

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-713

CHEMISTRY REVIEW(S)



NDA 21-713

Abilify™ (aripiprazole) Oral Solution

Otsuka Pharmaceuticals Company, Ltd

Sherita D. McLamore, Ph.D.

HFD-120



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Chemistry Review Data Sheet

1. NDA 21-713
2. REVIEW #2
3. REVIEW DATE: November 19, 2004
4. REVIEWER: Sherita D. McLamore, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents

Original Submission
Amendment
Amendment

Document Date

November 18, 2003
August 16, 2004
June 8, 2004

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Response to AE Letter

Document Date

October 18, 2004

7. NAME & ADDRESS OF APPLICANT:

Name: Otsuka Pharmaceuticals Co., Ltd.
Address: 2-9 Kanda Tsukasa-cho
Chiyoda-ku Tokyo, 101-8535, Japan
Otsuka America Pharmaceutical, Inc.
Representative: 2440 Research Boulevard
Rockville, MD 20850
Telephone: 301-497-0900



CHEMISTRY REVIEW



Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Abilify
- b) Non-Proprietary Name (USAN): Aripiprazole
- 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)(1)

10. PHARMACOL. CATEGORY: Schizophrenia

11. DOSAGE FORM: Oral Solution

12. STRENGTH/POTENCY: 1 mg/mL

13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED: Rx OTC

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

SPOTS product – Form Completed

Not a SPOTS product

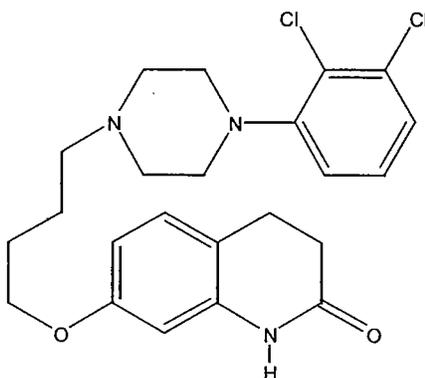
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

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

Molecular Formula: $C_{23}H_{27}Cl_2N_3O_2$

Molecular Weight: 448.38

Chemistry Review Data Sheet



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
1	III	L	J	4	Adequate		N/A
	III			4	Adequate		N/A
	III			4	Adequate		N/A
	III			4	Adequate		N/A

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:



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Chemistry Review Data Sheet

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	42,776	Commercial IND Indication: Treatment of Schizophrenia Sponsor: Otsuka America Pharm
IND	62,216	Commercial IND Indication: Management of the manifestation of psychotic disorder Sponsor: Otsuka Pharm
Original NDA	21-436	Abilify™ (aripiprazole) Tablets Approved 11/15/2002

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	N/A
EES	Acceptable	11/29/04	N/A
Pharm/Tox	Pending	Pending	Sonia Tabacova, Ph.D.
Biopharm	Approval	8/25/04	Kofi Kumi, Ph.D.
LNC	N/A	N/A	N/A
Methods Validation	Pending	Pending	Sherita McLamore, Ph.D.
OPDRA	N/A	N/A	N/A
EA	Categorical Exclusion Acceptable	9/17/04	Sherita McLamore, Ph.D.
Microbiology	N/A	N/A	N/A



The Chemistry Review for NDA 21-713

The Executive Summary

A. Recommendation and Conclusion on Approvability

From a Chemistry, Manufacturing, and Controls (CMC) perspective, it is recommended that NDA 21-713 be approved.

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)

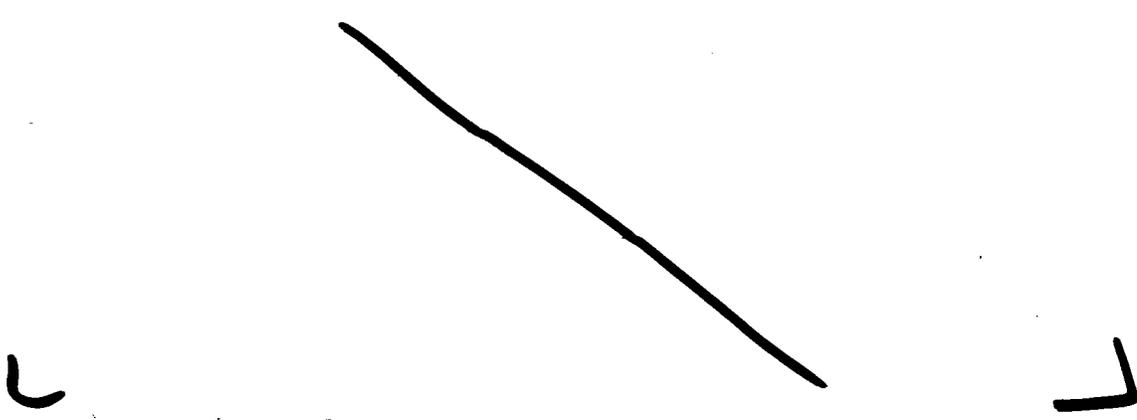
Aripiprazole is a member of the quinolinone class of compounds and is indicated for the treatment of patients with schizophrenia. Aripiprazole was originally investigated under IND 42,776 in 1993. In 1999, the applicant, Otsuka Pharmaceuticals and Bristol-Myers Squibb entered into a collaborative agreement to market the drug product. The drug substance was approved for use on November 11, 2002 in NDA 21-436. NDA 21-436 was submitted and approved for Abilify™ (aripiprazole) Tablets. The tablets are available in 2-, 5-, 10-, 15-, 20- and 30-mg strengths.

The current application is for aripiprazole oral solution. The oral solution formulation was developed to increase compliance in patients that have difficulty swallowing tablets. The drug product is a ready-to use solution containing glycerin, propylene glycol, DL-lactic acid sodium hydroxide methylparaben, propylparaben, fructose, natural orange flavor and aripiprazole. The drug product will be manufactured and packaged at the Bristol Myers Squibb facility in Mt. Vernon, Indiana or the Bristol Myers Squibb facility in Evansville, Indiana. The 1 mg/mL oral solution will be packaged in [redacted] bottles with a two-piece child resistant continuous thread closures.

The applicant referenced NDA 21-436 for all information pertaining to the drug substance. The drug substance is identical to the drug substance approved in NDA 21-436 for Abilify™ Tablets. The drug substance is described as a white crystalline powder with a melting point of [redacted]. The molecular formula for the drug substance is $C_{23}H_{27}Cl_2N_3O_2$ and the molecular weight is 448.38. The applicant indicates that the drug substance will be manufactured by Otsuka Pharmaceuticals in Japan. The synthesis of the drug substance involves the [redacted]



Executive Summary Section



The proprietary name for aripiprazole tablets is Abilify™ (aripiprazole) Tablets. The applicant seeks continued use of this name in the current application. The intended name for the drug product is Abilify™ (aripiprazole) Oral Solution.

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

Abilify™ (aripiprazole) Oral Solution is being developed as a 1 mg/mL solution with a maximum daily dose (MDD) of 30 mg. The drug product is being developed for the treatment of schizophrenia. The solution will be packaged in _____ bottles with a child resistant closure. The _____ bottles correspond to 50- 150- and 480-mL product sizes, respectively. The applicant indicates that the oral solution will have a starting and target dose of 10 or 15 mg/day and that the oral solution can be given in place of the tablets on a mg per mg basis for the lower dosages (i.e. 2-, 5-, 10, 15-, and 20 mg). For the highest tablet strength, 30 mg, a 25 mg dose (25 mL) should be substituted.

The applicant has requested a 24-month shelf life and a 6-month in-use period for the drug product. In CMC review #1, the Office of Compliance recommended an overall recommendation of hold for this application because the Mt. Vernon drug product manufacturing site (CFN# 1825662) was not ready for inspection. Accordingly, a decision on the expiry was not made at that time. The site was inspected on October 7, 2004 and was found to be acceptable. The Office of Compliance issued an overall recommendation of acceptable for this application on November 29, 2004. The applicant provided the following stability data in the original applicant: 30 months of stability data for 2 batches of the 50 mL product size and 3 batches of the 150 mL product size of the drug product; 12 months of data 1 batch of the 480 mL product size and 26 weeks of data for 1 batch of the 50 mL product size and 2 batches of the 480 mL product size. The applicant also included 6 months of in-use stability for 1 batch of product size. All results were within the prescribed specifications. At the time tested, _____

➤ The applicant has provided sufficient data to support



Executive Summary Section

a 24 month shelf life and a 6 month in-use period. Accordingly the applicant should be granted a **24-month shelf life** and a **6-month in-use period** for the drug product.

C. Basis for Approvability or Not-Approval Recommendation

The recommendation for the Chemistry, Manufacturing, and Controls (CMC) section of NDA 21-713 is approval as the applicant has adequately addressed all of the CMC deficiencies outlined in review # 1 and there are no outstanding CMC issues.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

SMcLamore/Date
TOliver (TL)/Date
SHardeman (PM)/Date

C. CC Block

Orig. NDA 21-713
HFD-120/Division File
HFD-120/SHardeman
HFD-120/SMcLamore
HFD-120/TOliver

12 Page(s) Withheld

 § 552(b)(4) Trade Secret / Confidential

 § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

Withheld Track Number: Chemistry- 142

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

/s/

Sherita McLamore
11/29/04 02:23:42 PM
CHEMIST

Thomas Oliver
11/29/04 04:32:49 PM
CHEMIST



NDA 21-713

Abilify™ (aripiprazole) Oral Solution

Otsuka Pharmaceuticals Company, Ltd

Sherita D. McLamore, Ph.D.
HFD-120



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Chemistry Review Data Sheet

1. NDA 21-713
2. REVIEW #1:
3. REVIEW DATE: September 7, 2004
4. REVIEWER: Sherita D. McLamore, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous DocumentsDocument Date

n/a

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) ReviewedDocument Date

Original Submission

November 18, 2003

Amendment

August 16, 2004

Amendment

June 8, 2004

7. NAME & ADDRESS OF APPLICANT:

Name:

Otsuka Pharmaceuticals Co., Ltd.

Address:

2-9 Kanda Tsukasa-cho
Chiyoda-ku Tokyo, 101-8535, Japan
Otsuka America Pharmaceutical, Inc.

Representative:

2440 Research Boulevard
Rockville, MD 20850

Telephone:

301-497-0900



CHEMISTRY REVIEW



Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Abilify
- b) Non-Proprietary Name (USAN): Aripiprazole
- c) Code Name/# (ONDC only): N/A
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 1
 - Submission Priority: S

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

10. PHARMACOL. CATEGORY: Schizophrenia

11. DOSAGE FORM: Oral Solution

12. STRENGTH/POTENCY: 1 mg/mL

13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED: Rx OTC

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

SPOTS product – Form Completed

Not a SPOTS product

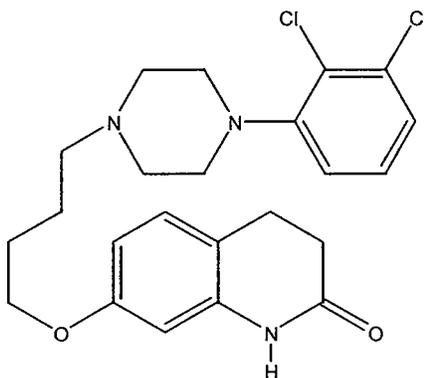
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

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

Molecular Formula: $C_{23}H_{27}Cl_2N_3O_2$

Molecular Weight: 448.38

Chemistry Review Data Sheet


17. RELATED/SUPPORTING DOCUMENTS:
A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
1	II	[Handwritten marks]	[Handwritten marks]	4	Adequate		N/A
	II			4	Adequate		N/A
	II			4	Adequate		N/A

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

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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	42,776	Commercial IND Indication: Treatment of Schizophrenia



CHEMISTRY REVIEW



Chemistry Review Data Sheet

IND	62,216	Sponsor: Otsuka America Pharm Commercial IND Indication: Management of the manifestation of psychotic disorder Sponsor: Otsuka Pharm
Original NDA	21-436	Aripiprazole Tablets Approved 11/15/2002

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	N/A
EES	Withhold	9/6/04	N/A
Pharm/Tox	Pending	Pending	Sonia Tabacova, Ph.D.
Biopharm	Approval	8/25/04	Kofi Kumi, Ph.D.
LNC	N/A	N/A	N/A
Methods Validation	Pending	Pending	Sherita McLamore, Ph.D.
OPDRA	N/A	N/A	N/A
EA	Categorical Exclusion Acceptable	9/17/04	Sherita McLamore, Ph.D.
Microbiology	N/A	N/A	N/A



The Chemistry Review for NDA 21-713

The Executive Summary

A. Recommendation and Conclusion on Approvability

The Chemistry, Manufacturing, and Controls (CMC) section of NDA 21-713 is approvable. The approval from a CMC standpoint is contingent on an acceptable recommendation from the Office of Compliance and an adequate response to the CMC deficiencies.

Methods validation will be submitted after all CMC deficiencies have been addressed.

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)

Aripiprazole is a member of the quinolinone class of compounds and is indicated for the treatment of patients with schizophrenia. Aripiprazole was originally investigated under IND 42,776 in 1993. In 1999, the applicant, Otsuka Pharmaceuticals and Bristol-Myers Squibb entered into a collaborative agreement to market the drug product. The drug substance was approved for use on November 11, 2002 in NDA 21-436. NDA 21-436 was submitted and approved for Abilify™ (aripiprazole) Tablets. The tablets are available in 2-, 5-, 10-, 15-, 20- and 30-mg strengths.

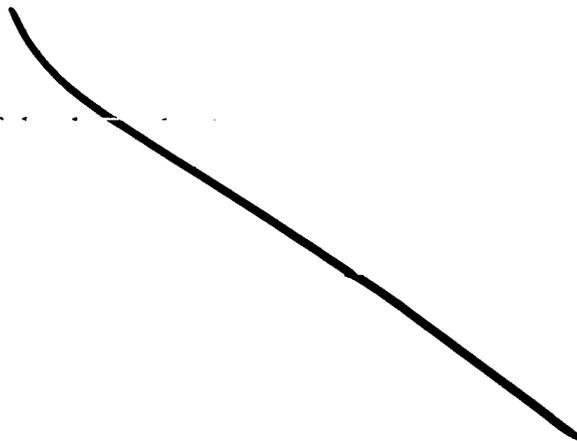
The current application is for aripiprazole oral solution. The oral solution formulation was developed to increase compliance in patients that have difficulty swallowing tablets. The drug product is a ready-to use solution containing glycerin, propylene glycol, DL-lactic acid sodium hydroxide methylparaben, propylparaben, fructose, natural orange flavor and aripiprazole. The drug product will be manufactured and packaged at the Bristol Myers Squibb facility in Mt. Vernon, Indiana or the Bristol Myers Squibb facility in Evansville, Indiana. The 1 mg/mL oral solution will be packaged in 2 bottles with a two-piece child resistant continuous thread closures. Calibrated dosing devices will be included with the drug product.

The applicant referenced NDA 21-436 for all information pertaining to the drug substance. The drug substance is identical to the drug substance approved in NDA 21-436 for Abilify™ Tablets. The drug substance is described as a white crystalline powder with a melting point of . The molecular formula for the drug



Executive Summary Section

substance is $C_{23}H_{27}Cl_2N_3O_2$ and the molecular weight is 448.38. The applicant indicates that the drug substance will be manufactured by Otsuka Pharmaceuticals in Japan. The synthesis of the drug substance involves



The proprietary name for aripiprazole tablets is Abilify™ (aripiprazole) Tablets. The applicant seeks continued use of this name in the current application. The intended name for the drug product is Abilify™ (aripiprazole) Oral Solution.

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The applicant has requested a 24-month shelf life and a 6-month in-use period for the drug product. On September 6, 2004, the Office of Compliance recommended an overall hold for this application because the Mt. Vernon drug product manufacturing site (Bristol Myers; CFN# 1825662) was unable to be inspected. As a result, the sponsor will be notified in the action letter that this site will either need to be withdrawn or the site will need to be found acceptable by the Office of Compliance. If the Mt. Vernon site is withdrawn, there will only be a limited number of primary stability batches which to base an expiry (Mt. Vernon data would be secondary). In light of the pending problems associated with the Mt. Vernon site, we will not set an expiry for the drug product at this time



Executive Summary Section

C. Basis for Approvability or Not-Approval Recommendation

NDA 21-713 is Approvable from a Chemistry standpoint due to chemistry, manufacturing and controls concerns related to the drug substance and the drug product as outlined in this review.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

SMcLamore/Date
TOliver (TL)/Date
SHardeman (PM)/Date

C. CC Block

Orig. NDA 21-713
HFD-120/Division File
HFD-120/SHardeman
HFD-120/SMcLamore
HFD-120/TOliver

69 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

 § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

Withheld Track Number: Chemistry-2072

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this page is the manifestation of the electronic signature.**

/s/

Sherita McLamore
9/17/04 02:41:29 PM
CHEMIST

Thomas Oliver
9/17/04 03:12:27 PM
CHEMIST