CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-866

CHEMISTRY REVIEW(S)

NDA 21-866

(Review #2)

ABILIFY® (aripiprazole) Injection
9.75 mg/1.3 mL
(7.5 mg/mL)

Otsuka Pharmaceutical Co.

Division of Psychiatry Drug Products

Donghao Robert Lu, Ph.D.

Division of Pre-Marketing Assessment
Office of New Drug Quality Assessment

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-866

2. REVIEW NUMBER: 2

3. REVIEW DATE: 6 September 2006

4. REVIEWER: Donghao R. Lu, Ph.D.

5. PREVIOUS DOCUMENTS:

PREVIOUS DOCUMENTS	DOCUMENT DATE

6. SUBMISSION(S) BEING REVIEWED:

SUBMISSION REVIEWED	DOCUMENT DATE
NDA 21-866	29 November 2005

7. NAME & ADDRESS OF APPLICANT:

NAME:	**Otsuka Pharmaceutical Co., Ltd.**
ADDRESS:	**2-9 Kanda Tsukasa - cho Chiyoda-ku Tokyo, 101 - 8535, Japan**
REPRESENTATIVE:	**Kusuma Mallikaarjun, Ph.D.**
TELEPHONE:	**301-990-0030**

8. DRUG PRODUCT NAME/CODE/TYPE:

PROPRIETARY NAME	**Abilify**
NON-PROPRIETARY NAME (USAN)	**Aripiprazole**
CODE NAME/ NUMBER (ONDC ONLY)	**OPC-14597, BMS - 337039**
CHEMISTRY TYPE / SUBMISSION PRIORITY	**3S**

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

10. PHARMACOL. CATEGORY: Antipsychotic

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 7.5 mg/mL

13. ROUTE OF ADMINISTRATION: Intramuscular

14. R_x/OTC DISPENSED: _x_ R_x ___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:

Name (USAN): Aripiprazole

Name (CAS): 7-[4-[4-(2,3-Dichlorophenyl)-1-piperazinyl]butoxy]-3,4-dihydrocarbostyril

7-[4-[4-(2,3-Dichlorophenyl)-1-piperazinyl]butoxy]-3,4-dihydro-2(1H)-quinolinone

Mol. Formula: $C_{23}H_{27}Cl_2N_3O_2$

Mol. Wt.: 448.38 g/mol.

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETE
					N/A	
					N/A	
					N/A	
					N/A	
					N/A	
					N/A	
					Adequate	28-AUG-06

[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.

Comments: The [redacted] does not maintain a DMF with the Food and Drug Administration for the [redacted] as the drug product is not in direct contact with this [redacted] component. A letter was provided from the [redacted] indicating that a DMF was deemed unnecessary.

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	21-436	ABILIFY® (aripiprazole) Tablet

18. STATUS:

CONSULTS & CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	31-AUG-06	S. Adams
Methods Validation	No validation request	31-AUG-06	D. R. Lu, Ph.D.
ODS DMETS	Labeling change	10-AUG-06	K. C. Arnwine, PharmD.
EA	Acceptable	12-JUL-06	D. R. Lu, Ph.D.
Micro Consultation	Pending		

The Chemistry Review for NDA 21-866

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The drug product Abilify (Aripiprazole) Intramuscular injection, 7.5 mg/mL, is recommended as APPROVAL from a CMC perspective, pending the acceptable recommendation from microbiology review.

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

There are no Phase IV commitments.

The sponsor has included a *Comparability Protocol* which involves packaging components. This protocol has been reviewed and found to be acceptable.

II. Summary of Chemistry Assessments

A. Description of the Drug Substance and Drug Product

1. Drug Substance

The drug substance is Aripiprazole.

The proposed commercial process for the preparation of parenteral-grade aripiprazole drug substance to be used for aripiprazole injection was provided. Information on starting materials and synthesis routes were provided in the ABILIFY® (aripiprazole) Tablet NDA #21-436. The NDA #21-436 was reviewed by Dr. Sherita D. McLamore on 8/1/2002 and recommended for approval. The synthesis of the parenteral-grade drug substance is identical to the synthesis of drug substance used for ABILIFY® Tablet, with the differences in the use of [redacted] instead of [redacted] in Step [redacted], the elimination of [redacted] prior to [redacted] in Step [redacted], and the use of a slightly different [redacted] in Step [redacted]. Because the related information was available in the NDA 21-436 for ABILIFY® Tablet, only the modifications (in Steps [redacted] and [redacted]) were described in this NDA.

For the drug substance, all other information were available in the ABILIFY® (aripiprazole) Tablet NDA #21-436 (see above). Therefore, the CMC information in the drug substance section was found to be adequate.

2. Drug Product

The drug product is ABILIFY® (aripiprazole) Injection, 9.75 mg/1.3 mL (7.5 mg/mL).

The drug product is a sterile solution intended for an intramuscular (IM) administration. The commercial product is packaged in [redacted] glass vials with [redacted] and [redacted] The ABILIFY® (aripiprazole) Injection is a ready-to-use (RTU) single-dose drug product. Sufficient amount of overfill is contained in the product to meet USP requirements for minimum fill and deliverable volume.

The major excipient in aripiprazole injection is Captisol® (Sulfobutylether-β-cyclodextrin) which is used as solubilizing agent for aripiprazole. Captisol can be characterized as a noncompendial and non-novel excipients because it has been approved by FDA for two Pfizer products: GEODON® for Injection (ziprasidone mesylate), and VFEND® I.V. (voriconazole) for Injection. The concentration used in aripiprazole injection is [redacted] than the Pfizer products. Each mL of aripiprazole injection contains [redacted] of Captisol, while the GEODON formulation and the VFEND formulation contain [redacted] of Captisol, respectively.

During the pharmaceutical development [redacted] formulation approaches were examined for enhancing the solubility of aripiprazole: [redacted]

[redacted] was submitted for approval.

Comprehensive details of the process were available in the manufacturing development data in the submission. The identified critical manufacturing parameters included [redacted]

[redacted]. Appropriate analytical tests and specifications have been developed and appropriately validated. Details of the validation studies were available in the submission. Analytical batch analyses were provided for drug product batches used in clinical studies and primary stability studies. A summary of drug product stability studies was provided in the NDA. The summary included the information on stability batches tested, storage conditions used, product attributes tested, shelf-life acceptance criteria, test schedule, amount of data available, and analysis of data. An 18-month expiration date is recommended based on the stability results under the storage condition of 25°C/60%RH for 78 weeks (1.5 years). The recommended storage conditions for the drug product are presented in the labeling statements: "Store at 25°C; excursions permitted between 15°-30°C (See USP Controlled Room Temperature)" and "Protect from light by storing in the original container." The stability data appears to provide adequate support for the expiration date and the labeling statements for the product storage conditions.

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

ABILIFY is indicated for the treatment of schizophrenia. The efficacy of ABILIFY in the treatment of schizophrenia was established in short-term (4- and 6-week) controlled trials of schizophrenic in-patients. ABILIFY is also indicated for the treatment of acute manic and mixed episodes associated with Bipolar Disorder. The recommended dose in these patients is 9.75 mg. A lower dose of 5.25 mg may be considered when clinical factors warrant. If agitation warranting a second dose persists following the initial dose, cumulative doses up to a total of 30 mg/day may be given.

C. Basis for Approvability or Not-Approval Recommendation

From a CMC perspective, Otsuka Pharmaceutical Co. has submitted sufficient and appropriate information to support the approval of the drug product. The physical and chemical characteristics, impurity profile, and stability for ABILIFY® (aripiprazole) Injection, 9.75 mg/1.3 mL (7.5 mg/mL) are adequately demonstrated in this NDA. The acceptance criteria are appropriate to ensure the identity, strength, quality, potency, and purity of the finished drug product. The criteria are also adequate to assure consistent quality so as to eliminate batch-to-batch variations. The site EES inspections were also found acceptable. As indicated on page 68, the microbiological method validation was found adequate. The stability tests also showed that the sterility data was adequate. It should be noted that the microbiology reviewer has not made the final recommendation in response to our consultation request. A memo to file will be submitted after the micro consultation is received.

III. Administrative

A. Reviewer's Signature

\s\ Robert Lu, Ph.D.

B. Endorsement Block

Ramesh Sood, Ph.D.

C. CC Block

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_____ § 552(b)(5) Deliberative Process

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/s/

Donghao Lu
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Ramesh Sood
9/6/2006 10:50:47 AM
CHEMIST

NDA 21-866

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9.75 mg/1.3 mL
(7.5 mg/mL)

Otsuka Pharmaceutical Co.

Division of Psychiatry Drug Products

Donghao Robert Lu, Ph.D.

Division of Pre-Marketing Assessment
Office of New Drug Quality Assessment

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3. REVIEW DATE: 1 August 2006

4. REVIEWER: Donghao R. Lu, Ph.D.

5. PREVIOUS DOCUMENTS:

PREVIOUS DOCUMENTS	DOCUMENT DATE

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During the pharmaceutical development, —— formulation approaches were examined for enhancing the solubility of aripiprazole: ———

[redacted]

[redacted]

[redacted] was submitted for approval.

Comprehensive details of the process were available in the manufacturing development data in the submission. The identified critical manufacturing parameters included ———

[redacted] Appropriate analytical tests and specifications have been developed and appropriately validated. Details of the validation studies were available in the submission. Analytical batch analyses were provided for drug product batches used in clinical studies and primary stability studies. A summary of drug product stability studies was provided in the NDA. The summary included the information on stability batches tested, storage conditions used, product attributes tested, shelf-life acceptance criteria, test schedule, amount of data available, and analysis of data. An 18-month expiration date is recommended based on the stability results under the storage condition of 25°C/60%RH for 78 weeks (1.5 years). The recommended storage conditions for the drug product are presented in the labeling statements: "Store at 25°C; excursions permitted between 15°-30°C (See USP Controlled Room Temperature)" and "Protect from light by storing in the original container." The stability data appears to provide adequate support for the expiration date and the labeling statements for the product storage conditions.

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III. Administrative

A. Reviewer's Signature

\s\ Robert Lu, Ph.D.

B. Endorsement Block

Ramesh Sood, Ph.D.

C. CC Block

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Donghao Lu
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Initial Quality Assessment
Branch I

OND Division:	Division of Psychiatry Products
NDA:	**21-866**
Applicant:	Otsuka Pharmaceuticals
Letter Date:	29-NOV-05
Stamp Date:	30-NOV-05
PDUFA Date:	30-SEP-05
Trademark:	Abilify®
Established Name:	aripiprazole
Dosage Form:	Injection
Route of Administration:	Intramuscular Injection
Indication:	Treatment of agitation in schizophrenia and bipolar Mania
Assessed by:	**Thomas F. Oliver, Ph.D.**

Summary and Critical Issues:

Summary

Abilify® (aripiprazole) Intramuscular Injection was developed to treat acutely agitated patients who require an injection to relieve their symptoms. Aripiprazole was discovered by Otsuka Pharmaceutical co., Ltd. and co-developed with Bristol-Myers Squibb Company. The sponsor has developed three other aripiprazole products: 1) Abilify Tablets [AP, 15-NOV-02], 2) Abilify Oral Solution [AP, 10-DEC-04], and 3) Abilify Orally Disintegrating Tablets [AE, 22-OCT-04]. In a telecon (15-Jul-04), it was agreed the sponsor could reference the previous drug substance information (NDA 21-436), as long as all changes are reported in the new NDA. Abilify Injection is being formulated as a 7.5 mg/mL solution in Captisol® (sulfbutylether-β-cyclodextrin).

Drug Substance

Commercial drug substance will be manufactured and packaged by Otsuka Pharmaceutical Co (Second Tokushima Factory; Tokushima-shi, Tokushima, Japan). This is the same site that manufactures and packages aripiprazole drug substance for Abilify Tablets (NDA 21-436, AP, 15-NOV-02). Investigational drug substance as presented in this NDA was also manufactured and packaged at the Second Tokushima Factory. The synthesis of parenteral-grade aripiprazole is identical to the synthesis of aripiprazole used for Abilify® Tablets except for: 1) use of [redacted] instead of [redacted] (in step [redacted]), 2) elimination of [redacted] prior to [redacted] (in step [redacted]), and 3) use of a different [redacted] procedure (in step [redacted]). In addition, the sponsor has modified the specifications as follows: 1) [redacted] The NDA 21-436 is referenced for drug substance information.

Drug Product

Abilify (aripiprazole) Injection for intramuscular (IM) use is a sterile ready-to-use solution formulated to deliver 7.5 mg/mL of aripiprazole. Aripiprazole injection is labeled as single-dose drug product for IM administration using a sterile syringe and needle. The commercial product (10 mg/vial) is filled into [redacted] glass vials, which are closed with [redacted]. The drug product is formulated with excipients of USP or NF technical grade, except for Captisol (sulfbutylether-β-cyclodextrin), which is referenced in DMF [redacted] (CyDex, Inc.). The commercial drug product will be manufactured at Bristol-Myers Squibb (Mayaguez, PR).

Critical Issues for Review

• The control of impurity [redacted] should be closely evaluated (in conjunction with pharm/tox), as it is an [redacted]

• The proposed patient exposure levels to excipient, sulfbutylether-β-cyclodextrin, will need to be evaluated. The adequacy of the acceptance criteria (e.g., impurities including [redacted] for the excipient will need to be determined. As aripiprazole has limited solubility, the adequacy of the formulation should be closely evaluated (e.g., compatibility studies, stability data). In addition, how the formulation performance is related to the degree of substitution on the [redacted] and whether there are sufficient controls in place to ensure future batch performance.

• The adequacy of the container closure system ([redacted]) is important for drug product performance. In addition, the compatibility of the aripiprazole injection with the container closure [redacted] should be evaluated (e.g., adequacy of compatibility and leachable studies).

•Even though the drug product is [redacted] the adequacy of the validation studies should be evaluated by microbiology.

Comments and Recommendation:

The NDA appears to be fileable from a CMC perspective. Given the cross-reference to information contained in the previous approved Abilify NDAs (21-436 and 21-713), Dr. Sherita McLamore is a logical reviewer choice, since she reviewed the two approved Abilify NDAs and is the most familiar with these products.

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/s/

Thomas Oliver
1/3/2006 07:59:42 AM
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