NDA 21-713

Abilify™ (aripiprazole) Oral Solution

Otsuka Pharmaceuticals Company, Ltd

Sherita D. McLamore, Ph.D.
HFD-120
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<td>III. List Of Deficiencies To Be Communicated</td>
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1. NDA 21-713

2. REVIEW #2

3. REVIEW DATE: November 19, 2004

4. REVIEWER: Sherita D. McLamore, Ph.D.

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<tr>
<td>Address:</td>
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</tr>
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<td></td>
<td>Chiyoda-ku Tokyo, 101-8535, Japan</td>
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<td>Otsuka America Pharmaceutical, Inc.</td>
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<tr>
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<td>2440 Research Boulevard</td>
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| Representative:       |                                |
| Telephone:            | 301-497-0900                   |
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:**  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:**

    Chemical Name: 7-[[4-[4-(2,3-Dichlorophenyl)-1-piperazinyl]butoxy]-3,4-dihydrocarbostyril
    Molecular Formula: C$_{23}$H$_{27}$Cl$_{2}$N$_{3}$O$_{2}$
    Molecular Weight: 448.38
17. RELATED/SUPPORTING DOCUMENTS:

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<sup>1</sup> 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")

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

B. Other Documents:
### CHEMISTRY REVIEW

Chemistry Review Data Sheet

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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 ad 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 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 . The molecular formula for the drug
substance is C23H27Cl2N3O2 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
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
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
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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   C. CC Block ............................................................................................................... 9

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1. NDA 21-713

2. REVIEW #1:

3. REVIEW DATE: September 7, 2004

4. REVIEWER: Sherita D. McLamore, Ph.D.

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<tr>
<td>Amendment</td>
<td>June 8, 2004</td>
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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
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:** _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:**  

   Chemical Name: 7-[4-{4-(2,3-Dichlorophenyl)-1-piperazinyl]butoxy}-3,4-dihydrocarbostyril  
   Molecular Formula: C_{23}H_{27}Cl_{2}N_{3}O_{2}  
   Molecular Weight: 448.38
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A. DMFs:

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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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<th>DESCRIPTION</th>
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|          |                    | Indication: Treatment of Schizophrenia |
## Chemistry Review Data Sheet

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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 ad 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 [ ] 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...
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Executive Summary Section

substance is C_{23}H_{27}Cl_{2}N_{3}O_{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.

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

____ § 552(b)(4) Draft Labeling

____ § 552(b)(5) Deliberative Process
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/s/

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