and men. It is also indicated as an adjuvant therapy in both node-positive and node-negative breast cancer following partial or total mastectomy, axillary dissection, and breast irradiation. Tamoxifen citrate has also reduced the occurrence of contralateral breast cancer in patients receiving adjuvant therapy. It has also been shown to reduce the risk of invasive breast cancer following surgery and radiation in women with ductal carcinoma *in situ*.

The stability test data submitted support a two year expiration dating period.

Drug substance:
Tamoxifen citrate is a potent nonsteroidal estrogen antagonist. Tamoxifen citrate is known to have complex pharmacological properties, and can behave as a pure estrogen agonist, a partial agonist, or an antagonist, depending on the species of animal, the target organ examined, and the endpoint measured. Tamoxifen citrate is known as a genotoxic carcinogen in the rat.

Tamoxifen citrate occurs as a fine, white to off-white, odorless, crystalline powder. It is the trans-isomer of a triphenylethylene derivative. Relevant information regarding chemistry, manufacturing, and controls of the bulk drug substance are provided in DMF [redacted] and was found adequate to support the original NDA 17-970 (in HFD-150), NDA 21-109 (in HFD-510) and the current NDA 21-807. Stability data to support the re-test period have been provided in the DMF.

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

SOLTAMOX™, an oral solution, is supplied in a multi-use amber glass bottle in a total volume of 150 mL. Each 5 mL of the finished drug product, SOLTAMOX™ contains 15.2 mg of tamoxifen citrate, equivalent to 10 mg of tamoxifen. The recommended dosage of Nolvadex®, the currently marketed solid form of tamoxifen citrate, is 20-40 mg/day for breast cancer treatment. SOLTAMOX™ is supplied with a graduated dosing cup. SOLTAMOX™ has an expiry period of 24 months, but contents of a bottle should be used within three months after the bottle is opened. The product should be stored protected from light at 15-25°C.

C. Basis for Approvability or Not-Approval Recommendation

This NDA is recommended for approval. This NDA describes a new formulation of an already approved API. No safety concerns are associated with the new formulation. Bioavailability of this new formulation is equivalent to the previously approved solid dosage form. This liquid formulation has been approved in Europe for the past five years and has sold over [redacted] patient doses. No market withdrawals have occurred. The SOLTAMOX™ adverse event profile in clinical trials is similar to that reported for Nolvadex®.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Chemist Name/Date: Ruth E. Wager/ Chengyi Liang
Chemistry Team Leader: Nallaperumal Chidambaram /Date
Project Manager Name: Christy Cottrell/Date

C. CC Block

23 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Chemistry- 1

CHEMISTRY REVIEW TEMPLATE

Chemistry Assessment Section

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Application : NDA 21807/000 Sponsor: SAVIENT PHARMS

Org Code : 150 1 TOWER CENTER BLVD 12TH FLOOR

Priority : 3 EAST BRUNSWICK, NJ 08816

Stamp Date : 27-DEC-2004 Brand Name : SOLTAMOX (TAMOXIFEN CITRATE)

PDUFA Date : 12-NOV-2005 10MG/5ML

Action Goal : Estab. Name:

District Goal: 13-SEP-2005 Generic Name: SOLTAMOX CITRATE ORAL SOLUTION

Dosage Form: (SOLUTION)

Strength : 10 MG/5 ML

FDA Contacts: C. COTTRELL Project Manager (HFD-150) 301-594-5778

ID = 130757 Review Chemist

N. CHIDAMBARAM Team Leader (HFD-810) 301-594-5765

Overall Recommendation: ACCEPTABLE on 08-SEP-2005by S. ADAMS (HFD-322) 301-827-9051

Establishment : [redacted]

[redacted]

DMF No: [redacted] AADA:

Responsibilities: [redacted]

Profile : CSN OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 09-FEB-05

Decision : ACCEPTABLE

Reason : BASED ON PROFILE

Establishmen

[redacted]

DMF No: AADA:

Responsibilities: [redacted]

Chemistry Assessment Section

Profile : CTL OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 09-FEB-05

Decision : ACCEPTABLE

Reason : BASED ON PROFILE

Establishment : CFN : FEI :

ROSEMONT PHARMACEUTICALS LTD

YORKDALE IND. PK., BRAITHWAITE ST.

LEEDS, , UK LS119XE

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Profile : LIQ OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 08-SEP-05

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

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

/s/

Chengyi Liang
9/12/2005 01:05:34 PM
CHEMIST

Nallaperumal Chidambaram
9/12/2005 01:10:25 PM
CHEMIST