CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-235

CHEMISTRY REVIEW(S)

CMC BRANCH CHIEF MEMORANDUM

To: NDA 22-235
From: Ramesh Sood, Branch Chief, ONDQA
Date: 19-Mar-2008
Drug name: Luvox (fluvoxamine maleate) Tablets
Subject: Approval recommendation for NDA 22-235

Introduction: This NDA was submitted to seek approval of Luvox (fluvoxamine maleate) tablets for the prevention of relapse in patients with Obsessive Compulsive Disorder (OCD). The earlier NDA 22-519 for this product was approved in December 2007 for obsession and compulsions in adults and in pediatric (8-17 years) patients with OCD. The tablets are available in 25 mg, 50 mg and 100 mg strengths. The tablets are packaged in 100-count bottles for commercial distribution and 7-count blisters as physician samples.

The CMC information for this NDA was referenced to the earlier NDA 21-519 approved in December 2007. No additional CMC information was submitted in this NDA. The CMC reviews and my earlier memorandum filed under NDA 21-519 should be consulted for further CMC information related to this NDA.

The applicant has requested a categorical exclusion in the submission dated 7-Mar-2008 as they expect that approval of this application will not increase the use of active moiety and that to their knowledge no extraordinary circumstances exist. All manufacturing sites have been found acceptable by Office of Compliance as of 15-Oct-07.

Recommended action: The application is recommended as "Approval" from CMC perspective pending agreement on the labeling.

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/s/

Ramesh Sood
3/19/2008 11:40:41 AM
CHEMIST

NDA 22-235

LUVOX® (fluvoxamine maleate) Tablets

Jazz Pharmaceuticals, Inc.

David J. Claffey Ph.D.
ONDQA

Table of Contents

Chemistry Review Data Sheet

1. NDA: 22-235

2. REVIEW NUMBER: 1

3. REVIEW DATE: 14 MAR 2008

4. REVIEWER: David J. Claffey, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date

6. SUBMISSION BEING REVIEWED:

Submission Reviewed	Document Date
Original	3 AUG 2007
Amendment	7 MAR 2008

7. NAME & ADDRESS OF APPLICANT:

Name: Jazz Pharmaceuticals, Inc.

CHEMISTRY REVIEW

Chemistry Review Data Sheet

Address: 3180 Porter Drive
Palo Alto, CA 94306

Representative: Anne Keane, Regulatory Affairs Manager

Telephone: 650-496-2729

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: LUVOX®
b) Non-Proprietary Name (USAN): Fluvoxamine Maleate
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type:
- Submission Priority: S (Standard)

1. LEGAL BASIS FOR SUBMISSION: 505 (b)(1)

10. PHARMACOL. CATEGORY: Obsessive Compulsive Disorder (OCD)

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 25 mg, 50 mg, 100 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: __X__Rx ____OTC

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

_____SPOTS product – Form Completed

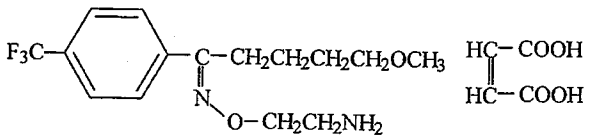
__X__Not a SPOTS product

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

USAN Name: 5-Methoxy-4'-(trifluoromethyl)-valerophenone (*E*)-*O*-(2-aminoethyl)oxime, maleate (1:1)

Molecular Formula: $C_{15}H_{21}F_3N_2O_2 \cdot C_4H_4O_4$

Molecular Weight: 434.41



Fluvoxamine maleate

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs (referenced in NDA 21-519):

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	II	[redacted]	[redacted]	1	**Adequate**	**Dec 7, 2007**	
	II			1	***Adequate***	***Dec 10, 2007***	
	III			3	Adequate	Sept. 26, 2000	
	III			3	Adequate	Sept. 1, 1999	
	III			3	Adequate	Sept. 1, 1999	
	III			3	Adequate	Sept. 11, 2003	
	III			3	Adequate	August 6, 2001	
	III			3	Adequate	March 14, 2002	
	III			3	Adequate	June 3, 2003	

b(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
NDA	21-519	LUVOX® Tablets (Approved DEC 2007))
NDA	20-243	LUVOX® Tablets (Withdrawn 13 May 2002)

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	All Site Acceptable	15 OCT 2007	Office of Compliance (Establishment Report Appended)
EA	Request for categorical exclusion claim accepted	14 MAR 2008	David J. Claffey, PhD

The Chemistry Review for NDA 22-235

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Recommend that this Application be approved from a CMC perspective as the cross-referenced NDA (21-519) was found to be adequate from a CMC perspective on 10 DEC 2007.

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

II. Summary of Chemistry Assessments

Regulatory background: The proposed drug product regulatory background is detailed in the referenced NDA 21-519 which was approved by the Agency in DEC 2007. This application proposes to extend the approved indications to include the prevention of relapse in patients with obsessive compulsive disorder (OCD).

A. Description of the Drug Product and Drug Substance

LUVOX® (fluvoxamine maleate) Tablets 25 mg, 50 mg and 100 mg are manufactured as elliptical, film-coated tablets with a unique color for each strength (25 mg, white; 50 mg, yellow;100 mg, beige). Tablets are debossed with "LT25", "LT50" or "LT100" for 25 mg, 50 mg and 100 mg strength, respectively. The 50 mg and 100 mg strength tablets are scored on the opposing side. The current submission proposes the use of 100-count bottles for commercial distribution and 7-count blisters as physician samples for each tablet strength.

LUVOX® (fluvoxamine maleate) Tablets 25 mg, 50 mg and 100 mg are manufactured using excipients which are USP/NF grade, and tablet colorants [redacted] All strengths of drug product are manufactured by [redacted] The sponsor maintains a sampling plan which assures that each lot of raw material (i.e., inactive ingredient and packaging components) is tested for identity, sampled, acceptance tested and released. In-process testing is performed on the [redacted], uncoated tablets,

b(4)

coated tablets and packaged finished product. The sponsor's sampling and testing assures that critical parameters such as tablet weight variation, tablet hardness, tablet friability and tablet disintegration are monitored during manufacture, and that the final product is release tested accorded to the regulatory release specifications.

The drug product formulation and carton labels for the LUVOX® Tablets 25 mg, 50 mg and 100 mg provided for in this application is identical to that of the cross referenced NDA (21-519).

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

Adults

The recommended starting dose for LUVOX Tablets in adult patients is 50 mg, administered as a single daily dose at bedtime. The dose should be increased in 50 mg increments every 4 to 7 days, as tolerated, until maximum therapeutic benefit is achieved, not to exceed 300 mg per day. It is recommended that a total daily dose of more than 100 mg should be given in two divided doses. If the doses are not equal, the larger dose should be given at bedtime.

Children and Adolescents

The recommended starting dose for LUVOX Tablets in pediatric populations (ages 8-17 years) is 25 mg, administered as a single daily dose at bedtime. In a controlled clinical trial establishing the effectiveness of LUVOX Tablets in OCD, pediatric patients (ages 8-17) were titrated within a dose range of 50 to 200 mg/day. Physicians should consider age and gender differences when dosing pediatric patients. The maximum dose in children up to age 11 should not exceed 200 mg/day. Therapeutic effect in female children may be achieved with lower doses. Dose adjustment in adolescents (up to the adult maximum dose of 300 mg) may be indicated to achieve therapeutic benefit. The dose should be increased in 25 mg increments every 4 to 7 days, as tolerated, until maximum therapeutic benefit is achieved. It is advisable that a total daily dose of more then 50 mg should be given in two divided doses. If the two divided doses are not equal, the larger dose should be given at bedtime.

Stability data support the Applicant's proposed 36 month expiration dating for all strengths packaged in bottles and 24 months for all strengths packaged in blisters. Drug product should be protected from high humidity and stored at controlled room temperature, 15°-30°C (59°-86°F).

C. Basis for Approvability or Not-Approval Recommendation

The approval recommendation from a CMC perspective is based on the previous approval recommendation for the cross referenced NDA 21-519, the overall acceptable

recommendation from the Office of Compliance and the acceptance of the Applicant's claim for a categorical exclusion (7 MAR 2008).

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

C. CC Block

1 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Chemistry- 1

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/s/

David Claffey
3/19/2008 11:23:31 AM
CHEMIST

Ramesh Sood
3/19/2008 11:28:02 AM
CHEMIST

Initial Quality Assessment
Branch I

OND Division:	Division of Psychiatry Products
NDA:	**22-235**
Applicant:	Solvay
Letter Date:	20-JUN-07
Stamp Date:	21-JUN-07
PDUFA Date:	21-APR-08
Trademark:	Luvox®
Established Name:	fluvoxamine maleate
Dosage Form:	Tablets (25, 50, and100 mg)
Route of Administration:	Oral
Indication:	Obsessive Compulsive Disorder: prevention of relapse
Assessed by:	**Thomas F. Oliver, Ph.D.**

Summary
A second approvable letter (November 16, 2006) was issued for NDA 21-519 [Luvox® (fluvoxamine maleate) Tablets], which contained four CMC issues. The applicant has now responded to this second approvable letter (June 20, 2007). In addition, the applicant provided data from a clinical study evaluating the risk of occurrence of OCD symptoms within a few weeks in patients who were first adequately treated with fluvoxamine, and then discontinued under double-blind conditions. As the new claim was to be added to an unapproved NDA, the division issued a new **NDA 22-235** to cover the prevention of OCD relapse claim. NDA 22-235 references NDA 21-519 for all CMC information.

Comments and Recommendation:
The response is fileable from a CMC perspective. As Dr. David Claffey is assigned to NDA 21-519, he would be a prudent choice to cover this NDA as well. The same sites as listed for NDA 21-519 were submitted into EES (07-AUG-07 by T.Oliver).

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/s/

Thomas Oliver
8/8/2007 12:30:30 PM
CHEMIST

Ramesh Sood
8/17/2007 03:08:29 PM
CHEMIST